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Original Research

The Efficacy and Tolerability of Irbesartan/Amlodipine Combination Therapy in Patients With Essential Hypertension Whose Blood Pressure Were not Controlled by Irbesartan Monotherapy

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ABSTRACT

Purpose: This study aimed to evaluate the efficacy and tolerability of irbesartan (IRB) and amlodipine (AML) combination therapy in patients with essential hypertension whose blood pressure (BP) was not controlled by IRB monotherapy.

Methods: Two multicenter, randomized, double-blind, placebo-controlled, phase III studies were conducted in Korea (the I-DUO 301 study and the I-DUO 302 study). After a 4-week run-in period with either 150 mg IRB (I-DUO 301 study) or 300 mg IRB (I-DUO 302 study), patients with uncontrolled BP (ie, mean sitting systolic BP [MSSBP] ≥140 mmHg to <180 mmHg and mean sitting diastolic BP <110 mmHg) were randomized to the placebo, AML 5 mg, or AML 10 mg group. A total of 428 participants were enrolled in the 2 I-DUO studies. In the I-DUO 301 study, 271 participants were randomized in a 1:1:1 ratio to receive either IRB/AML 150/5 mg, IRB/AML 150/10 mg, or IRB 150 mg/placebo. In the I-DUO 302 study, 157 participants were randomized in a 1:1 ratio to receive IRB/AML 300/5 mg or IRB 300 mg/placebo. The primary endpoint was the change in MSSBP from baseline to week 8. Tolerability was assessed according to the development of treatment-emergent adverse events (TEAEs) and clinically significant changes in physical examination, laboratory tests, pulse, and 12-lead electrocardiography.

Findings: In I-DUO 301, the mean (SD) changes of MSSBP at week 8 from baseline were −14.78 (12.35) mmHg, −21.47 (12.78) mmHg, and −8.61 (12.19) mmHg in the IRB/AML 150/5 mg, IRB/AML 150/10 mg, and IRB 150 mg/placebo groups, respectively. In I-DUO 302, the mean (SD) changes of MSSBP at week 8 from baseline were −13.30 (12.47) mmHg and −7.19 (15.37) mmHg in the IRB/AML 300/5 mg and IRB 300 mg/placebo groups, respectively. In both studies, all combination groups showed a significantly higher reduction in MSSBP than the IRB monotherapy groups ($P < 0.001$ for both). TEAEs occurred in 10.00%, 10.99%, and 12.22% of participants in the IRB/AML 150/5 mg, IRB/AML 150/10 mg, and IRB 150 mg/placebo groups, respectively, in I-DUO 301 and in 6.33% and 10.67% of participants in the IRB/AML 300/5 mg and IRB 300 mg/placebo groups, respectively, in I-DUO 302, with no significant between-group differences. Overall, there was one serious adverse event throughout I-DUO study.

Implications: The combination of IRB and AML has superior antihypertensive effects compared with IRB alone over an 8-week treatment period, with placebo-like tolerability.

Clinical Trial Registration: ClinicalTrials.gov identifier: NCT05476354 (I-DUO 301), NCT05475665 (I-DUO 302).

Introduction

Hypertension, defined as a systolic blood pressure (SBP) of ≥140 mmHg and/or diastolic BP (DBP) of ≥90 mmHg, is a key risk factor for the progression of cardiovascular diseases (CVDs) and cerebrovascular diseases that contribute to mortality.[1,2] According to the Korean hypertension fact sheet 2022, as of 2020, 29.4% (approximately 12.6 million people) of the Korean adult population aged 20 years or older have hypertension, with 40% of them being aged 65 years or older and 10% aged 80 years or older.[3]

Although adequate blood pressure (BP) control can nearly completely reduce the CVD risk in hypertension patients, monotherapy often fails to achieve adequate BP control to the target goal, and most patients require the combination of at least 2 drugs to achieve BP control.[1] Hence, a common approach involves using combination therapy with drugs that exert different mechanisms to achieve adequate BP control.[4,5] In addition, single-pill combination (SPC) drugs are strongly recommended to improve medication adherence by reducing the number of pills, leading to better BP control.[1] SPCs have been developed to simplify treatment regimens, improve treatment compliance, and potentially reduce healthcare costs.[6,7]

Irbesartan (IRB)/amlodipine (AML) is a once-daily SPC medication that is composed of IRB, a well-tolerated potent and highly selective angiotensin receptor blocker (ARB) that significantly reduces BP, and AML, a long-acting dihydropyridine calcium channel blocker (CCB) effective in hypertension treatment.[8] IRB has reno-protective effects, increasing renal blood flow and reducing vascular resistance in hypertension patients.[9] It delays chronic kidney disease (CKD) progression in those with type 2 diabetes mellitus (T2DM) and microalbuminuria and slows damage in T2DM and nephropathy, partly independent of BP.[9,10] IRB also improves glycemic control and insulin sensitivity, with no significant lipid changes.[11] Meanwhile, AML increases renal blood flow and the glomerular filtration rate, lowering renal vascular resistance and microalbumin excretion without affecting renal or insulin-related physiological factors.[8] Overall, IRB and AML exhibit distinct but favorable renal and metabolic effects in hypertension patients.[8] Hence, the use of IRB and AML in combination is expected to offer enhanced effectiveness for patients who do not achieve the target BP goal by either monotherapy.

This phase III study conducted as part of a clinical development program in Korea for the registration of a new SPC for IRB and AML for the treatment of hypertension. The main objective of this study was to evaluate whether the antihypertensive effect of IRB and AML combination therapy was superior to that of IRB monotherapy in patients with hypertension whose BP was not adequately controlled by IRB monotherapy. The design of the study was structured in accordance with the Korean guideline on clinical trials of antihypertensive drugs. The guideline advocates for an add-on therapy design for the development of combination therapy, with monotherapy serving as the designated control group.

Participants and Methods

Study Design and Population

I-DUO 301 and I-DUO 302 (ClinicalTrials.gov identifier: NCT05476354, NCT05475665) were both phase III multicenter, randomized, double-blind, placebo-controlled, parallel-design clinical trials conducted across South Korea. I-DUO 301 was conducted at 25 sites from August 2022 to April 2023, while I-DUO 302 was conducted at 19 sites from August 2022 to March 2023. The protocols were approved by the Ministry of Food and Drug Safety and the Institutional Review Board of each clinical study site before the initiation of both

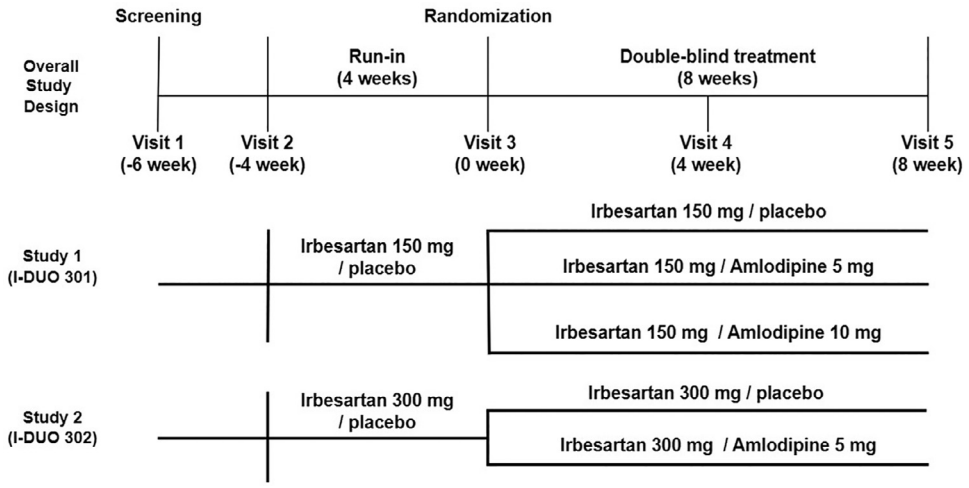

Figure 1. Schematic representation of the study designs for I-DUO 301 and I-DUO 302.

studies. The studies were conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice. All participants signed an informed consent form before participating in any study-related procedures.

To assess eligibility, all participants were screened for medical history, concomitant medication use, physical examination, clinical laboratory tests, and vital signs at the screening visit. Men or women aged 19 years or older with a diagnosis of essential hypertension who met the predefined BP criteria of a mean sitting systolic blood pressure (MSSBP) ≥140 mmHg to <180 mmHg and a mean sitting diastolic blood pressure (MSDBP) <110 mmHg for antihypertensive medication-naïve patients and MSSBP ≥130 mmHg to <180 mmHg and MSDBP <110 mmHg for patients with antihypertensive drugs were eligible for screening. The exclusion criteria encompass participants with difference of MSSBP ≥20 mmHg and MSDBP ≥10 mmHg between arms. Participants with certain medical conditions including severe obesity (body mass index ≥40.0 kg/m^2), significant electrolyte imbalances (sodium <130 mmol/L or potassium >5.5 mmol/L), uncontrolled diabetes (glycated hemoglobin concentration ≥9.0%), moderate/severe CKD, suspected secondary hypertension, severe heart failure defined as New York Heart Association class III or IV, recent cerebrovascular events, significant eye disorders, and autoimmune or inflammatory diseases were also excluded from the study (Table SI).

After a 4-week run-in period with IRB monotherapy (150 mg in I-DUO 301 and 300 mg in I-DUO 302), participants with MSSBP ≥140 mmHg to <180 mmHg and MSDBP <110 mmHg were randomized to the treatment (Figure 1).

Study Protocol

The study involved a 2-week screening period, followed by a 4-week run-in period, in which participants maintained a dose of 150 mg of IRB (I-DUO 301) or 300 mg of IRB (I-DUO 302) and were administered a placebo for AML daily. The placebos matching the AML tablets were identical in appearance, taste, and smell to each corresponding AML tablet dosage. After IRB monotherapy, participants with uncontrolled BP were eligible to enter an 8-week double-blind treatment.

In the I-DUO 301 study, the enrolled participants were randomized into 3 groups in a 1:1:1 ratio to receive IRB/AML 150/5 mg, IRB/AML 150/10 mg, or IRB 150 mg/placebo. In the I-DUO 302 study, the enrolled participants were randomized into 2 groups in a 1:1 ratio to receive IRB/AML 300/5 mg or IRB 300 mg/placebo. The study design is summarized in Figure 1. At randomization, the participants were stratified using the Interactive Web Response System based on their medical history (T2DM or CKD, without T2DM or CKD) and baseline MSSBP levels (MSSBP ≥160 mmHg, MSSBP <160 mmHg). T2DM, CKD and baseline MSSBP levels were selected as stratification factors because those were considered to have an impact on the efficacy endpoint.

In both studies, compliance of treatment was evaluated by comparing the actual number of investigational product (IP) administered, calculated by subtracting the remaining quantity of IP brought by the participants from the number of IP distributed in each visit, and the planned number of IP, defined as multiplying the planned duration of administration (day) by the daily dosage of treatment.

Study Endpoints and Measures

The primary efficacy endpoint was the mean change in MSSBP from baseline to week 8 in the IRB/AML and IRB monotherapy groups. The secondary efficacy endpoints were the mean change in MSSBP from baseline to week 4 and the mean change in MSDBP from baseline to weeks 4 and 8 in the IRB/AML and IRB monotherapy groups. The control and response rates were also assessed. The control rate was determined as the proportion of participants who achieved controlled BP (defined as MSSBP <140 mmHg and MSDBP <90 mmHg). The response rate was determined as the proportion of participants whose SBP and DBP were reduced by ≥20 mmHg and ≥10 mmHg, respectively, after the treatment. The key safety endpoints were the incidence of treatment-emergent adverse events (TEAEs) and clinically significant changes in physical examination results, vital signs, and clinical laboratory tests. BP was measured using an electronic sphygmomanometer (HEM-7155T, Omron Healthcare) supplied by the sponsor at each institution. BP measurements were performed after at least 5 min of rest, and the average of 2 values, measured at intervals of at least 1 min, was recorded.

Sample Size Determination

To confirm the superiority of combination therapy over IRB monotherapy, we compared the change in MSSBP between IRB and AML combination therapy and IRB monotherapy in participants with essential hypertension whose BP was not adequately controlled with IRB monotherapy. The sample size was determined based on the literature evaluating the change in MSSBP after the administration of SPCs (ARB/AML) compared to ARB monotherapy.[12–14]

To determine the sample size for the I-DUO 301 study, we calculated a target number of 77 participants per group, assuming a potential difference of −6.8 mmHg in the change of MSSBP between the IRB and AML combination therapy group and the IRB monotherapy group, with a standard deviation of 13.5 mmHg for each group. This sample size was selected to ensure a 2-sided significance level of 2.5% and a statis-

tical power of 80% in each test when compared with the monotherapy group while considering Bonferroni correction. Considering a dropout rate of 15%, a total of 273 participants (91 per group) were required for enrollment.

For the I-DUO 302 study, assuming a difference of −6.4 mmHg in the change of MSSBP between the combination therapy group and the monotherapy group, with a standard deviation of 13.5 mmHg for each group, we calculated the needed sample size as 71 participants per group. This sample size ensured a 2-sided significance level of 5% and statistical power of 80%. Considering a dropout rate of 15%, 84 participants (168 participants in total) were needed per group.

Statistical Analysis

The full analysis set (FAS) included all randomized participants who underwent at least 1 assessment of the primary efficacy variables after the administration of the study drug. The per-protocol set (PPS) was a subset of the FAS and involved participants who completed the study without any major protocol deviations that directly affected the efficacy assessment. The safety analysis set included all randomized participants who received at least 1 dose of the study drug during the treatment period.

The primary and secondary efficacy variables for BP change were compared using analysis of covariance (ANCOVA) with baseline BP as a covariate. The results of the endpoints were expressed as least-squares means (LSMs) and their 95% confidence intervals (CIs). The control and response rates in each treatment group were summarized and analyzed using the chi-square test or Fisher's exact test. Missing primary and secondary efficacy values were handled using the last observation carried forward method.

For comparison of baseline characteristics and safety variables between the IRB/AML combination therapy and IRB monotherapy groups, continuous variables were analyzed using analysis of variance, or the Kruskal–Wallis test. Meanwhile, categorical variables were analyzed using the chi-square test or Fisher's exact test. The TEAEs were coded according to the system organ class and preferred term using MedDRA (V25.1). All statistical analyses were performed using the SAS software (version 9.4; SAS Institute, Cary, NC). Statistical significance was defined as a 2-tailed *P*-value of <0.05.

Results

Participant Characteristics

In the I-DUO 301 study, 445 participants from 25 sites were screened for eligibility; among them, 271 participants were randomized to the 8-week double-blind treatment with IRB/AML 150/5 mg (n = 90), IRB/AML 150/10 mg (n = 91), or IRB 150 mg/placebo (n = 90). In total, 268 participants were included in the FAS, and 244 participants were included in the PPS (Figure 2, Table SII).

The baseline demographics and clinical characteristics were comparable between the treatment groups (Table 1). In total, 65.30% of participants were men, and the mean (SD) age at screening was 62.97 (12.89) years, with 52.99% of the participants aged ≥65 years. The baseline MSSBP and MSDBP were 150.21 mmHg and 91.62 mmHg, respectively, and 42.16% of the participants had a medical history of either T2DM or CKD. Proportion of smokers and drinkers, BMI, and duration of essential hypertension were comparable among the IRB/AML 150/5 mg, IRB/AML 150/10 mg, and IRB 150 mg/placebo groups.

In I-DUO 302, 288 participants from 19 sites were screened for eligibility. Among them, 157 participants were randomized to receive IRB/AML 300/5 mg (n = 79) or IRB 300 mg/placebo (n = 78). In total, 154 participants were included in the FAS, and 140 participants were included in the PPS (Figure 2, Table SII). The baseline demographics and clinical characteristics were also comparable between the 2 treatment groups in the I-DUO 302 trial (Table 1). Overall, 62.34% of the participants were men, and the mean (SD) age at screening was 62.88 (12.35) years, with 52.60% of the participants aged ≥65 years. The baseline MSSBP and MSDBP were 150.64 mmHg and 92.45 mmHg, respectively, and 35.71% of the participants had a medical history of either T2DM or CKD. Comparable patterns in smoking, drinking, BMI, and duration of essential hypertension were observed between the IRB/AML 300/5 mg and IRB 300 mg monotherapy groups.

Efficacy Outcomes

In I-DUO 301, all treatment groups showed significant reductions in both MSSBP and MSDBP at weeks 4 and 8 (Table 2, Figure 3A). In the FAS group (n = 268), the mean (SD) change in MSSBP from

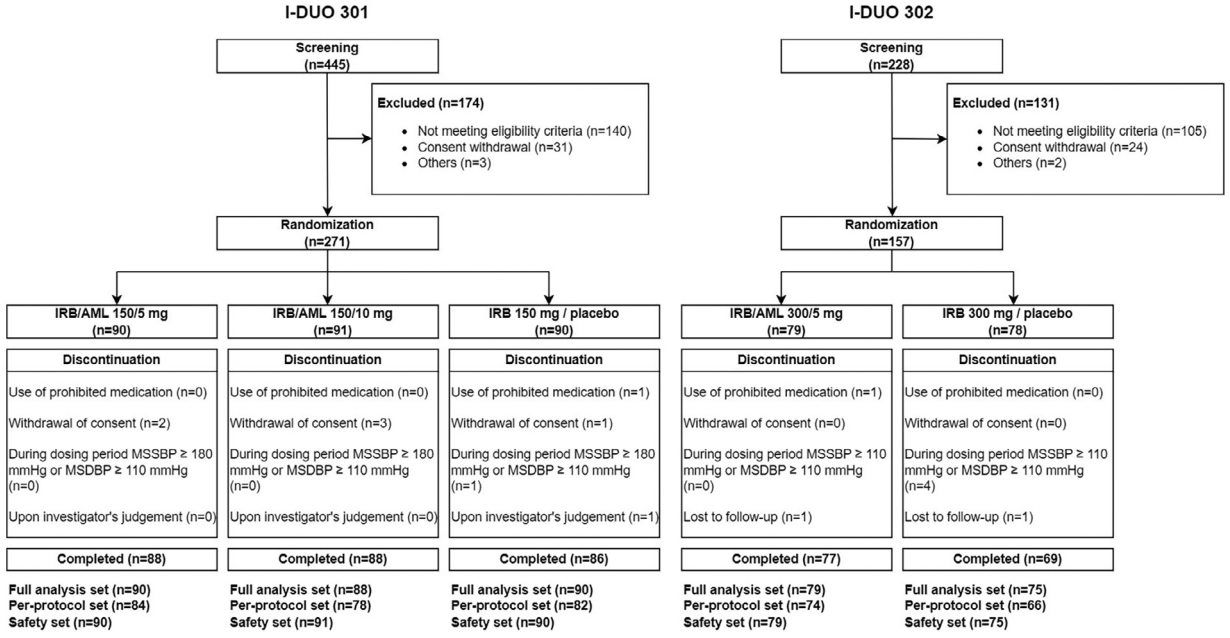

Figure 2. Participant selection flowchart in the I-DUO 301 and I-DUO 302 trials. AML = amlodipine; IRB = irbesartan; MSDBP = mean sitting diastolic blood pressure; MSSBP = mean sitting systolic blood pressure; n = number of participants.

Table 1
Demographic and baseline characteristics.

	I-DUO 301					I-DUO 302			
	IRB/AML 150/5 mg (n = 90)	IRB/AML 150/10 mg (n = 90)	IRB 150 mg/placebo (n = 88)	Total (n = 268)	*P*-Value*	IRB/AML 300/5 mg (n = 79)	IRB 300 mg/placebo (n = 75)	Total (n = 154)	*P*-Value†
Sex (male), n (%)	54 (60.00)	62 (68.89)	59 (67.05)	175 (65.30)	0.4178	49 (62.03)	47 (62.67)	96 (62.34)	0.9346
Age (years), Mean (SD)	62.60 (13.18)	64.91 (10.85)	61.35 (14.31)	62.97 (12.89)	0.3619	62.62 (12.09)	63.16 (12.70)	62.88 (12.35)	0.6459
Age ≥ 65 years, n (%)	46 (51.11)	52 (57.78)	44 (50.00)	142 (52.99)	0.5295	40 (50.63)	41 (54.67)	81 (52.60)	0.6163
Smoking, n (%)	13 (14.44)	16 (17.78)	19 (21.59)	48 (17.91)	0.4613	16 (20.25)	8 (10.67)	24 (15.58)	0.1011
Drinking, n (%)	39 (43.33)	36 (40.00)	40 (45.45)	115 (42.91)	0.7595	33 (41.77)	32 (42.67)	65 (42.21)	0.9106
BMI (kg/m^2), Mean (SD)	25.91 (3.19)	25.97 (3.81)	26.32 (3.61)	26.07 (3.54)	0.6854	25.80 (3.60)	25.88 (3.28)	25.84 (3.44)	0.8949
MSSBP (mmHg), Mean (SD)	149.63 (10.91)	150.57 (10.63)	150.43 (10.49)	150.21 (10.65)	0.7797	149.47 (9.94)	151.87 (11.07)	150.64 (10.54)	0.1228
MSDBP (mmHg), Mean (SD)	90.30 (10.84)	92.67 (9.61)	91.89 (9.87)	91.62 (10.14)	0.2809	92.28 (9.41)	92.64 (9.64)	92.45 (9.49)	1.0000
Duration of Essential Hypertension (month), Mean (SD)	141.58 (99.61)	143.91 (121.78)	121.91 (92.40)	135.90 (105.50)	0.4765	141.23 (126.41)	156.96 (113.74)	148.89 (120.28)	0.2718
Diabetes or CKD, n (%)	38 (42.22)	38 (42.22)	37 (42.05)	113 (42.16)	0.9996	29 (36.71)	26 (34.67)	55 (35.71)	0.7915
Diabetes, n (%)	35 (38.89)	38 (42.22)	37 (42.05)	110 (41.04)	0.8777	28 (35.44)	26 (34.67)	54 (35.06)	0.9196
CKD, n (%)	2 (2.22)	0 (0.00)	1 (1.14)	3 (1.12)	0.5481	2 (2.53)	1 (1.33)	3 (1.95)	1.0000

AML = amlodipine; BMI = body mass index; CKD = chronic kidney disease; IRB = irbesartan; MSDBP = mean sitting diastolic blood pressure; MSSBP = mean sitting systolic blood pressure; n = number of participants; SD = standard deviation.
The percentage is calculated using the number of participants in each group as the denominator.
Demographic data are collected at visit 1; MSSBP and MSDBP data are collected at visit 3.
* Continuous variables: ANOVA or Kruskal-Wallis test; categorical variables: chi-square test or Fisher's exact test.
† Continuous variables: independent t-test or Wilcoxon rank-sum test; categorical variables: chi-square test or Fisher's exact test.

Table 2
Change in MSSBP and MSDBP from baseline to weeks 4 and 8.

	I-DUO 301			I-DUO 302	
	IRB/AML 150/5 mg (n = 90)	IRB/AML 150/10 mg (n = 90)	IRB 150 mg/placebo (n = 88)	IRB/AML 300/5 mg (n = 79)	IRB 300 mg/placebo (n = 75)
MSSBP					
Baseline, mean (SD)	149.63 (10.91)	150.57 (10.63)	150.43 (10.49)	149.47 (9.94)	151.87 (11.07)
Week 4, mean (SD)	135.03 (12.06)	130.47 (11.29)	144.13 (14.65)	136.05 (14.18)	145.41 (15.95)
Week 8, mean (SD)	134.86 (12.13)	129.10 (11.96)	141.82 (14.84)	136.16 (11.31)	144.68 (16.54)
Change from baseline to week 4					
Mean (SD)	−14.08 (12.76)	−19.64 (12.12)	−6.42 (12.09)	−13.40 (13.05)	−6.21 (13.97)
P-value* (paired comparison)	<0.0001	<0.0001	<0.0001	<0.0001	0.0004
LSM difference (95% CI)	−8.19 (−11.78, −4.60)†	−13.43 (−16.94, −9.91)‡	−5.06 (−8.31, −1.81)§	−8.21 (−12.62, −3.79)‖	
P-value (ANCOVA)	<0.0001†	<0.0001‡	0.0025§	0.0003‖	
Change from baseline to week 8					
Mean (SD)	−14.78 (12.35)	−21.47 (12.78)	−8.61 (12.19)	−13.30 (12.47)	−7.19 (15.37)
P-value[1)] (paired comparison)	<0.0001	<0.0001	<0.0001	<0.0001	0.0001
LSM difference (95% CI)	−6.48 (−9.94, −3.03)†	−12.79 (−16.26, −9.32)‡	−6.03 (−9.24, −2.82)§	−7.38 (−11.52, −3.24)‖	
P-value (ANCOVA)	0.0003†	<0.0001‡	0.0003§	0.0006‖	
MSDBP					
Baseline, mean (SD)	90.30 (10.84)	92.67 (9.61)	91.89 (9.87)	92.28 (9.41)	92.64 (9.64)
Week 4, mean (SD)	83.94 (9.98)	82.20 (9.18)	90.28 (9.63)	85.09 (9.62)	89.68 (10.77)
Week 8, mean (SD)	83.63 (9.06)	80.93 (9.49)	89.19 (9.74)	84.58 (9.25)	89.91 (11.20)
Change from baseline to week 4					
Mean (SD)	−5.93 (7.12)	−9.96 (6.68)	−1.66 (7.23)	−7.01 (7.41)	−3.06 (7.24)
P-value* (paired comparison)	<0.0001	<0.0001	0.0066	<0.0001	0.0002
LSM Difference (95% CI)	−4.94 (−6.92, −2.95)†	−8.23 (−10.19, −6.28)‡	−3.36 (−5.23, −1.48)§	−4.08 (−6.41, −1.75)‖	
P-value (ANCOVA)	<0.0001†	<0.0001‡	0.0005§	0.0007‖	
Change from baseline to week 8					
Mean (SD)	−6.67 (7.28)	−11.73 (7.29)	−2.69 (8.32)	−7.70 (8.50)	−2.73 (8.55)
P-value* (paired comparison)	<0.0001	<0.0001	0.0031	<0.0001	0.0078
LSM difference (95% CI)	−4.58 (−6.61, −2.54)†	−8.79 (−10.92, −6.67)‡	−4.33 (−6.22, −2.44)§	−5.10 (−7.65, −2.54)‖	
P-value (ANCOVA)	<0.0001†	<0.0001‡	<0.0001§	0.0001‖	

AML = amlodipine; ANCOVA = analysis of covariance; CI = confidence interval; IRB = irbesartan; LSM = least square mean; MSDBP = mean sitting diastolic blood pressure; MSSBP = mean sitting systolic blood pressure; n = number of participants; SD = standard deviation.
* Paired comparison within groups via paired t-test or Wilcoxon signed-rank test.
† IRB/AML 150/5 mg vs IRB 150 mg/placebo.
‡ IRB/AML 150/10 mg vs IRB 150 mg/placebo.
§ IRB/AML 150/10 mg vs IRB/AML 150/5 mg.
‖ IRB/AML 300/5 mg vs IRB 300 mg/placebo.

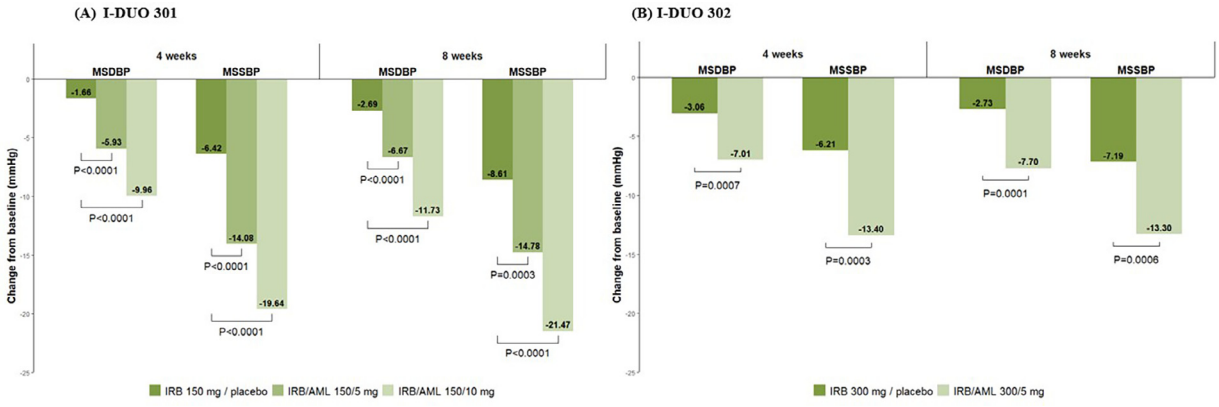

Figure 3. Change in mean blood pressure after 4 and 8 weeks of treatment with irbesartan and amlodipine in combination and with irbesartan alone. The bars represent the mean change in MSSBP or MSDBP from baseline to weeks 4 and 8 in the I-DUO 301 (A) and I-DUO 302 (B) studies. *P*-values are calculated using ANCOVA model to determine the differences in least-squares means: MSSBP (MSDBP) change from baseline to week 4 or week 8. AML = amlodipine; IRB = irbesartan; MSDBP = mean sitting diastolic blood pressure; MSSBP = mean sitting systolic blood pressure.

baseline to week 8 was −14.78 (12.35) mmHg in the IRB/AML 150/5 mg group, −21.47 (12.78) mmHg in the IRB/AML 150/10 mg group, and −8.61 (12.19) mmHg in the IRB 150 mg monotherapy group (all $P < 0.0001$). After 8 weeks, the LSM differences for IRB/AML 150/5 mg and IRB/AML 150/10 mg compared to IRB 150 mg monotherapy, were −6.48 mmHg (95% CI, −9.94 to −3.03; $P = 0.0003$) and −12.79 mmHg (95% CI, −16.26 to −9.32; $P < 0.0001$), respectively. This indicated a superior antihypertensive effect for both combination treatments over IRB 150 mg monotherapy. Furthermore, the LSM difference between the IRB/AML 150/5 mg group and the IRB/AML 150/10 mg group was −6.03 mmHg (95% CI, −9.24 to −2.82; $P = 0.0003$), indicating that IRB/AML 150/10 mg treatment has a more significant antihypertensive effect compared to IRB/AML 150/5 mg treatment.

After 4 weeks of treatment (FAS), the mean (SD) change in MSSBP from baseline was −14.08 (12.76) mmHg in the IRB/AML 150/5 mg group, −19.64 (12.12) mmHg in the IRB/AML 150/10 mg group, and −6.42 (12.09) mmHg in the IRB 150 mg monotherapy group (all $P < 0.0001$). After 4 weeks, the LSM difference for IRB/AML 150/5 mg and IRB/AML 150/10 mg, compared to IRB 150 mg monotherapy, was −8.19 mmHg (95% CI, −11.78 to −4.60; $P < 0.0001$) and −13.43 mmHg (95% CI, −16.94 to −9.91; $P < 0.0001$), respectively. The LSM difference between the IRB/AML 150/5 mg group and the IRB/AML 150/10 mg group was −5.06 mmHg (95% CI, −8.31 to −1.81; $P = 0.0025$).

Additionally, IRB and AML combination therapy resulted in a more pronounced reduction in MSDBP than IRB monotherapy after 4 and 8 weeks of treatment (Table 2 and Figure 3A). The overall results of the FAS were consistent with those of the PPS analysis (n = 244) in the I-DUO 301 trial (Table SIII).

At week 8, the control rate was notably higher in the IRB/AML 150/10 mg group (65.56%; $P < 0.0001$) and the IRB/AML 150/5 mg group (51.11%; $P = 0.0056$) than in the IRB 150 mg monotherapy group (30.68%). In addition, the response rate was significantly higher in the IRB/AML 150/10 mg group (47.78%; $P < 0.0001$) and the IRB/AML 150/5 mg group (23.33%; $P = 0.0353$) than in the IRB 150 mg monotherapy group (11.36%) (Figure 4A).

In I-DUO 302, the IRB/AML 300/5 mg group showed significantly greater reductions in MSSBP and MSDBP than the IRB 300 mg monotherapy group at both weeks 4 and 8 (Table 2 and Figure 3B). In the FAS group (n = 154), the mean (SD) reductions in MSSBP from baseline to week 8 were −13.30 (12.47) mmHg in the IRB/AML 300/5 mg group and −7.19 (15.37) mmHg in the IRB 300 mg monotherapy group (IRB/AML 300/5 mg, $P < 0.0001$; IRB 300 mg/placebo, $P = 0.0001$). The LSM difference for the change in MSSBP at week 8 between the 2 groups was −7.38 mmHg (95% CI, −11.52 to −3.24; $P = 0.0006$).

After 4 weeks of treatment (FAS), the mean (SD) reductions in MSSBP were −13.40 (13.05) mmHg in the IRB/AML 300/5 mg group

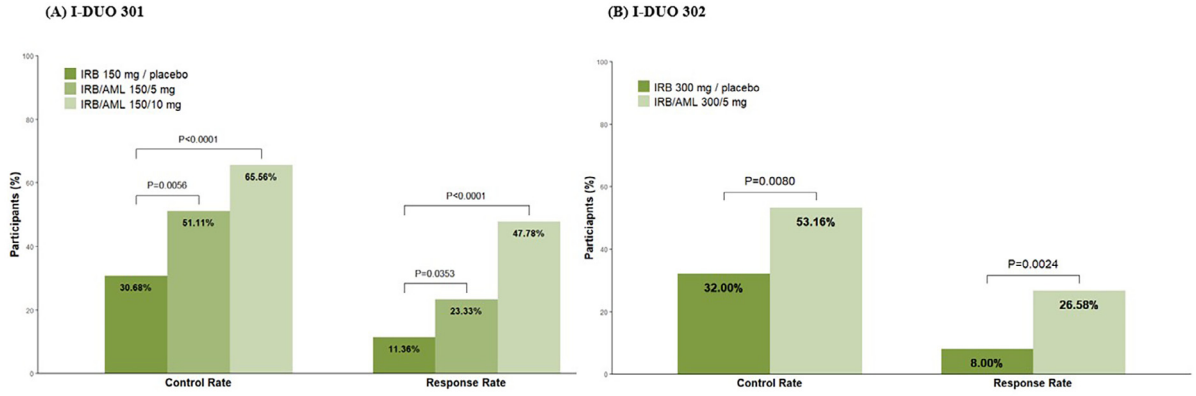

Figure 4. Comparison of control rate and response rate at week 8 between the irbesartan and amlodipine combination group and the irbesartan monotherapy group. The bars represent the control rate (left) and response rate (right) after 8 weeks of treatment in the I-DUO 301 (A) and I-DUO 302 (B) trials. *P*-values are calculated using the chi-square test. The control rate is defined as the proportion of participants with an MSSBP <140 mmHg and an MSDBP <90 mmHg after treatment. The response rate is defined as the proportion of patients whose MSSBP and MSDBP are decreased by ≥20 mmHg and ≥10 mmHg, respectively, after treatment compared to baseline. AML = amlodipine; IRB = irbesartan; MSDBP = mean sitting diastolic blood pressure; MSSBP = mean sitting systolic blood pressure.

Table 3
Summary of TEAEs

Variable	I-DUO 301					I-DUO 302			
	IRB/AML 150/5 mg (n = 90)	IRB/AML 150/10 mg (n = 91)	IRB 150 mg/placebo (n = 90)	Total (n = 271)	*P*-value*	IRB/AML 300/5 mg (n = 79)	IRB 300 mg/placebo (n = 75)	Total (n = 154)	*P*-value*
TEAEs	9 (10.00), [9]	10 (10.99), [12]	11 (12.22), [11]	30 (11.07), [32]	0.8929	5 (6.33), [7]	8 (10.67), [12]	13 (8.44), [19]	0.3332
Intensity									
Mild	6 (6.67), [6]	10 (10.99), [12]	6 (6.67), [6]	22 (8.12), [24]	-	4 (5.06), [6]	7 (9.33), [9]	11 (7.14), [15]	-
Moderate	3 (3.33), [3]	0	4 (4.44), [4]	7 (2.58), [7]	-	1 (1.27), [1]	3 (4.00), [3]	4 (2.60), [4]	-
Severe	0	0	1 (1.11), [1]	1 (0.37), [1]	-	0	0	0	-
SAEs	0	0	1 (1.11), [1]	1 (0.37), [1]	0.6642	0	0	0	-
ADRs	1 (1.11), [1]	2 (2.20), [2]	1 (1.11), [1]	4 (1.48), [4]	1.0000	0	1 (1.33), [1]	1 (0.65), [1]	0.4870
Serious ADRs	0	0	0	0	-	0	0	0	-
Common TEAEs									
Headache	1 (1.11), [1]	0	1 (1.11), [1]	2 (0.74), [2]	-	0	1 (1.33), [1]	1 (0.65), [1]	-
Dyslipidaemia	0	0	1 (1.11), [1]	1 (0.37), [1]	-	1 (1.27), [1]	0	1 (0.65), [1]	-
Constipation	1 (1.11), [1]	0	1 (1.11), [1]	2 (0.74), [2]	-	0	0	0	-
Dizziness	1 (1.11), [1]	0	1 (1.11), [1]	2 (0.74), [2]	-	0	0	0	-
Hypertriglyceridaemia	0	0	0	0	-	0	2 (2.67), [2]	2 (1.30), [2]	-

Data are presented as a number (% of participants), [number of cases]. TEAEs are all new adverse events occurring in participants who received the investigational product (IP) regardless of causality. ADRs are TEAEs those with an undeniable causal relationship to the IP. SAEs are TEAEs that resulting in death, life-threatening, requiring or prolonging hospitalization, causing persistent or significant disability/damage, leading to congenital anomalies/birth defects, and other medically significant conditions. The intensity of TEAE was assessed by investigators based on their severity, categorized as mild, moderate, or severe. Mild events caused mild or transient discomfort, without the need for intervention or treatment, and did not limit daily activities. Moderate events resulted in discomfort to interfere daily activities, allowing participants to continue in the study but potentially requiring interventional treatment. Severe events led to significant symptoms preventing normal daily activities, rendering participants unable to continue in the study, and possibly requiring hospitalization or invasive intervention.
ADRs = adverse drug reactions; AML = amlodipine; IRB = irbesartan; n = number of participants; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events.
* Between-group comparison using the chi-square test or Fisher's exact test.

($P < 0.0001$) and −6.21 (13.97) mmHg in the IRB 300 mg monotherapy group ($P = 0.0004$). The LSM difference for the change in MSSBP at week 4 between the IRB/AML 300/5 mg group and the IRB 300 mg monotherapy group was −8.21 mmHg (95% CI, −12.62 to −3.79; $P = 0.0003$). Furthermore, there were significant decreases in MSDBP in all treatment groups at both weeks 4 and 8 (Table 2, Figure 3B). Similar findings were observed in the PPS analysis (n = 140, Table SIII).

At week 8, the control rate was significantly higher in the IRB/AML 300/5 mg group than in the IRB 300 mg monotherapy group (53.16% vs 32.00%, $P = 0.0080$; Figure 4B). Similarly, the response rate was significantly higher in the IRB/AML 300/5 mg group than in the IRB 300 mg monotherapy group (26.58% vs 8.00%, $P = 0.0024$; Figure 4B).

Consistent with the results above, the outcomes of the subgroup analysis in the elderly and T2DM patient populations showed that the combination therapy groups had consistently higher reductions in MSSBP and MSDBP compared to the monotherapy groups (Tables SIV and SV).

Safety Outcomes

In I-DUO 301, of the 271 participants in the safety set, 30 participants (11.07%) developed a total of 32 TEAEs, with no significant differences among the treatment groups ($P = 0.8929$; Table 3). Four cases of ADRs were observed in 4 participants (1.48%), and there were no significant differences in ADRs among the treatment groups ($P = 1.0000$). No serious ADRs occurred during the study period. Overall, 1 participant (0.37%) in the IRB 150 mg monotherapy group experienced a SAE of a spinal fracture. Investigator judged the SAE was not related to the study drugs and the patient recovered after undergoing kyphoplasty during hospitalization.

In I-DUO 302, 154 participants were included in the safety analysis (Table 3). Overall, 19 TEAEs occurred in 13 participants (8.44%), and there were no significant differences between the 2 groups ($P = 0.3332$). A single event of ADR occurred in 1 participant (0.65%) in the IRB 300 mg monotherapy group, and there was no SAE reported in any of the treatment groups.

In both studies, no specific TEAEs were observed to be more prevalent in the elderly population compared to the overall study population, and importantly, no occurrences of orthostatic hypotension were noted. Occurrences of dizziness and postural dizziness, symptoms associated with orthostatic hypotension, were solely identified in participants under 65 years of age. In addition, the occurrence rates of TEAEs in elderly population were lower than overall population. This observation suggests that combination of IRB and AML can be safely used, even in elderly patients, without an elevated risk of orthostatic hypotension.

Discussion

Both the I-DUO 301 and I-DUO 302 studies demonstrated that the combination of IRB and AML was significantly more effective than IRB monotherapy in reducing BP while also improving the control and response rates after 4 and 8 weeks of treatment. Significant reductions in MSSBP and MSDBP were observed by week 4 and were sustained up to week 8 in all IRB and AML combination groups, including the IRB/AML 150/5mg, IRB/AML 150/10 mg, and IRB/AML 300/5 mg groups.

The results are consistent with previous findings that the combination of IRB/AML achieves a BP control rate of >40%.[12,15] Further, the combination of IRB and AML demonstrated consistent efficacy in various subgroups, including but not limited to the subgroups aged ≥65 years and with T2DM. The incidence of comorbid diabetes is higher in essential hypertension patients, as hyperglycemia increases vascular stiffness and aggravates atherosclerosis. In both the I-DUO 301 and I-DUO 302 studies, 41.04% and 35.06% of the participants had diabetes. This prevalence of T2DM is notably higher than the national average of 27.26% in South Korea,[3] and exceeds the rates in other hypertension studies.[12,16] Specifically, more than 100 participants with diabetes were treated with IRB/AML, and they showed higher reductions in MSSBP and MSDBP, confirming the BP-lowering effects in these populations. The safety profile was tolerable in T2DM population, as indicated by the numerically similar incidence of TEAEs with 10.81% and 7.41% in I-DUO 301 and I-DUO 302 studies, respectively, compared to the overall participants. In addition, the regimens also effectively controlled the BP with favorable tolerability profiles in elderly patients aged ≥65 years with TEAE occurrence rate of 9.72% and 4.94% in I-DUO 301 and I-

DUO 302 studies, respectively, which is numerically comparable with the rate of 11.07% and 8.44% in overall participants (Table SVI).

Among the combination treatments, the combination with a higher AML dose (IRB/AML 150/10 mg) demonstrated higher efficacy for BP control than that with a lower AML dose (IRB/AML 150/5 mg) in the I-DUO 301 study. These results are consistent with those of a recent meta-analysis that evaluated the efficacy of SPC antihypertensive drugs in patients with uncontrolled essential hypertension. The IRB/AML combination was the most effective for reducing SBP, and the ARB/CCB combination was superior to other SPCs with respect to overall BP control.[17] Regarding the management of hypertension, the renin-angiotensin system blockers, including angiotensin-converting enzyme inhibitors and ARBs, play a crucial role. ARBs demonstrate comparable effectiveness to each other and other major drug classes regarding cardiovascular events and mortality outcomes, as per the 2023 ESH guidelines.[1] Notably, ARBs exhibit significantly lower treatment discontinuation rates for adverse events compared to other antihypertensive therapies, resembling rates seen with placebo.[18] Focusing on irbesartan within the ARB class, it selectively binds to the angiotensin II receptor subtype 1 (AT1), inhibiting angiotensin II activity. Studies on normotensive volunteers reveal that irbesartan has a prolonged inhibitory effect on the pressor response to exogenous angiotensin II. When compared to other ARBs like losartan and valsartan, irbesartan stands out for inducing a more significant and longer-lasting AT1 blockade.[11] In ex vivo/in vivo studies suggest higher antagonistic activity for irbesartan compared to candesartan, with similar AT1 antagonistic activity in vivo. Irbesartan further demonstrates a more substantial reduction in aldosterone levels and a greater increase in plasma renin activity compared to candesartan. These findings provide valuable insights into the pharmacological distinctions within the ARB class.[11]

A flat dose-response relationship has been frequently noted with other ARBs.[19] In the current study, IRB/AML 300/5 mg appeared to have flat efficacy compared with IRB/AML 150/5 mg. These results are similar to those found between IRB 300 mg and IRB 150 mg in current studies. Although the I-DUO 301 and 302 trials were 2 separate trials, the BP-lowering efficacy of the IRB 150 mg-containing regimen was numerically higher than that of the IRB 300 mg-containing regimen. However, the dose-response relationship observed in the previous I-ADD study indicated that the decrease in BP was greater when the IRB dose was titrated from 150 mg to 300 mg. When the dose was titrated, the change in MSSBP/MSDBP from baseline increased from −14.7/-7.3 mmHg to −17.9/−7.7 mmHg in the IRB/AML SPC group and from −5.1/−2.4 mmHg to −8.4/−3.5 mmHg in the IRB monotherapy group.[12] The trial is designed as a dose-titration study, which is considered appropriate for representing clinical practice because different doses are assessed within the same patient.[19] Importantly, the results support that uptitration of IRB is favorable for lowering BP under real-world conditions.

The combination of an ARB and a CCB has a synergistic effect on reducing adverse events, especially peripheral edema associated with CCB.[20] ARBs can block the activation of the sympathetic nervous system caused by CCB-induced vasodilation, and CCB-induced activation of the renin-angiotensin-aldosterone system is also blocked by ARBs.[21] In this study, only 1 case of edema occurred in the IRB 300 mg monotherapy group in I-DUO 302 study, which had no causal relationship with irbesartan, and none in I-DUO 301 study. In summary, amlodipine-induced edema did not occur in both studies. The current study findings also suggest a better safety profile for IRB/AML combination treatments than for monotherapy. The incidence rate of TEAEs in the IRB/AML combination therapy group was lower than that in the monotherapy group. In I-DUO 301, the incidence of TEAEs was 10.00% in the IRB/AML 150/5 mg group and 10.99% in the IRB/AML 150/10 mg group, lower than the 12.22% rate in the IRB 150 mg monotherapy group. Similarly, in I-DUO 302, the incidence of TEAEs was 6.33% in the IRB/AML 300/5 mg group, lower than the 10.67% rate in the IRB 300 mg monotherapy group. Coronavirus Disease-19 (COVID-19) infection was the most frequently reported adverse event (2.21% in I-DUO 301 and 1.95% in I-DUO 302 study); however, considering the pandemic situation and the association with ARB and CCB has not been proven and the existing literature is strongly discordant, it was not included in the Table 3.

Although these 2 phase III clinical trials were well-controlled and appropriately addressed many predictable biases, there are still a few limitations. First, the results should be generalized with caution to other racial groups because the study was limited to South Koreans. The IRB/AML 300/10 mg combination was excluded from the development regimen, considering the market size and tolerability of AML 10 mg in South Korea. However, limitations in dosage selection still exist for clinicians. Additionally, due to the short follow-up duration of this study (8 weeks), there was limitation in confirming the long-term safety of the IRB/AML combination. However, this duration was set in accordance with the Korean guideline on clinical trials of antihypertensive drugs and the long-term safety data will be monitored by postmarketing surveillance study in Korea. Finally, in adherence to the recommendations outlined in the 2023 ESH guideline, which advocates for the broader utilization of out-of-office BP measurement methods such as ABPM and/or HBPM, we acknowledge the limitation that no ABPM and/or HBPM data were collected in the current study. It is important to note that, during the I-DUO trial, participants were provided with electronic sphygmomanometers for Home Blood Pressure Monitoring (HBPM) to monitor BP control. Given the specific purpose of our trial, which serves as a registration study, the decision to collect only office BP data was deemed sufficient for the evaluation of efficacy.

Despite these limitations, this study is significant as it provides, to our best knowledge, the first clear confirmation of the efficacy and safety of 3 fixed-dose regimens (150/5, 150/10, and 300/5 mg) for IRB and AML in South Korea, supporting the clinical utility of the drug. Further studies are required to identify the comparative effectiveness and tolerance profiles of IRB/AML combinations in real-world settings.

Conclusion

IRB and AML fixed-dose regimens exhibit superior antihypertensive efficacy compared to IRB monotherapy with respect to reducing MSSBP and MSDBP. Furthermore, the treatments are well tolerated, with a placebo-like safety profile compared with monotherapy.

CRediT authorship contribution statement

Hae-Young Lee: Conceptualization, Methodology, Writing – review & editing, Writing – original draft, Conceptualization, Methodology, Writing – review & editing. **Kyung Wan Min:** Conceptualization, Methodology, Writing – review & editing. **Kyung Ah Han:** Conceptualization, Methodology, Writing – review & editing. **Jeong Su Kim:** Conceptualization, Methodology, Writing – review & editing. **Jeong Cheon Ahn:** Conceptualization, Methodology, Writing – review & editing. **Moo Hyun Kim:** Conceptualization, Methodology, Writing – review & editing. **Jin Bae Lee:** Conceptualization, Methodology, Writing – review & editing. **Sung-Hee Shin:** Conceptualization, Methodology, Writing – review & editing. **Chong-Jin Kim:** Conceptualization, Methodology, Writing – review & editing. **Kye Hun Kim:** Conceptualization, Methodology, Writing – review & editing. **Deok-Kyu Cho:** Conceptualization, Methodology, Writing – review & editing. **Junghyun Choi:** Conceptualization, Methodology, Writing – review & editing. **Moo-Yong Rhee:** Conceptualization, Methodology, Writing – review & editing. **Sung-Ho Her:** Conceptualization, Methodology, Writing – review & editing. **Weon Kim:** Conceptualization, Methodology, Writing – review & editing. **Jin Oh Na:** Conceptualization, Methodology, Writing – review & editing. **Goo-Yeong Cho:** Conceptualization, Methodology, Writing – review & editing. **Seok Yeon Kim:** Conceptualization, Methodology, Writing – review & editing. **Gyung-Min Park:** Conceptualization, Methodology, Writing – review & editing. **Bong-Ki Lee:** Conceptualization, Methodology, Writing – review & editing. **Sang-Ho Jo:** Conceptu-

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Disclosures

All authors participated in the study as principal investigators of each centers. The authors have no conflicts of interest regarding the content of this article. The sponsor and all authors agreed on the study design, protocol, and statistical plan. An independent clinical research organization was responsible for trial management and data collection, and all statistical analyses were done by an independent data management team (ADM Korea Inc., Seoul, Korea). The study interpretation, writing of the manuscript, and the decision to publish this manuscript were the sole responsibility of the authors and were thus independent of the funders.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2024.04.004.

References

1. Mancia G, Kreutz R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA): Erratum. *J Hypertens*. 2024;42(1):194. doi:10.1097/HJH.0000000000003480.
2. Kim HL, Lee EM, Ahn SY, et al. The 2022 focused update of the 2018 Korean Hypertension Society Guidelines for the management of hypertension. *Clin Hypertens*. 2023;29(1):11. doi:10.1186/s40885-023-00234-9.
3. Kim HC, Lee H, Lee HH, et al. Korea hypertension fact sheet 2022: analysis of nationwide population-based data with a special focus on hypertension in the elderly. *Clin Hypertens*. 2023;29(1):22. doi:10.1186/s40885-023-00243-8.
4. Lee JY, Bak JK, Kim M, et al. Long-term cardiovascular events in hypertensive patients: full report of the Korean Hypertension Cohort. *Korean J Intern Med*. 2023;38(1):56–67. doi:10.3904/kjim.2022.249.
5. Kim HC, Lee H, Lee HH, et al. Korea hypertension fact sheet 2021: analysis of nationwide population-based data with special focus on hypertension in women. *Clin Hypertens*. 2022;28(1):1. doi:10.1186/s40885-021-00188-w.
6. Sherrill B, Halpern M, Khan S, Zhang J, Panjabi S. Single-pill vs free-equivalent combination therapies for hypertension: a meta-analysis of health care costs and adherence. *J Clin Hypertens (Greenwich)*. 2011;13(12):898–909. doi:10.1111/j.1751-7176.2011.00550.x.
7. Zeng F, Patel BV, Andrews L, et al. Adherence and persistence of single-pill ARB/CCB combination therapy compared to multiple-pill ARB/CCB regimens. *Curr Med Res Opin*. 2010;26(12):2877–2887. doi:10.1185/03007995.2010.534129.
8. Garnock-Jones KP. Irbesartan/amlodipine: a review of its use in adult patients with essential hypertension not adequately controlled with monotherapy. *Am J Cardiovasc Drugs*. 2013;13(2):141–150. doi:10.1007/s40256-013-0014-7.
9. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med*. 2001;345(12):870–878. doi:10.1056/NEJMoa011489.
10. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345(12):851–860. doi:10.1056/NEJMoa011303.
11. Croom KF, Curran MP, Goa KL, Perry CM. Irbesartan: a review of its use in hypertension and in the management of diabetic nephropathy. *Drugs*. 2004;64(9):999–1028. doi:10.2165/00003495-200464090-00011.
12. Bobrie GInvestigators IAS. I-ADD study: assessment of efficacy and safety profile of irbesartan/amlodipine fixed-dose combination therapy compared with irbesartan monotherapy in hypertensive patients uncontrolled with irbesartan 150 mg monotherapy: a multicenter, phase III, prospective, randomized, open-label with blinded-end point evaluation study. *Clin Ther*. 2012;34(8):1720–1734.e1723. doi:10.1016/j.clinthera.2012.07.001.
13. Sinkiewicz W, Glazer RD, Kavoliuniene A, et al. Efficacy and tolerability of amlodipine/valsartan combination therapy in hypertensive patients not adequately controlled on valsartan monotherapy. *Curr Med Res Opin*. 2009;25(2):315–324. doi:10.1185/03007990802630588.
14. Hong BK, Park CG, Kim KS, et al. Comparison of the efficacy and safety of fixed-dose amlodipine/losartan and losartan in hypertensive patients inadequately controlled with losartan: a randomized, double-blind, multicenter study. *Am J Cardiovasc Drugs*. 2012;12(3):189–195. doi:10.2165/11597410-000000000-00000.
15. Ishimitsu T, Fukuda H, Uchida M, et al. The therapeutic advantage of combination antihypertensive drug therapy using amlodipine and irbesartan in hypertensive patients: analysis of the post-marketing survey data from PARTNER (Practical combination therapy of Amlodin and angiotensin II Receptor blocker; safety and efficacy in patients with hypertension) study. *Clin Exp Hypertens*. 2015;37(7):542–550. doi:10.3109/10641963.2015.1026037.
16. Zhu JR, Zhang SY, Gao PJ. Efficacy and safety of olmesartan medoxomil/amlodipine fixed-dose combination for hypertensive patients uncontrolled with monotherapy. *Arch Pharm Res*. 2014;37(12):1588–1598. doi:10.1007/s12272-014-0446-x.
17. Xie M, Tang T, Liang H. Efficacy of single-pill combination in uncontrolled essential hypertension: a systematic review and network meta-analysis. *Clin Cardiol*. 2023;46(8):886–898. doi:10.1002/clc.24082.
18. Hasford J, Mimran A, Simons WR. A population-based European cohort study of persistence in newly diagnosed hypertensive patients. *J Hum Hypertens*. 2002;16(8):569–575. doi:10.1038/sj.jhh.1001451.
19. Smith DH. Dose-response characteristics of olmesartan medoxomil and other angiotensin receptor antagonists. *Am J Cardiovasc Drugs*. 2007;7(5):347–356. doi:10.2165/00129784-200707050-00004.
20. Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. *Clin Ther*. 2007;29(4):563–580. doi:10.1016/j.clinthera.2007.03.018.
21. Miura S, Saku K. Efficacy and safety of angiotensin II type 1 receptor blocker/calcium channel blocker combination therapy for hypertension: focus on a single-pill fixed-dose combination of valsartan and amlodipine. *J Int Med Res*. 2012;40(1):1–9. doi:10.1177/147323001204000101.