Efficacy and Safety of a Fixed-Dose Combination of Candesartan and Rosuvastatin on Blood Pressure and Cholesterol in Patients With Hypertension and Hypercholesterolemia: A Multicenter, Randomized, Double-Blind, Parallel Phase III Clinical Study

Kyoung Im Cho, MD, PhD[1,*]; Bo Hyun Kim, MD, PhD[2,*]; Yong Hyun Park, MD, PhD[3]; Jeong-Cheon Ahn, MD, PhD[5]; Sang Hyun Kim, MD, PhD[6]; Wook Jin Chung, MD, PhD[4]; Weon Kim, MD, PhD[7]; Il Suk Sohn, MD, PhD[8]; Jin Ho Shin, MD, PhD[9]; Yong Jin Kim, MD, PhD[10]; Kiyuk Chang, MD, PhD[11]; Cheol Woong Yu, MD, PhD[12]; Soe Hee Ahn, MD, PhD[13]; Seok Yeon Kim, MD, PhD[14]; Jae Kean Ryu, MD, PhD[15]; Jong Young Lee, MD, PhD[16]; Bum Kee Hong, MD, PhD[17]; Taek Jong Hong, MD, PhD[1]; and Chang Gyu Park, MD, PhD[4]

[1]Department of Internal Medicine, Kosin University College of Medicine, Busan, South Korea; [2]Department of Internal Medicine, Pusan National University Hospital and Biomedical Research Institute, Busan, South Korea; [3]Department of Internal Medicine, Pusan National University Yangsan Hospital, Yangsan, South Korea; [4]Department of Internal Medicine, Korea University Guro Hospital, Seoul, South Korea; [5]Department of Internal Medicine, Korea University Ansan Hospital, Seoul, South Korea; [6]Department of Internal Medicine, Seoul Boramae Hospital, Seoul National University College of Medicine, Seoul, South Korea; [7]Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, South Korea; [8]Department of Internal Medicine, Kyung Hee University School of Medicine, Kyung Hee University Hospital at Gangdong, Seoul, South Korea; [9]Department of Internal Medicine, Hanyang University College of Medicine, Seoul, South Korea; [10]Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; [11]Department of Internal Medicine, The Catholic University of Korea Seoul St. Mary's Hospital, Seoul, South Korea; [12]Department of Internal Medicine, Korea University Anam Hospital, Seoul, South Korea; [13]Department of Internal Medicine, Ulsan University Hospital, Ulsan, South Korea; [14]Department of Internal Medicine, Seoul Medical Center, Seoul, South Korea; [15]Department of Internal Medicine, Daegu Catholic University Hospital, Daegu, South Korea; [16]Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea; and [17]Department of Internal Medicine, Gangnam Severance Hospital, Seoul, South Korea

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* These authors contributed equally to this work.

ABSTRACT

Purpose: The aim of this study was to evaluate the blood pressure–lowering and cholesterol-lowering effects of a fixed-dose combination therapy using candesartan (CND)/rosuvastatin (RSV) compared with CND or RSV monotherapy in patients with hypertension and hypercholesterolemia.

Methods: This study was a 12-week, randomized, double-blind, placebo-controlled, multicenter study. A total of 394 patients were screened. After a 4-week run-in period, 219 of these patients with hypertension and primary hypercholesterolemia were randomized. Patients received 1 of 3 regimens for 8 weeks: (1) CND 32 mg/RSV 20 mg, (2) RSV 20 mg, or (3) CND 32 mg. The primary outcome variables were changes in the systolic blood pressure (SBP) and diastolic blood pressure (DBP) and the percentage changes in LDL-C from baseline to the drug treatment at 8 weeks. The secondary outcome variables were percentage changes of total cholesterol, triglycerides, HDL-C, non–HDL-C, apolipoprotein B, apolipoprotein A-I, high-sensitivity C-reactive protein, and glucose metabolic indices, including percentage changes of the homeostasis model assessment of insulin resistance (HOMA-IR), adiponectin, and hemoglobin A_{1c}. Tolerability of combination therapy was compared with other monotherapy groups.

Findings: The percentage changes of LDL-C were –48.6% (from 157.2 to 80.1 mg/dL) in the RSV group and –49.8% (from 160.2 to 78.9 mg/dL) in the CND/RSV group from baseline to the end of 8 weeks of treatment. Mean SBP and DBP were significantly decreased in the CND/RSV and CND groups after 8 weeks ($P < 0.001$ for all); however, no significant differences were found between the 2 groups. Total cholesterol levels, triglycerides, non–HDL-C, and apolipoprotein B were significantly reduced in the CND/RSV and RSV groups, with no significant differences between the groups compared with the CND group ($P < 0.001$ for all). The percentage changes of HOMA-IR, adiponectin, and hemoglobin A_{1c} had no significant differences between the combination groups and monotherapy groups. However, in a 2-sample *t* test, HOMA-IR was significantly decreased in the CND/RSV group compared with the RSV group in nondiabetic patients (mean [SD] percentage change of HOMA-IR, –8.7% [37.6%] vs 17.1% [53.1%]; $P = 0.048$). There were no significant differences in metabolic indices between the diabetic groups. Adverse events in the CND/RSV group were similar to those in the monotherapy group.

Implications: Once-daily fixed-dose combination therapy with CND/RSV is an effective, tolerable, convenient treatment option for patients with essential hypertension and hypercholesteremia. ClinicalTrials.gov identifier: NCT02770261. (*Clin Ther*. 2019;41:1508–1521)

Keywords: candesartan, drug combination, dyslipidemia, hypertension, rosuvastatin calcium.

INTRODUCTION

It is well established that hyperlipidemia and hypertension are the most common and major risk factors for cardiovascular disease (CVD), which is leading cause of death worldwide. Importantly, hypertension and dyslipidemia tend to occur concurrently in those with metabolic syndrome and elderly individuals. Therefore, these 2 diseases should be continuously managed to avoid cardiovascular complications through an appropriate medication and lifestyle changes.[1] Statins are important for preventing adverse cardiovascular events by reducing the levels of LDL-C and pleiotropic effects. Thus, statins are getting wider therapeutic indications, and high-dose statins are recommended in the current guidelines.[2–4] However, high-dose statins are associated with deteriorating glucose homeostasis and high risk of new-onset diabetes (NOD).[5–8] Recent clinical trials have found that statins have a dose-dependent on-target effect on insulin resistance and glucose metabolic homeostasis; consequently, potent statin might cause insulin resistance and a decrease of β-cell function.[6,9,10] However, this diabetogenic risk of statins has different effects, depending on underlying metabolic risk; indeed, the risk of NOD is high in patients with metabolic syndrome.[7] Angiotensin receptor blockers (ARBs) are widely prescribed in patients with hypertension and a high cardiovascular risk because of their established efficacy and favorable safety profile.[11] It is also well known that ARBs have been reported to have favorable effects on glucose metabolism.[12]

Telmisartan in particular has been reported to be associated with a partial activity of peroxisome proliferator-activated receptor γ (PPAR-γ) agonist compared with other ARBs.[13]

It would be advantageous for patients to have a single fixed-dose combination therapy that treats both of these conditions because of frequent coexistence of hypertension and hyperlipidemia and considering drug therapy adherence. In this regard, previous Phase III clinical studies reported that a once-daily combination of irbesartan/atorvastatin[14] and rosuvastatin/valsartan[15] provided an effective, tolerable, and more compliable treatment for patients with coexisting hypertension and hyperlipidemia. However, no randomized clinical trial on the blood pressure− and cholesterol-lowering effects and tolerability of fixed-dose combination therapy of candesartan (CND)/rosuvastatin (RSV) in patients who have essential hypertension accompanied with hyperlipidemia has been performed to date. The aim of this study was to investigate the efficacy on the blood pressure− and cholesterol-lowering effect and the safety of CND/RSV combination therapy versus CND or RSV monotherapy in patients who have essential hypertension accompanied with hyperlipidemia.

PATIENTS AND METHODS

Study design and patient recruitment

Initially, men and women aged ≥19 years with essential hypertension and primary hypercholesterolemia were screened. After therapeutic lifestyle modifications for a 4-week run-in period, individuals who met the following treatment guidelines were enrolled in this study: (1) patients with coronary artery disease or its equivalent and a LDL-C level ≥100 mg/dL and systolic blood pressure (SBP) ≥130 mm Hg or diastolic blood pressure (DBP) ≥80 mm Hg (high risk); (2) individuals with ≥2 risk factors, including hypertension and a 10-year CVD risk of 10%−20%, and a LDL-C level ≥130 mg/dL (moderately high risk) and SBP ≥140 mm Hg or DBP ≥90 mm Hg; or (3) individuals with ≥1 risk factors, including hypertension and a 10-year CVD risk <10%, and an LDL-C level ≥160 mg/dL (low risk) and SBP ≥140 mm Hg or DBP ≥90 mm Hg. Exclusion criteria included uncontrolled hypertension (SBP ≥180 mm Hg or DBP ≥110 mm Hg), history of acute coronary syndrome, cerebrovascular disease diagnosed in the past 6 months, arrhythmia requiring treatment, interventional or surgical coronary revascularization in that period; congestive heart failure (New York Heart Association class III or IV); uncontrolled diabetes mellitus (hemoglobin A_{1c} [HbA_{1c}] ≥9.0%); thyroid dysfunction; active hepatobiliary disease; coagulopathy; serum creatinine clearance <30 mL/min; serum transaminase >2 times the upper limit of normal; creatine kinase ≥2 times the upper limit of normal; malignant tumors within 5 years; history of psychiatric disorder or autoimmune disease; and history of myopathy or hypersensitivity to test drugs. Pregnant women, breastfeeding women, and women of child-bearing potential not taking contraception were not eligible to join the study. This study was conducted in accordance with the Declaration of Helsinki for experiments involving humans. The study protocol was approved by institutional review boards at each participating center. Written informed consents from all participants.

Randomization and study treatments

This study was a 12-week (4 weeks of therapeutic lifestyle changes and 8 weeks of drug treatment), randomized, placebo-controlled, double-blind, multicenter study conducted at 19 sites in Korea. At the screening visit, patients were interviewed regarding their medical history and underwent a physical examination and laboratory assessment. After discontinuation of use of any lipid-modifying agents, participants entered a 4-week run-in period. After discontinuation of use of any hypertensive agents, participants entered a 2-week run-in period. Individuals who met the treatment guidelines after the period were randomly assigned to receive 1 of the following 3 regimens: (1) CND 32 mg (Atacand, AstraZeneca Korea, Seoul, Korea), (2) CND 32 mg/RSV 20 mg (DP-R208, Alvogen, Seoul, Korea) (CND/RSV), or (3) RSV 20 mg (Crestor, AstraZeneca Korea, Seoul, Korea) (RSV). After randomization, follow-up sessions were held with the participants at the end of the fourth and eighth weeks for efficacy and tolerability.

Patient data collection

Blood pressure and laboratory values, including lipid profiles, liver enzymes, and muscle enzymes, were measured at randomization and at the end of

the fourth and eighth weeks. Samples were analyzed within 4 h of collection by a local laboratory that was certified by the Korean Society of Laboratory Medicine. All participants were required to measure their blood pressure daily in the morning at home with the blood pressure device supplied before randomization. When the self-measured blood pressure was high or low (SBP >180 mm Hg or <90 mm Hg and diastolic BP $\geq$ 110 mm Hg or <60 mm Hg), individuals visited their health care center to have their pressures measured and dropped out if the same result occurred.

Efficacy and safety assessment

The primary outcome variables were changes in the mean SBP and mean DBP and the percentage changes of LDL-C from baseline to drug treatment at 8 weeks. The secondary outcome variables were percentage changes of total cholesterol, triglycerides, HDL-C, non−HDL-C, apolipoprotein B, apolipoprotein A-I, and high-sensitivity C-reactive protein (hs-CRP). In addition, secondary outcome variables were glucose metabolic indices, including percentage changes of the homeostasis model assessment of insulin resistance (HOMA-IR), adiponectin (Human Adiponectin ELISA Kit, EMD Millipore Corporation, Burlington, MA) and HbA_{1c} from baseline to the drug treatment at 8 weeks. Blood samples were analyzed within 4 h of collection by a local laboratory that was certified by the Korean Society of Laboratory Medicine. Changes of variables in the same group from baseline to week 8 were also analyzed. Tolerability assessments were based on reported adverse reactions, history taking, physical examinations, and laboratory evaluations. Investigators determined the association between test agents and adverse events.

Statistical analysis

A minimum of 55 participants per treatment group were required, assuming a power of 0.95 to indicate superiority of the CND/RSV combination compared with monotherapy. In expectation of a 20% dropout rate, at least 69 individuals per each group were recruited. Baseline continuous variables were analyzed by using ANOVA and the Pearson χ^2 test. Efficacy analyses were conducted in the population

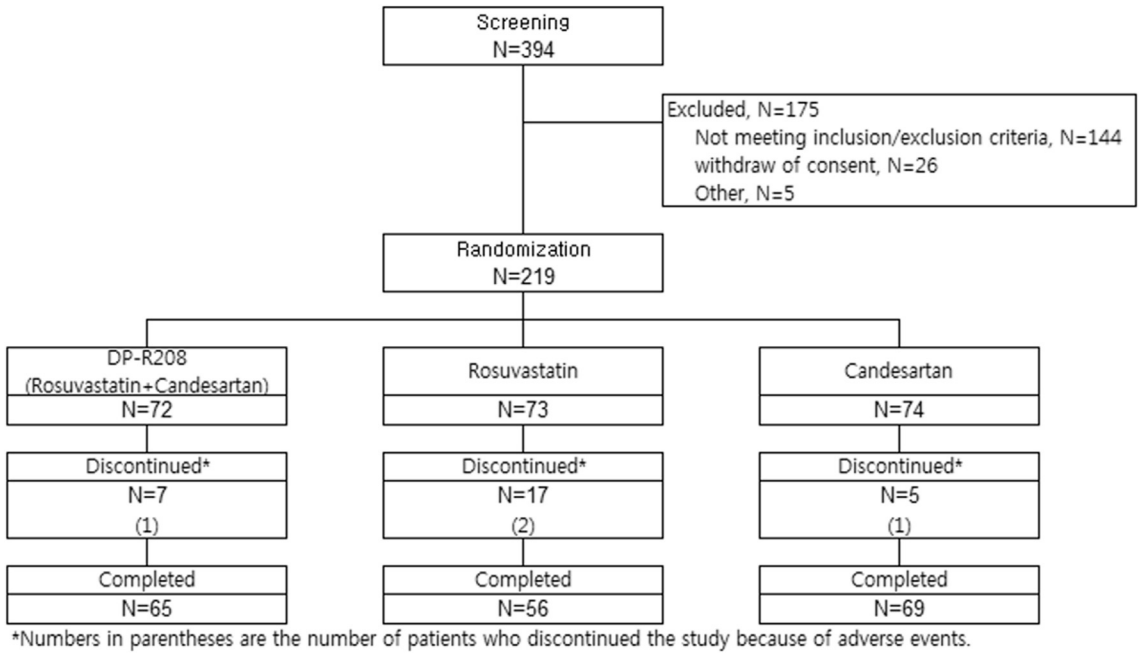

Figure 1. Patient disposition from enrollment to the end of study.

Table I. Baseline characteristics of the study participants.

Characteristic	CND/RSV (n = 70)	RSV (n = 70)	CND (n = 72)	P
Age, mean (SD), y	63.6 (9.4)	62.0 (10.6)	63.0 (10.5)	0.660*
Male sex	44 (62.9)	38 (54.3)	43 (59.7)	0.580†
History of diabetes	20 (28.6)	24 (34.3)	22 (30.6)	0.760†
Risk group				
High	7 (10.0)	13 (18.6)	8 (11.1)	0.611†
Moderate high	16 (22.9)	15 (21.4)	16 (22.2)	
Low	47 (67.1)	42 (60.0)	48 (66.7)	

CND = candesartan; RSV = rosuvastatin.
Variables are expressed as mean ± SD or number (%)
* ANOVA.
† Pearson χ^2 test.

that underwent follow-up tests for laboratory values. Tolerability analyses were performed for all participants who took the study agents more than once. Group differences in categorical variables were examined using ANOVA, whereas continuous variables were assessed using the *t* test. The paired *t* test was used to evaluate the differences before and after treatment in each group. Differences between the 2 groups were considered significant a $P < 0.05$ (2-sided). All data were analyzed using SAS 6 software, version 9.3 (SAS Korea, Seoul, Korea).

RESULTS

Patient characteristics and baseline variables

From the 19 centers, a total of 394 patients were screened; after the run-in period, 144 patients did not meet the inclusion criteria and were excluded in the study. In addition, 31 patients were also excluded because of withdrawal of consent or other causes. Therefore, 219 patients were randomized (Fig. 1). Of the 219 randomized participants, 190 finally completed the study, whereas 29 patients (13.2%) dropped out for the following reasons: 12 because of withdrawal of consent, 5 because of protocol violation, 1 because of failure to follow-up, 6 because of blood pressure response (SBP >180 mm Hg or <90 mm Hg and DBP ≥110 mm Hg or <60 mm Hg), 4 because of adverse events, and 1 for other reason. The baseline clinical characteristics of the patients are given in Table I. There were no significant differences in mean age, proportion of male, history of diabetes, and CVD risk group between study groups. Table II gives the baseline laboratory values and changes after 8 weeks of treatment. Baseline laboratory values, including LDL-C, total cholesterol, triglycerides, HDL-C, non−HDL-C, apolipoprotein B, apolipoprotein A-I, and hs-CRP, did not differ significantly between the groups randomized per regimen.

Primary efficacy evaluation

Changes in primary outcome variables at week 8 after therapy are presented in Table II and Fig. 2. The percentage changes of LDL-C were −48.6% (from 157.2 to 80.1 mg/dL) in RSV group and −49.8% (from 160.2 to 78.9 mg/dL) in the CND/RSV group from baseline to the end of 8 weeks of treatment. However, the percentage changes of LDL-C in the CND group was insignificant. Compared with the RSV group, the change of LDL-C after 8 weeks was not significantly different in the CND/RSV group. However, compared with the CND group, LDL-C was decreased in the CND/RSV group.

Changes in blood pressure at week 8 after therapy are presented in Table III and Fig. 3. Mean SBP and DBP were significantly decreased in the CND/RSV and CND groups after 8 weeks; however, there was no significant difference between the 2 groups. All

Table II. Changes In laboratory values from baseline to week 8.*

Laboratory Component	CND/RSV (n = 70)	RSV (n = 70)	CND (n = 72)	*P*
LDL-C				
Before, mg/dL	160.2 (34.7)	157.2 (24.4)	154.7 (27.9)	0.534†
After week 8, mg/dL	78.9 (29.7)	80.1 (26.4)	149.9 (29.9)	<0.001†
Change, %	−49.8 (18.8)	−48.6 (17.1)	−2.6 (14.0)	<0.001†
Within *P*	<0.001‡	<0.001‡	0.127‡	
TC				
Before, mg/dL	226.4 (35.8)	226.9 (29.9)	222.4 (31.1)	0.658†
After week 8, mg/dL	146.0 (32.3)	151.9 (29.0)	220.5 (35.0)	<0.001†
Change, %	−34.8 (13.8)	−32.4 (13.5)	−0.58 (10.5)	<0.001†
Within *P*	<0.001‡	<0.001‡	0.640‡	
Triglycerides, median (IQR)				
Before, mg/dL	141 (107—213)	138 (91—210)	137 (103—204)	0.807§
After week 8, mg/dL	114 (87—161)	98 (78—164)	148 (105—227)	0.006§
Change, %	−12.9 (−35.3 to 6.9)	−16.9 (−41.1 to 10.2)	0.72 (−10.9 to 40.9)	<0.001§
Within *P*	<0.001‖	<0.001‖	0.022‖	
HDL-C				
Before, mg/dL	46.9 (8.6)	49.8 (14.9)	48.7 (10.7)	0.322†
After week 8, mg/dL	49.9 (9.6)	54.5 (12.8)	49.2 (12.9)	0.017†
Change, %	7.1 (14.1)	12.3 (20.1)	1.2 (15.9)	0.001†
Within *P*	<0.001‡	<0.001‡	0.510‡	
Non—HDL-C				
Before, mg/dL	179.5 (33.9)	177.1 (28.8)	173.7 (31.7)	0.539†
After week 8, mg/dL	96.1 (32.3)	97.4 (32.5)	171.3 (34.8)	<0.001†
Change, %	−45.8 (17.4)	−44.6 (17.8)	−1.0 (12.8)	<0.001†
Within *P*	<0.001‡	<0.001‡	0.502‡	
Apo-B				
Before, mg/dL	140.5 (25.5)	139.8 (22.9)	135.3 (25.6)	0.400†
After week 8, mg/dL	80.4 (24.2)	82.1 (23.1)	133.0 (27.2)	<0.001†
Change, %	−42.0 (16.7)	−40.9 (15.5)	−1.4 (11.2)	<0.001†
Within *P*	<0.001‡	<0.001‡	0.308‡	
Apo-A-I				
Before, mg/dL	142.8 (20.3)	147.3 (26.1)	145.6 (19.5)	0.477†
After week 8, mg/dL	149.0 (21.4)	157.5 (26.3)	148.5 (25.6)	0.052†
Change, %	5.1 (13.3)	8.2 (16.0)	2.3 (12.7)	0.044†
Within *P*	0.002‡	<0.001‡	0.137‡	
hs-CRP				
Before, mg/L	0.68 (0.42—1.21)	0.72 (0.45—1.47)	0.76 (0.55—1.81)	0.293§
After week 8, mg/L	0.56 (0.39—0.89)	0.61 (0.33—1.08)	0.81 (0.59—1.37)	0.002§
Change, %	−13.0 (−53.7 to 14.3)	−21.42 (−57.1 to 16.4)	−11.60 (−34.1 to 44.1)	0.258§
Within *P*	0.142‖	0.122‖	0.693‖	

apo A-I = apolipoprotein A-I; apo B = apolipoprotein B; CND = candesartan; hs-CRP, high-sensitivity C-reactive protein; RSV = rosuvastatin; TC, total cholesterol.

* Data are expressed as mean (SD) unless otherwise indicated.

† ANOVA.

‡ Paired *t* test.

§ Kruskal—Wallis test.

‖ Wilcoxon signed rank test.

these results indicate that the combination of CND and RSV did not interact or disturb the individual blood pressure–lowering property of CND or lipid-lowering property of RSV.

Secondary efficacy evaluation

Total cholesterol levels, triglycerides, non–HDL-C, and apolipoprotein B were significantly reduced in both the CND/RSV and RSV groups, with no significant differences between the groups compared with CND group (Table II). HDL-C levels were significantly increased in the CND/RSV and RSV groups compared with the CND group after 8 weeks. Apolipoprotein A-I was significantly increased in the CND/RSV and RSV groups compared with the CND group; however, there was no significant difference between the CND/RSV and RSV groups. The hs-CRP levels were not significantly decreased in all 3 groups (Table II).

Changes in glucose homeostasis outcome variables at 8 weeks after therapy are presented in Table IV. The percentage changes of HOMA-IR, adiponectin, and HbA_{1c} were not statistically significant in all 3 groups. Changes in glucose homeostasis outcome variables at 8 weeks after therapy according to the presence of diabetes are presented in Table V. There were no significant changes in HOMA-IR, adiponectin, and HbA_{1c} in patients with diabetes among all 3 groups. In the 2-sample *t* test, HOMA-IR was significantly decreased in nondiabetic patients in the CND/RSV group compared with the RSV group (mean [SD] percentage change of HOMA-IR, –8.7% [37.6%] vs 17.1% [53.1%]; $P = 0.048$). Contrary to improvement in HOMA-IR, adiponectin was significantly decreased in the CND/RSV group compared with the RSV and CND groups (mean [SD] percentage change of adiponectin, –14.0% [19.9%] vs –9.2% [20.9%], $P = 0.042$, and vs –1.0% [22.7%], $P = 0.025$).

Safety evaluation

The proportions of patients who experienced any treatment-emergent adverse events in the CND/RSV (19.7%), RSV (15.1%), and CND (21.9%) groups

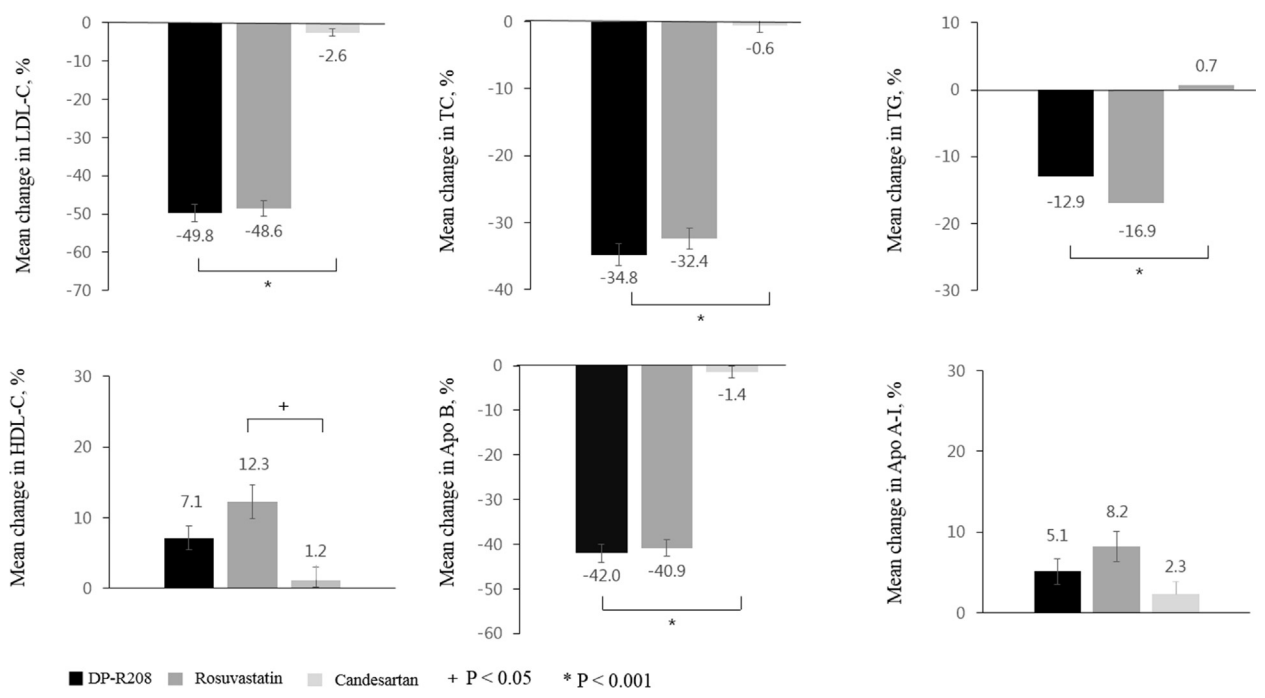

Figure 2. Changes in lipid profiles at week 8 after therapy. apo A-I = apolipoprotein A-I; apo B = apolipoprotein B; TC, total cholesterol. *$P < 0.001$.

Table III. Changes in blood pressure from baseline to week 8.*

	CND/RSV (n = 70)	RSV (n = 70)	CND (n = 72)	*P*
mSBP				
Before, mm Hg	145.7 (10.2)	146.5 (10.4)	147.4 (9.2)	0.596†
After week 8, mm Hg	132.2 (15.9)	144.7 (19.1)	131.5 (17.3)	0.001†
Change, %	−13.5 (14.7)	−1.8 (17.3)	−15.9 (16.1)	0.001†
Within *P*	<0.001‡	0.386‡	<0.001‡	
mDBP				
Before, mm Hg	85.6 (7.9)	85.7 (9.9)	86.5 (9.3)	0.815†
After week 8, mm Hg	78.8 (9.5)	86.2 (11.7)	78.8 (10.7)	0.001†
Change, %	−6.8 (8.8)	0.4 (9.50)	−7.7 (9.3)	0.001§
Within *P*	<0.001‡	0.705‡	<0.001‡	

CND = candesartan; mDBP, mean diastolic blood pressure; mSBP, mean systolic blood pressure; RSV = rosuvastatin.
* Data are expressed as mean (SD).
† ANOVA.
‡ Paired *t* test.

were similar (Table VI). Headache was the most common treatment-emergent adverse event in all groups. Serious adverse events occurred in only 1 patient (hospitalization because of a renal stone) in the RSV group. Most of treatment-emergent adverse events were adjudged as unlikely to be related to the study. No individuals had rhabdomyolysis, liver enzyme level elevations, or muscle enzyme level elevations.

DISCUSSION

The major findings of this study are (1) the blood pressure−lowering efficacy of CND/RSV combination therapy was similar to CND monotherapy; (2) the

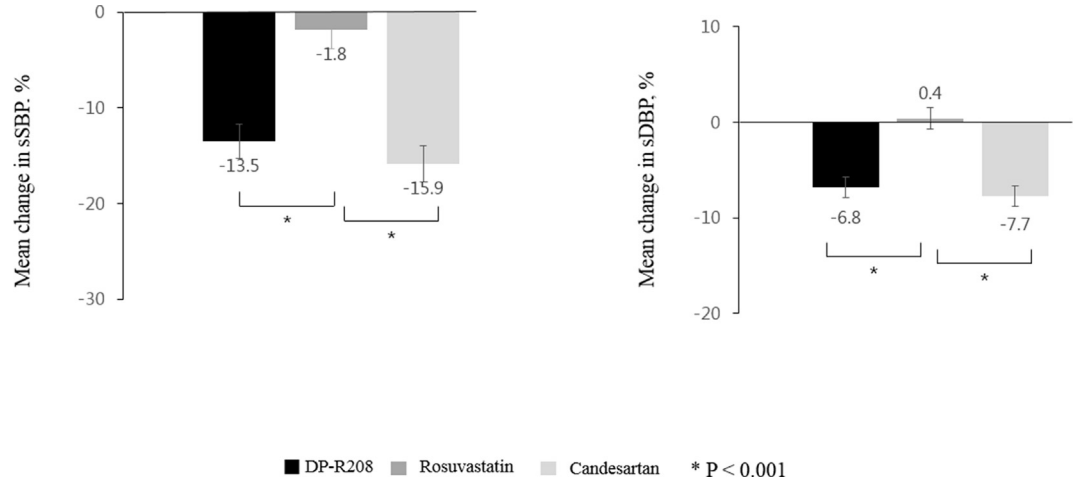

Figure 3. Mean changes in sitting systolic blood pressure (sSBP) and sitting diastolic blood pressure (sDBP) at week 8 after therapy. *$P < 0.001$.

Table IV. Changes of metabolic profiles from baseline to week 8.*

Metabolic Profile	CND/RSV (n = 70)	RSV (n = 70)	CND (n = 72)	*P*
HOMA-IR				
Before	4.0 (3.5)	3.5 (2.3)	3.4 (3.8)	0.697†
After week 8	3.1 (2.5)	3.3 (2.0)	3.6 (6.2)	0.831†
Change, %	14.8 (147.1)	18.7 (62.0)	23.3 (196.0)	0.968†
Within *P*	0.534‡	0.084‡	0.458‡	
Adiponectin				
Before, μg/mL	7395.2 (4981.2)	7953.7 ± 4765.5	8020.2 ± 5995.8	0.831§
After week 8, μg/mL	6168.1 (3515.7)	6942.4 ± 4580.3	7010.7 ± 5092.5	0.517§
Change, %	−12.8 (18.6)	−2.2 ± 25.7	−2.0 ± 23.0	0.058§
Within *P*	<0.001§§	0.615§§	0.594§§	
HbA_{1c}				
Before, %	6.2 (0.9)	6.2 (1.1)	5.9 (0.7)	0.195†
After week 8, %	6.1 (0.8)	6.2 (0.9)	6.1 (0.7)	0.531†
Change, %	0.7 (5.6)	0.6 (6.9)	−0.2 (5.0)	0.779†
Within *P*	0.431‡	0.619‡	0.852‡	

CND = candesartan; HbA_{1c}, glycosylated hemoglobin; HOMA-IR, homeostatic model assessment−insulin resistance; RSV = rosuvastatin.
* Data are expressed as mean (SD).
† ANOVA.
‡ Paired *t* test.

lipid-lowering efficacy of CND/RSV combination therapy was similar to RSV monotherapy; (3) the combination therapy of CND/RSV had favorable effects on HOMA-IR compared with rosuvastatin monotherapy in nondiabetic patients; and. (4) the safety profile of the CND/RSV combination was comparable to that of monotherapy by either drug, suggesting that the combination therapy is acceptable for management of coexistent hypertension and hyperlipidemia.

This Phase III clinical study evaluated the blood pressure− and lipid-lowering effects, metabolic effects, and tolerability of CND/RSV combination therapy versus CND or RSV monotherapy in patients with essential hypertension and primary hypercholesterolemia. As expected, the blood pressure−lowering efficacy of CND/RSV combination therapy was similar to candesartan monotherapy. The lipid-lowering efficacy of CND/RSV combination therapy was similar to rosuvastatin monotherapy. Some previous studies have found that statins might modestly lower blood pressure in patients with hypertension compared with the placebo.[15–17] Although the mechanism of the blood pressure−lowering effect of statins remains unclear, possible explanations were improvement of endothelium-dependent vasodilation,[18] increase in peripheral arterial compliance,[19] improvement of vasodilatory capacity,[20] up-regulation of vascular nitric oxide synthase,[21] and down-regulation of angiotensin II type 1 receptor.[22] However, in the present study, there was no synergistic effect on blood pressure by the combination of CND/RSV compared with CND monotherapy. This result suggests that the synergistic effect of blood pressure lowering of statin was sometimes inconsistent with previous results and the blood pressure reduction effect of statin was larger in patients with higher blood pressure.[23]

It is well known that statins dose-dependently deteriorate glucose homeostasis and increase the risk of NOD.[5–10] These risks of statins have different effects, depending on the underlying metabolic risk, such as patients with metabolic syndrome.[7] Recent

Table V. Changes of glucose metabolic profiles from baseline to week 8 according to presence of diabetes. *

Metabolic Profile	Diabetes mellitus				Non−Diabetes Mellitus			
	CND/RSV (n = 20)	RSV (n = 24)	CND (n = 22)	*P*	CND/RSV (n = 50)	RSV (n = 46)	CND (n = 50)	*P*
HOMA-IR								
Before	4.5 (3.1)	4.3 (2.5)	3.2 (1.8)	0.374†	3.8 (3.7)	3.0 (2.0)	3.5 (4.3)	0.741†
After week 8	4.7 (4.5)	4.2 (2.4)	3.1 (1.2)	0.279†	2.6 (0.8)	2.6 (1.4)	3.8 (7.4)	0.408†
Change, %	83.0 (282.9)	21.0 (75.6)	−9.4 (29.8)	0.386†	−8.7 (37.6)	17.1 (53.1)	37.2 (233.3)	0.488†
Within *P*	0.378‡	0.318‡	0.298‡		0.222‡	0.156‡	0.406‡	
Adiponectin								
Before μg/mL	8192.4 (6792.7)	5423.5 (2880.0)	9006.4 (8080.7)	0.304†	7061.0 (4088.6)	9316.1 (5059.6)	7643.2 (5083.0)	0.192†
After week 8, μg/mL	6697.4 (4401.8)	5595.95 (4029.0)	6846.6 (7121.2)	0.705†	5991.7 (3206.5)	7865.7 (4759.2)	7082.7 (4004.3)	0.110†
Change, %	−9.5 (14.7)	8.29 (29.3)	−4.3 (24.5)	0.194†	−14.0 (19.9)	−9.2 (20.9)	−1.0 (22.7)	0.073†
Within *P*	0.070‡	0.310‡	0.560‡		<0.001‡	0.057‡	0.822‡	
HbA_{1c}								
Before, %	7.11 (0.94)	7.33 (1.01)	6.71 (0.82)	0.226†	5.80 (0.40)	5.62 (0.39)	5.61 (0.40)	0.107†
After week 8, %	6.85 (1.14)	7.05 (0.74)	6.69 (0.72)	0.404†	5.86 (0.46)	5.65 (0.43)	5.78 (0.46)	0.122†
Change, %	1.53 (8.80)	0.60 (9.18)	−2.56 (5.54)	0.449†	0.44 (4.22)	0.57 (5.02)	0.88 (4.53)	0.932†
Within *P*	0.596‡	0.810‡	0.138‡		0.582‡	0.608‡	0.311‡	

CND = candesartan; HbA_{1c}, glycosylated hemoglobin; HOMA-IR, homeostatic model assessment−insulin resistance; RSV = rosuvastatin.
* Data are expressed as mean (SD).
† ANOVA.
‡ Paired *t* test.

Table VI. Summary of adverse events.*

Adverse Event	CND/RSV (n = 121)	RSV (n = 123)	CND (n = 123)	P
Any TEAEs	14 (19.7)	11 (15.1)	16 (21.9)	0.745
Treatment-related AEs	4 (5.6)	3 (4.1)	5 (6.9)	1.000
Serious AEs	0 (0)	1 (3.7)	0 (0)	—

AE, adverse event; CND = candesartan; RSV = rosuvastatin; TEAE, treatment-emergent adverse events.
* Data are presented as number (percentage).

studies have found that statin had an on-target effect on insulin resistance and glucose homeostasis; thus, more potent LDL-C–lowering efficacy caused insulin resistance and NOD, although more potent statins significantly reduced cardiovascular morbidity and mortality.[9,10,24] Previous reports suggest that the possible major mechanisms of NOD by high-dose statin are an increase of insulin resistance and a decrease of β-cell function. Therefore, it is important that potent statins, including RSV and atorvastatin, should be carefully prescribed in patients at high risk of NOD development, such as patients who are overweight or obese, patients with hypertension, older patients, and women at risk for the metabolic syndrome.[5,25,26] Considering that coexistence of hypertension and dyslipidemia is a high-risk factor for NOD, when the use of a potent statin is necessary, choice of anti-hypertensive medications is important for avoiding occurrence of NOD.

ARBs are most widely prescribed in patients with hypertension because of long-term established efficacy and a favorable safety profile. ARBs also have been reported to have favorable effects on glucose metabolism. Telmisartan in particular is the most potent ARB in terms of activity of PPAR-γ agonist.[12,13] CND and irbesartan are also less potent PPAR-γ agonists.[13,27,28] However, a recent clinical study found that olmesartan or irbesartan in combination with RSV significantly deteriorated glucose metabolism.[29] In our study, a significant decrease of HOMA-IR was observed in nondiabetic patients with the combination therapy of CND/RSV compared with RSV monotherapy despite a decrease in adiponectin level.

In addition, ARBs are beneficial for the prevention and treatment of type 2 diabetes by decreasing weight, producing anti-inflammatory effects, improving insulin sensitivity, and preventing development of insulin resistance.[30–33] In addition, some ARBs have PPAR-γ agonist activity. PPAR-γ modifies the expression of numerous metabolism-related genes and plays an important role in glucose metabolism in various tissues.[34] Previous animal studies have found that CND improves insulin sensitivity, increases expression of adiponectin and PPAR-γ, and decreases plasma lipid values and adiposity.[27,28,35,36] These results are consistent with our result of improvement of HOMA-IR; however, the finding of a decrease in adiopnectin level was inconsistent with previous animal studies. It is not clear why CND/RSV combination therapy produces different results on glucose homeostasis in our study. We postulated the reasons of these concerns, including a relatively small sample size in each group and wide SD of adiponectin values. Further clinical studies are necessary to define the effect of CND/RSV combination therapy on glucose homeostasis in nondiabetic patients.

In the safety profile, the occurrence rates of adverse events, including adverse drug reactions and serious adverse events, in the CND/RSV combination therapy group were similar to the respective monotherapy group. One case of nephrolithiasis was reported as a serious adverse event in the RSV monotherapy group during this study period, and when considering the medical history of the patient and the start date of the investigational product administration, it was concluded that there was no causal relationship with the investigational product and the investigational product administration was maintained without dose adjustment. Hence, CND/RSV combination therapy was well tolerated in patients with hypertension and hypercholesterolemia. Although single–pill combinations deliver improved convenience and patient adherence, it is difficult to

withhold one drug in case of occurrence of any adverse event.

We recognize some of the inherent limitations of a Phase III study. First, study patients were carefully selected based on strict inclusion and exclusion criteria; hence, they cannot accurately reflect a real-world scenario. Thus, the sample size of each group was small, which could be a significant contributing factor to why we found the opposite result on indices of glucose homeostasis between the CND/RSV combination and RSV alone. Second, the follow-up was relatively short, considering the long-term nature of the cardiovascular risk factors.

CONCLUSIONS

Our data reveal that the SBP-lowering effect of CND/RSV combination therapy was similar to CND monotherapy and that the LDL-C–lowering effect of CND/RSV combination therapy was similar to RSV monotherapy. Furthermore, the study found a significant improvement on other blood pressure and lipid-related levels. In the safety profile, the occurrence pattern of adverse events in the CND/RSV combination therapy group was similar to the respective monotherapy group with no concern observed for overlapping toxic effects. We conclude that a once-daily fixed-dose combination therapy of CND/RSV is an effective, tolerable, convenient treatment option for patients with essential hypertension and hypercholesterolemia and improves treatment adherence through a combination therapy.

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CONFLICTS OF INTEREST

The authors have no competing interests to declare. The sponsor had no involvement in the design, conduct, or analysis of the study.

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Address correspondence to: Chang Gyu Park, MD, PhD, Division of Cardiovascular, Department of Internal Medicine, Korea University Guro Hospital, 148, Gurodong-ro, Guro-gu, Seoul 08308, South Korea. E-mail: parkcg@kumc.or.kr