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ORIGINAL RESEARCH

Effectiveness and Safety of a Fixed-Dose Combination of Valsartan and Rosuvastatin (Rovatitan® Tablet) in Patients with Concomitant Hypertension and Hyperlipidemia: An Observational Study

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Purpose: This study aimed to assess the effectiveness and safety of a fixed-dose combination of rosuvastatin and valsartan (Rovatitan®) in Korean patients with concomitant hypertension and hyperlipidemia.

Patients and Methods: A total of 1008 eligible patients with concomitant hypertension and hyperlipidemia were enrolled and treated for 12 weeks. Both upward and downward drug dose titrations were allowed based on the investigator's discretion. This study evaluated the effectiveness of the study drug, defined by the percentage of patients achieving the blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) treatment targets. Additionally, regression analyses were conducted to evaluate the factors associated with the effectiveness and safety of the study drug. Of the 1008 patients enrolled in the study, 911 were analyzed for clinical effectiveness.

Results: At 12 weeks, 84.6% and 75.9% of patients treated with the study drug achieved their BP and LDL-C targets, respectively, and 64.8% of patients achieved both targets simultaneously. Furthermore, the percentage of patients who achieved their BP and LDL-C treatment targets demonstrated a trend across the respective risk groups; the higher the risk group, the lower the success of attaining the respective target. This trend was also observed regardless of the prior antihypertensive and/or lipid-lowering treatments. According to regression analysis, poor metabolic profiles, including a higher body mass index (BMI) and higher BP and LDL-C levels at baseline, were significantly associated with treatment failure for BP. Among the 1005 patients included in the safety analysis, 17 patients (1.7%) experienced serious adverse events; however, none were considered related to the study drug.

Conclusion: The study drug used for the treatment of concomitant hypertension and hyperlipidemia in a real-world setting was effective and was well tolerated. Therefore, the study drug is suggested as a good alternative to increase patient convenience and compliance, particularly in those taking multiple medications.

Keywords: hypertension, hyperlipidemia, rosuvastatin, valsartan, effectiveness, safety

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, accounting for 32% of global deaths.[1] Hypertension and hyperlipidemia, which frequently coexist, are the two major risk factors contributing to the

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development of CVD.[2,3] These factors have an additive effect on CVD progression; the risk associated with concomitant hypertension and hyperlipidemia is more than a multiplicative effect compared with the sum of risk of individual factors.[4–6] Therefore, comprehensive management of blood pressure (BP) and serum lipid levels is required to reduce the risk of future CVD. Current guidelines for the management of hypertension and hyperlipidemia have also emphasized the need for an overall assessment of BP and serum lipid levels to evaluate cardiovascular risk, rather than an individual assessment of risk factors.[5–10]

Despite numerous control strategies and the wide range of drugs available, hypertension and hyperlipidemia are still poorly controlled.[11] The study conducted by Spanella et al even suggests that oftentimes dyslipidemia is overlooked in hypertensives, especially in patients with higher CV risk.[11] As part of a multifactorial approach to manage cardiovascular risk, the concept of a single combination pill containing antihypertensive and lipid-lowering agents has gained popularity. Considering the co-existence of these diseases, a fixed-dose combination (FDC) that can lower BP and lipid levels provides a rational approach for simultaneous management of hypertension and hyperlipidemia. An FDC may offer an advantage, particularly in "polypharmacy patients", as polypharmacy is one of the major reasons for drug non-compliance and consequently treatment failure.[12–14] An FDC may reduce "pill burden" in these patients and ensures patient compliance. Real-world data analysis showed that patients taking FDC containing antihypertensive and lipid-lowering agents demonstrated higher medication persistence and adherence than those taking free combinations of each component.[15]

Of the available combination therapies containing antihypertensive and lipid-lowering agents, amlodipine (calcium channel blocker; CCB) and atorvastatin have been the most studied in various clinical settings.[16–19] Overall, a single pill of amlodipine and atorvastatin was found efficacious and safe in treating patients with concomitant hypertension and hyperlipidemia.[18] Combination therapies containing angiotensin receptor blockers (ARBs) and statins have also shown an acceptable efficacy and safety profile and help patients achieve their targets of BP and low-density lipoprotein cholesterol (LDL-C).[20–26] ARBs are widely used in patients with hypertension and high cardiovascular risk; recent findings suggest that they have favorable effects on glucose metabolism.[27,28] Statins lower LDL-C and exert pleiotropic effects, thereby preventing adverse cardiovascular events.[29,30]

Rosuvastatin calcium is a widely prescribed statin that lowers cholesterol by blocking 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase.[31,32] Rosuvastatin reduces the incidence of adverse cardiovascular events in patients with other risk factors, such as hypertension and type 2 diabetes.[33] In addition, valsartan, a member of the ARB class of drugs, selectively inhibits angiotensin receptor type II and efficiently reduces BP.[34] Despite numerous efficacy studies conducted on different combinations of ARBs and statins, only a few studies have examined how a single pill can be used in real-world setting. Hence, this observational study aimed to assess the effectiveness and safety of an FDC containing rosuvastatin and valsartan (Rovatitan®, LG Chem, Ltd., Seoul, Republic of Korea) in patients with concomitant hypertension and hyperlipidemia in real-world clinical setting. A previous randomized, controlled, double-blind, Phase 3 study demonstrated that the concomitant administration of rosuvastatin and valsartan was safe and efficacious in lowering both BP and LDL-C when compared with that of either drug administered alone.[21] The primary objective was to demonstrate the efficacy of the study drug as defined by the percentage of patients achieving BP and LDL-C targets. Additionally, multiple regression analyses were conducted to identify baseline factors associated with the effectiveness and safety of the study drug.

Material and Methods

This clinical trial was conducted in compliance with relevant guidelines that comply with the Declaration of Helsinki.

Study Design

This was a prospective, multicenter, observational study conducted from August 11, 2020 to December 1, 2021 in 28 centers in Korea (NCT04398771). Prior to starting the study, ethical approval was obtained for all protocols from the Institutional Review Boards (IRBs). The list of IRBs is added as a Supplementary File to this manuscript. Data were collected as part of routine clinical monitoring. All subjects provided written informed consent before study enrollment for the collection and handling of personal data.

Study Population

Participants aged ≥ 19 years who were diagnosed with concomitant hypertension and hyperlipidemia were eligible. The major exclusion criterion was the previous administration of drug combinations containing both rosuvastatin and valsartan. Moreover, patients with contraindications to any component of the study drug and those with uncontrolled hypertension (systolic blood pressure (SBP) ≥ 180 mmHg or diastolic blood pressure (DBP) ≥ 110 mmHg) were not eligible to participate in the study.

Study Definition

Data of the participants' demographic characteristics, previous and concurrent medical conditions, family history of premature coronary artery disease (CAD), and lifestyle factors (smoking and alcohol intake) were collected at enrollment. A family history of CAD was defined as the occurrence of premature CAD in first-degree relatives (< 55 or < 65 years of age in men and women, respectively). Smoking status was classified as non-smoker (smoked <100 cigarettes in their lifetime), former smoker (smoked ≥100 cigarettes in their lifetime and currently a non-smoker), and current smoker (smoked ≥100 cigarettes in their lifetime and currently a smoker). Alcohol drinking status was classified as non-drinker or drinker. Subgroup analyses were performed by stratifying the patients according to age (< 65 or ≥ 65 years), sex (male or female), body mass index (BMI; < 25 or ≥ 25 kg/m^2), menopausal status (yes or no), smoking status (non-smoker, former smoker, or current smoker), baseline hypertension stage (normal, prehypertension, stage 1, or stage 2), baseline LDL-C stage (low-risk, moderate-risk, high-risk, or very high-risk), family history of premature CAD (yes, no, or unknown), presence of diabetes and/or renal comorbidities (yes or no), and the type of antihypertensive and/or lipid-lowering therapy used at screening (treatment-naïve, antihypertensive monotherapy, lipid-lowering monotherapy, or antihypertensive and lipid-lowering combination therapy). Hypertension stages were classified based on the criteria outlined in the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) VII (normal, SBP < 120 mmHg and DBP < 80 mmHg; prehypertension, 120 mmHg ≤ SBP < 140 mmHg or 80 mmHg ≤ DBP < 90 mmHg; stage 1, 140 mmHg ≤ SBP < 160 mmHg or 90 mmHg ≤ DBP < 100 mmHg; and stage 2, SBP ≥ 160 mmHg or DBP ≥ 100 mmHg); hyperlipidemia and LDL-C stages were based on the criteria outlined in the Korean Guidelines for the Management of Dyslipidemia IV (low-risk, one or fewer major risk factors [age, family history of premature CAD, hypertension, smoking, low levels of high-density lipoprotein cholesterol]; moderate-risk, two or more major risk factors; high-risk, carotid disease (significant carotid artery stenosis), abdominal aortic aneurysm, or diabetes; and very high-risk, CVD [CAD, peripheral artery disease, ischemic stroke, or transient ischemic attack]).[35,36]

Study Intervention

The study flexibly enrolled patients from different treatment backgrounds; thus, the study drug was administered as 1) an initial therapy for patients who were treatment-naïve, 2) a switch therapy for patients who were already receiving other antihypertensive and lipid-lowering agents, or 3) an add-on therapy to a patient's existing treatment with antihypertensive or lipid-lowering agents. Each patient was administered an appropriate daily dose of the study drug and followed up for 12 weeks. Patients received the study drug containing rosuvastatin calcium/valsartan at one of six doses: 5/80, 5/160, 10/80, 10/160, 20/80, or 20/160 mg. Both upward and downward drug dose titrations were allowed at the investigator's clinical discretion.

Effectiveness and Safety Assessments

The primary efficacy measures were the percentage of patients achieving the JNC VIII BP targets (for patients aged ≥ 60 years, < 150/90 mmHg; patients aged < 60 years, < 140/90 mmHg) and the Korean Guidelines for the Management of Dyslipidemia IV LDL-C targets (for very high-risk group < 70 mg/dL; high-risk group, < 100 mg/dL; moderate-risk group, < 130 mg/dL; low-risk group < 160 mg/dL) at the end of the 12-week treatment period. [35,37] Secondary effectiveness measures included 1) the percentage of patients achieving both BP and LDL-C targets at 12 weeks, 2) the absolute change in SBP and DBP from the baseline at 12 weeks, and 3) the absolute and percentage changes in LDL-

C from the baseline at 12 weeks. Other supplementary effectiveness measures included the absolute changes in total cholesterol, HDL-C and triglycerides from the baseline at 12 weeks. To evaluate the safety of the study drug, data of adverse events (AEs) and abnormal laboratory findings, either voluntarily reported by subjects or identified by the treating physician during follow-up, were collected and assessed. The nature, date of onset, duration, severity, action taken (if any), and causal relationship to the study drug for all AEs were documented. There were no pre-specified AEs of interest.

Statistical Analysis

The study sample size was not statistically derived, but the study was planned to enroll approximately 1000 patients. Effectiveness analyses were based on the evaluable population, defined as subjects who received at least one dose of the study drug and completed the effectiveness assessment (BP and/or LDL-C level) at least once. Safety analysis was based on the evaluable population, defined as subjects who received at least one dose of the study drug and were followed up for safety assessment.

Continuous variables are presented as the mean and standard deviation, whereas categorical variables are presented as the number and percentage. The exact Clopper-Pearson method was used to calculate 95% confidence interval (CI) of the percentage of subjects achieving the targets at 12 weeks. Subgroup analyses were conducted using the Pearson's chi-squared test or Fisher's exact test to determine the factors associated with the effectiveness and incidence rate of AEs. These data were further analyzed using multiple logistic regression models to identify factors that were significantly correlated with the effectiveness and safety of the study drug. All variables that showed a difference with a $p < 0.2$ in subgroup analyses were included in multiple logistic regression models. Factors associated with the effectiveness of the study drug and incidence of AEs were presented as odds ratio (OR) and 95% CI. All statistical analyses were performed using the SAS software (version 9.4; SAS Institute, Inc., Cary, NC, USA).

Results

Patient Disposition

Of the 1008 patients screened, 1005 were administered the study drug. Of these, 914 completed the study. Among the patients screened, three subjects were excluded, and 1005 were included in the safety analysis. For the effectiveness analysis, 94 subjects who were not considered evaluable were excluded, and data from the remaining 911 subjects were analyzed. Patient disposition is shown in Figure 1.

Patient Demographics and Clinical Characteristics

The patient demographics and clinical characteristics at baseline are summarized in Table 1. The mean (± standard deviation [SD]) age of patients at baseline was 66.1 (± 11.1) years, with a BMI of 25.2 (± 3.5) kg/m^2. There were more males (56.6%) than females, and more than half of the patients were non-smokers (63.7%) and non-drinkers (78.9%). In addition, more than 60% of patients did not have a family history of premature CAD (60.0%) or diabetes as a comorbidity (68.0%). Very few patients (5.0%) had a renal disorder. The mean (± SD) baseline SBP and DBP were 131.1 (± 16.0) mmHg and 76.7 (± 11.5) mmHg, respectively, and the mean baseline LDL-C was 96.3 (± 37.5) mg/dL (Supplementary File 1A and B). The mean (± SD) duration of hypertension and hyperlipidemia were 8.4 (± 8.0) years and 5.5 (± 5.5) years, respectively (Supplementary File 2).

At study initiation, 79.2% and 60.5% of patients were already receiving treatment for hypertension and hyperlipidemia, respectively, whereas, 60.4% and 18.6% of patients concomitantly received treatment for hypertension and hyperlipidemia, in addition to the study drug. Approximately half (43.5%) of the patients received a dose of 10/80 mg rosuvastatin/valsartan, and 19.2% and 18.7% of patients received doses of 20/80 mg and 10/160 mg rosuvastatin/valsartan, respectively. Very few patients switched doses during the study (Supplementary File 3).

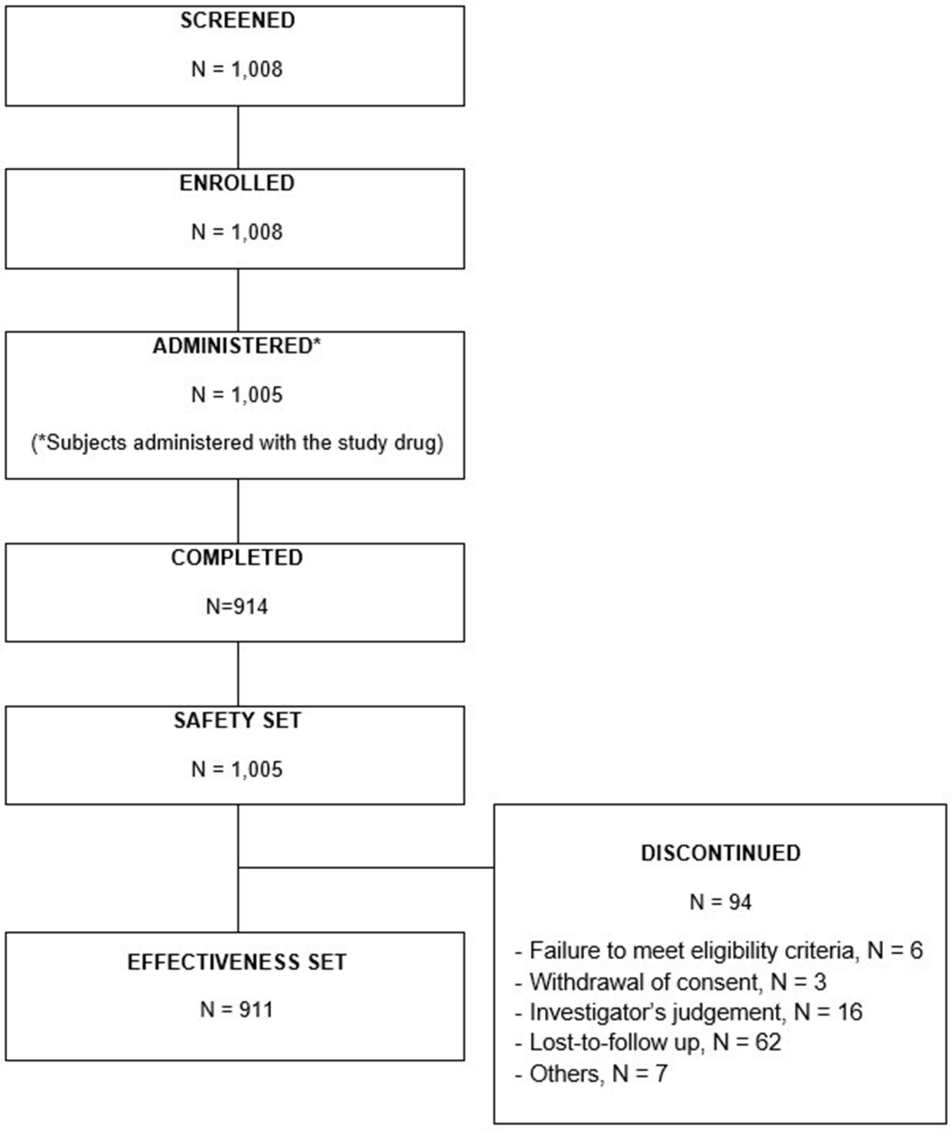

Figure 1 Study flowchart.

Effectiveness Analysis

At baseline, 76.6% and 36.1% of patients respectively had already reached their BP and LDL-C therapeutic targets. At 12 weeks, 84.6% and 75.9% of patients treated with the study drug achieved their BP and LDL-C therapeutic targets, respectively (Figure 2A and B). A higher percentage of patients aged ≥ 60 years attained the BP target; however, no specific trend was observed for patient groups classified according to hyperlipidemia risk. Over 90% of patients achieved their LDL-C targets in the high-, moderate-, and low-risk LDL-C groups. At the end of the study period, 64.8% of patients treated with the study drug achieved their BP and LDL-C targets simultaneously, compared to 29.0% observed at study initiation (Figure 2C). The mean (± SD) changes in mean sitting SBP and DBP from baseline at 12 weeks were −1.9 (± 16.6) mmHg and −1.7 (± 11.2) mmHg, respectively (Supplementary File 1A). The absolute and percent mean (± SD) changes in LDL-C level from baseline at 12 weeks were −26.3 (± 35.4) mg/dL and −18.9 (± 29.0) %, respectively (Supplementary File 1B). Furthermore, statistically significant reductions in total cholesterol and triglycerides from baseline at 12 weeks were observed. The mean (± SD) changes in total cholesterol and triglycerides from baseline at 12 weeks were −23.1 (± 41.7) mg/dL and −15.0 (± 79.8) mg/dL, respectively (Supplementary File 4A and B). A relatively small reduction (0.2 [± 14.5] mg/dL) was observed for HDL-C at 12 weeks from baseline (Supplementary File 4C).

Table 1 Baseline Characteristics

	Total (N=1005)
Age (years)	
n	1005
Mean ± SD	66.06 ± 11.14
Median	67.00
Min, Max	26.00, 95.00
Age (years) by category, n (%)	
<65 years	436 (43.38)
≥65 years	569 (56.62)
Sex, n (%)	
Male	569 (56.62)
Female	436 (43.38)
Menopausal status, n (%)	
Yes	412 (94.71)
No	23 (5.29)
BMI (kg/m^2)	
n	725
Mean ± SD	25.23 ± 3.47
Median	24.80
Min, Max	16.90, 40.00
BMI (kg/m^2) by category, n (%)	
<25 kg/m^2	377 (52.00)
≥25 kg/m^2	348 (48.00)
Smoking history, n (%)	
Non-Smoker	634 (63.65)
Former Smoker	244 (24.50)
Current Smoker	118 (11.85)
Alcohol history, n (%)	
Non-drinker	787 (78.94)
Drinker	210 (21.06)
Family history of early onset of CAD, n (%)	
Yes	25 (2.49)
No	603 (60.00)
Unknown	377 (37.51)
Diabetes comorbidity, n (%)	
Yes	322 (32.04)
No	683 (67.96)
Renal disorders comorbidity, n (%)	
Yes	50 (4.98)
No	955 (95.02)

Abbreviation: BMI, body mass index.

Effectiveness Analysis Based on Prior Hypertension and Hyperlipidemia Treatments

An ad hoc analysis was conducted to evaluate the effectiveness based on prior hypertension and hyperlipidemia treatments. At baseline, 89.4% and 76.6% of patients were previously treated with antihypertensive and lipid-lowering drugs, respectively (i.e., 10.6% and 23.4% of patients were respectively treatment-naive). At baseline, 42.4% and 23.7%

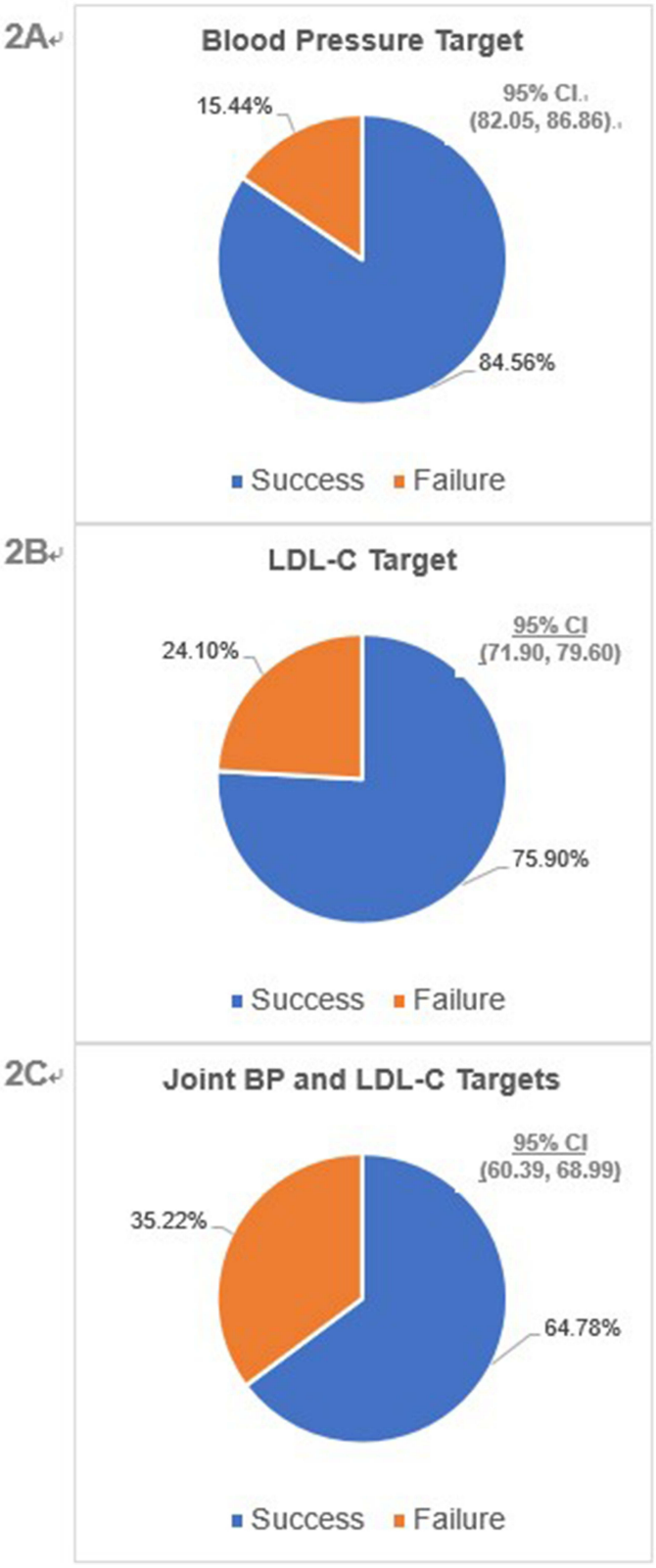

Figure 2 Treatment target achievement.

of these treatment-naïve patients had already reached their BP and LDL-C therapeutic targets. At 12 weeks, 83.1% and 87.2% of patients treated with the study drug achieved their BP and LDL-C therapeutic targets, respectively. Of the patients who received prior antihypertensive or lipid-lowering treatments, 79.0% and 37.0% had already reached their BP and LDL-C therapeutic targets at baseline. At 12 weeks, 84.7% and 74.9% of patients treated with the study drug achieved their BP and LDL-C therapeutic targets.

Regardless of the prior treatments, the percentage of patients who achieved their BP and LDL-C targets demonstrated a trend across the respective risk groups; the higher the risk group, the lower the success of attaining the respective targets (Table 2 and Table 3). More than 80% of patients achieved the target BP, regardless of the prior treatment status. More than 90% of subjects who were treatment-naïve to prior hyperlipidemia treatment and approximately 70% of subjects who had received hyperlipidemia treatment at baseline attained the target LDL-C level. Statistically significant reduction in BP was observed in patients classified as having stage 1 or 2 hypertension (all p <0.0007), regardless of the prior treatment status. All patients except two patient groups showed a significant reduction in both absolute and percent mean changes in LDL-C levels, regardless of the prior treatment status. The patients in the high- and moderate-risk groups who had received prior hyperlipidemia treatment showed a significant reduction in the mean absolute LDL-C level at 12 weeks; however, the percent mean change in LDL-C level in these groups was not statistically significant.

Regression Analysis

Variables that showed a difference with $p < 0.2$ in subgroup analyses and were included in multiple logistic regression models are available in the Supplementary File 5A–C. The results of multiple logistic regression analyses showed that BMI ≥ 25 kg/m^2 ($p = 0.0246$) and hypertension stages (prehypertension, $p = 0.0047$; stage 1, $p < 0.0001$; stage II, $p < 0.0001$) were statistically significant risk factors associated with the treatment failure in achieving the target BP compared with that of BMI < 25 kg/m^2 and normal hypertension stage, respectively (Table 4). Patient group classified as very high-risk group for LDL-C at baseline was also significantly associated with an increased risk of failure in achieving the target LDL-C level compared with that of the low-risk group ($p = 0.0271$; Table 5). Furthermore, patients with BMI ≥ 25 kg/m^2 ($p = 0.0042$) and higher stages of hypertension (stage 1, $p = 0.0002$; stage II, $p < 0.001$) at baseline had greater odds of treatment failure in achieving the target BP and LDL-C levels simultaneously than those with BMI < 25 kg/m^2 and normal stage of hypertension, respectively (Table 6). In addition, patients who had already received antihypertensive and/or lipid-lowering medications (hypertension monotherapy, $p = 0.0233$; hyperlipidemia monotherapy, $p = 0.0190$; combination, $p = 0.0098$) at baseline had greater odds of failure in achieving the target BP and LDL-C simultaneously than those who were treatment-naïve (Table 6).

Safety Analysis

Among the 1005 patients, 143 (14.2%) reported 205 AEs; of these, 30 events (24 patients, 2.4%) were considered related to the study drug. The most frequently reported AEs, regardless of causality, were dizziness (1.3%), chest pain (1.2%), headache (1.0%), and dyspnea (1.0%; Supplementary File 6). Headache was the most frequently reported adverse drug reaction (ADR), occurring in four patients (0.4%). Most AEs were "unlikely" related to the study drug and were either mild or moderate in severity. Overall, 17 patients (1.7%) experienced serious adverse events (SAEs); however, none of these events were considered related to the study drug. Twenty-five (2.5%) patients discontinued treatment because of AEs. However, the severity of AEs leading to withdrawal was mild or moderate, and most of these events were considered to be "unlikely" related to the study drug.

Logistic regression analyses showed that sex, family history of premature CAD, and types of antihypertensive and/or lipid-lowering medications used at screening were risk factors associated with an increased risk of occurrence of AEs. Male patients were less likely to experience AEs ($p = 0.0010$). In addition, subjects with an unknown family history of premature CAD and who had received antihypertensive monotherapy at baseline had greater odds of experiencing AEs than those without a family history ($p = 0.0081$) and those who were treatment-naïve ($p = 0.0039$) at baseline, respectively (Supplementary File 7).

Table 2 Percentage of Subjects Who Achieved Target Blood Pressure (BP) and Changes in BP from Baseline at Week 12 by Prior Hypertension Treatment and Hypertension Stage at Baseline

	Yes (N=814)					No (N=97)					
Hypertension stage[a]	**Normal (N=179)**	**Prehypertension (N=406)**	**Stage 1 (N=185)**	**Stage 2 (N=41)**	**Total (N=814)**	**Normal (N=3)**	**Prehypertension (N=22)**	**Stage 1 (N=48)**	**Stage 2 (N=23)**	**Stage 1+2 (N=71)**	**Total (N=97)**
Number of Subjects who achieved target blood pressure at Week 12[b] (%)	171 (96.07)	348 (86.35)	144 (77.84)	24 (58.54)	689 (85.06)	3 (100.00)	20 (90.91)	39 (81.25)	15 (65.22)	54 (76.06)	78 (80.41)
Changes in SBP (mmHg) from baseline at Week 12											
n	178	403	185	41	807	3	22	48	23	71	96
Mean ± SD	12.23 ± 13.71	0.35 ± 12.90	−10.62 ± 13.81	−18.37 ± 14.31	−0.49 ± 15.93	3.00 ± 14.80	−3.45 ± 15.85	−15.31 ± 16.60	−23.26 ± 16.11	−17.89 ± 16.75	−13.93 ± 17.69
95% CI[c]	(10.20, 14.26)	(−0.91, 1.62)	(−12.62, −8.61)	(−22.88, −13.85)	(−1.59, 0.61)	(−33.76, 39.76)	(−10.48, 3.57)	(−20.13, −10.49)	(−30.23, −16.29)	(−21.85, −13.92)	(−17.51, −10.34)
p-value[d]	<0.0001	0.9226	<0.0001	<0.0001	0.2309	0.7590	0.3184	<0.0001	<0.0001	<0.0001	<0.0001
Changes in DBP (mmHg) from baseline at Week 12											
n	178	403	184	41	806	3	22	48	23	71	96
Mean ± SD	4.72 ± 9.93	−0.28± 9.50	−5.48 ± 10.79	−13.41 ± 11.40	−1.03 ± 10.94	1.33 ± 1.53	−4.27 ± 12.19	−7.73 ± 11.48	−11.91 ± 11.12	−9.08 ± 11.46	−7.66 ± 11.68
95% CI[c]	(3.26, 6.19)	(−1.21, 0.65)	(−7.05, −3.91)	(−17.01, −9.82)	(−1.79, −0.27)	(−2.46, 5.13)	(−9.68, 1.13)	(−11.06, −4.39)	(−16.72, −7.10)	(−11.80, −6.37)	(−10.02, −5.29)
p-value[d]	<0.0001	0.4020	<0.0001	<0.0001	0.0038	0.2697	0.1150	<0.0001	<0.0001	<0.0001	<0.0001

Notes: [a]Classification according to the JNC-7 guidelines: normal, SBP < 120 mmHg and DBP < 80 mmHg; prehypertension, 120 mmHg ≤ SBP < 140 mmHg or 80 mmHg ≤ DBP < 90 mmHg; stage 1, 140 mmHg ≤ SBP < 160 mmHg or 90 mmHg ≤ DBP < 100 mmHg; stage 2, SBP ≥ 160 mmHg or DBP ≥ 100 mmHg. [b]Target blood pressure: for patients aged ≥ 60 years, < 150/90 mmHg; for patients aged < 60 years, < 140/90 mmHg. [c]95% CI is a two-sided 95% confidence interval for the mean. [d]p-value using Wilcoxon signed-rank test or Paired *t*-test. Missing in msSBP (hypertension treatment = "Yes"):- Week 12: Normal (1 subject), Prehypertension (3 subjects). Missing in msDBP (hypertension treatment = "Yes"): - Baseline: Stage 1 HTN (1 subject). - Week 12: Normal (1 subject), Prehypertension (3 subjects).

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Table 3 Percentage of Subjects Who Achieved Target LDL-C and Changes in LDL-C from Baseline at Week 12 by Prior Hypertension Treatment and Hypertension Stage at Baseline

LDL-C Stage[a]	Yes (N=698)					No (N=213)				
	Very High-Risk (N=484)	High-Risk (N=85)	Moderate-Risk (N=115)	Low-Risk (N=14)	Total (N=698)	Very High-Risk (N=41)	High-Risk (N=31)	Moderate-Risk (N=118)	Low-Risk (N=23)	Total (N=213)
Number of subjects who achieved target LDL-C at Week 12[b] (%)	126 (55.26)	56 (91.80)	58 (98.31)	8 (100.00)	248 (69.66)	15 (62.50)	18 (94.74)	78 (97.50)	19 (100.00)	130 (91.55)
Changes in LDL-C (mg/dL) from baseline at Week 12										
n	196	55	52	6	309	19	19	67	18	123
Mean ± SD	−12.48± 20.82	−10.57 ± 28.18	−12.40 ± 32.58	−32.67 ± 23.85	−12.52 ± 24.64	−44.15 ± 40.49	−61.05 ± 36.22	−64.20 ± 31.91	−65.17 ± 36.05	−60.76 ± 34.92
95% CI[c]	(−15.41, −9.55)	(−18.19, −2.96)	(−21.47, −3.33)	(−57.69, −7.64)	(−15.28, −9.76)	(−63.66, −24.63)	(−78.51, −43.60)	(−71.98, −56.42)	(−83.09, −47.24)	(−66.99, −54.52)
p-value[d]	<0.0001	0.0071	0.0168	0.0202	<0.0001	0.0002	<0.0001	<0.0001	<0.0001	<0.0001
Percentage changes in LDL-C (%) from baseline at Week 12										
n	196	55	52	6	309	19	19	67	18	123
Mean ± SD	−11.64 ± 26.60	−7.48 ± 28.48	−5.87 ± 28.08	−23.97 ± 13.38	−10.17 ± 27.08	−30.64 ± 29.92	−44.28 ± 19.90	−42.33 ± 17.13	−41.96 ± 21.69	−40.77 ± 20.84
95% CI[c]	(−15.39, −7.90)	(−15.18, 0.22)	(−13.69, 1.95)	(−38.01, −9.93)	(−13.20, −7.14)	(−45.06, −16.22)	(−53.87, −34.68)	(−46.51, −38.15)	(−52.74, −31.17)	(−44.49, −37.05)
p-value[d]	<0.0001	0.0567	0.1378	0.0071	<0.0001	0.0008	<0.0001	<0.0001	<0.0001	<0.0001

Notes: [a]Classification according to the Korean Guidelines for the Management of Dyslipidemia IV: low-risk, one or fewer major risk factors (age, family history of premature CAD, hypertension, smoking, low levels of high-density lipoprotein cholesterol); moderate-risk, two or more major risk factors; high-risk, carotid disease (significant carotid artery stenosis), abdominal aortic aneurysm, or diabetes; very high-risk, CVD (CAD, peripheral artery disease, ischemic stroke, or transient ischemic attack). [b]Target LDL-C: for very high-risk group, < 70 mg/dL; high-risk group, < 100 mg/dL; moderate-risk group, < 130 mg/dL; low-risk group < 160 mg/dL. [c]95% CI is a two-sided 95% confidence interval for the mean. [d]p-value using Wilcoxon signed-rank test or Paired *t*-test. Missing in LDL-C (hyperlipidemia treatment = "Yes"): - Baseline: Very high risk group (106 subjects), High risk group (9 subjects), Moderate risk group (24 subjects), Low risk group (5 subjects). - Week 12: Very high risk group (256 subjects), High risk group (24 subjects), Moderate risk group (56 subjects), Low risk group (6 subjects). Missing in LDL-C (hyperlipidemia treatment = "No"): - Baseline: Very high risk group (6 subjects), High risk group (1 subject), Moderate risk group (22 subjects), Low risk group (2 subjects). - Week 12: Very high risk group (17 subjects), High risk group (12 subjects), Moderate risk group (38 subjects), Low risk group (4 subjects).

Table 4 Risk Factors Leading to Failure to Achieve Target BP at Week 12

	Reference	Odds Ratio Estimate	95% CI for Odds Ratio	p-value[a]
Age (years)	≥65 years vs <65 years*	0.913	(0.57, 1.46)	0.7038
BMI (kg/m^2)	≥25 kg/m^2 vs <25 kg/m^2 *	1.663	(1.07, 2.59)	0.0246
Smoking	Former smoker vs Non-smoker* Current smoker vs Non-smoker*	0.966 1.421	(0.56, 1.66) (0.74, 2.71)	0.9007 0.2870
Hypertension at baseline	Prehypertension vs Normal* Stage 1 vs Normal* Stage 2 vs Normal*	3.994 7.435 14.435	(1.53, 10.42) (2.83, 19.55) (4.95, 42.13)	0.0047 <0.0001 <0.0001
LDL-C stage at baseline	Very high-risk group vs Low-risk group* High-risk group vs Low-risk group* Moderate-risk group vs Low-risk group*	0.443 0.863 0.792	(0.15, 1.33) (0.27, 2.80) (0.26, 2.42)	0.1458 0.8067 0.6820

Notes: [a]Multiple logistic regression; *Reference level.

Table 5 Risk Factors Leading to Failure to Achieve Target LDL-C at Week 12

	Reference	Odds Ratio Estimate	95% CI for Odds Ratio	p-value[a]
Sex	Male vs Female*	1.208	(0.63, 2.31)	0.5693
BMI (kg/m^2)	≥25 kg/m^2 vs <25 kg/m^2 *	1.550	(0.90, 2.67)	0.1146
Smoking	Former smoker vs Non-smoker* Current smoker vs Non-smoker*	1.274 0.745	(0.62, 2.62) (0.26, 2.13)	0.5103 0.5824
LDL-C stage at baseline	Very high-risk group vs Low-risk group* High-risk group vs Low-risk group* Moderate-risk group vs Low-risk group*	25.165 3.065 0.653	(1.44, >99.99) (0.15, 61.34) (0.03, 15.05)	0.0271 0.4638 0.7900
Diabetes comorbidity	Yes vs No*	0.931	(0.53, 1.64)	0.8043
Renal disorder comorbidity	Yes vs No*	1.211	(0.50, 2.96)	0.6735
Prior hypertension and/or hyperlipidemia treatment	Monotherapy for hypertension treatment vs Naive* Monotherapy for hyperlipidemia treatment vs Naive* Combination vs Naive*	0.448 1.399 0.633	(0.07, 2.80) (0.22, 8.93) (0.12, 3.28)	0.3904 0.7228 0.5865

Notes: [a]Multiple logistic regression; *Reference level.

Discussion

This Phase 4 study evaluated the effectiveness and safety of an FDC containing rosuvastatin and valsartan in patients with concomitant hypertension and hyperlipidemia. Overall, the study drug was highly effective in achieving the BP and LDL-C targets and was well tolerated with no new safety findings.

A previous study that evaluated the effectiveness of an FDC containing amlodipine (CCB) and atorvastatin showed that 65.0%, 74.7%, and 57.5% of all patients, respectively, achieved the target BP, LDL-C, and both parameters simultaneously at 14 weeks.[18] A previous study that evaluated the effectiveness of an FDC containing irbesartan and atorvastatin demonstrated that target BP and LDL-C targets were achieved by 86.0% and 85.6% of patients at 12 weeks, respectively. In the same study, both targets were simultaneously attained by 74.5% of patients at 12 weeks.[21] Although these studies were conducted in different clinical settings, the responder rate to our study drug appeared to be within the reported range of other combination therapies containing antihypertensive and lipid-lowering agents. The responder rate

Table 6 Risk Factors Leading to Failure to Achieve Target Blood Pressure and LDL-C Simultaneously at Week 12

	Reference	Odds Ratio Estimate	95% CI for Odds Ratio	p-value[a]
BMI (kg/m^2)	≥25 kg/m^2 vs <25 kg/m^2 *	2.024	(1.25, 3.28)	0.0042
Smoking	Former smoker vs Non-smoker*	1.443	(0.83, 2.52)	0.1967
	Current smoker vs Non-smoker*	1.214	(0.54, 2.71)	0.6362
Hypertension at baseline	Prehypertension vs Normal*	1.876	(0.96, 3.65)	0.0636
	Stage 1 vs Normal*	4.173	(1.95, 8.94)	0.0002
	Stage 2 vs Normal*	10.327	(3.47, 30.70)	<0.0001
LDL-C stage at baseline	Very high-risk group vs Low-risk group*	2.324	(0.65, 8.27)	0.1929
	High-risk group vs Low-risk group*	0.696	(0.18, 2.70)	0.6008
	Moderate-risk group vs Low-risk group*	0.621	(0.17, 2.22)	0.4640
Renal disorder comorbidity	Yes vs No*	1.106	(0.46, 2.68)	0.8228
Prior hypertension and/or hyperlipidemia treatment	Monotherapy for hypertension treatment vs Naive*	4.660	(1.23, 17.61)	0.0233
	Monotherapy for hyperlipidemia treatment vs Naive*	5.867	(1.34, 25.73)	0.0190
	Combination vs Naive*	5.504	(1.51, 20.07)	0.0098

Notes: [a]Multiple logistic regression; *Reference level.

demonstrated in our study is highly encouraging, given the universally low percentage of control rate for both BP and LDL-C simultaneously. In an observational study conducted by Spanella et al, where the prevalence and control rate of dyslipidemia was evaluated in hypertensive patients based on real-life data, only 12.4% had both BP and LDL-C controlled at the same time.[11] Contrary to the 41.6% of patients with controlled BP, only 28.5% of patients had controlled LDL-C, suggesting that comprehensive evaluation of lipid profile is often neglected, and thus patients' CV risks underestimated and lipid-lowering agents under-prescribed.[11] The percentage of patients with controlled LDL-C in our study was also lower than that of BP (76.6% vs 36.1%) at study initiation, suggesting that the clinical picture described by Spanella et al may be true to some extent. However, unlike the study conducted by by Spanella et al, where lipid-lowering agents were taken by only 23.1% of patients, lipid-lowering agents were taken by more than 70% of patients in our study prior to the study initiation.[11] The differences observed in the responder rates in different studies could also be attributed to differences in the characteristics of the study population and study design. Most importantly, different classifications for determining the baseline risk groups and target BP and LDL-C levels were utilized across these studies; therefore, a direct comparison cannot be made. Nonetheless, the use of a fixed dose combination of anti-hypertensive and lipid-lowering agents may play a critical role in improving control rates of BP and hyperlipidemia, especially in clinical circumstances where one of the two major CV risk factors are often overlooked.

The reported absolute or percentage mean changes in BP and LDL-C levels from baseline varied considerably across studies.[18–22] In this study, reductions in BP and LDL-C at 12 weeks after administration of the study drug were not as significant as those observed in the phase 3 study conducted with the study drug.[21] However, unlike the controlled phase 3 study, a large proportion of patients already received antihypertensive and lipid-lowering medications prior to initiation of the study. Consequently, many patients enrolled in this study had relatively low BP and LDL-C levels at baseline; the mean baseline LDL-C level was within the normal range and BP was within the lower range of stage 1 hypertension. Previous studies have suggested that higher baseline LDL-C and SBP levels are associated with an increased reduction in LDL-C and SBP levels, respectively.[23–26] Consistently, relatively smaller reduction in BP and LDL-C levels was observed in our study. The significant reduction observed in total cholesterol and triglycerides from baseline at 12 weeks is promising, especially when recent studies suggest that circulating plasma lipid may also be associated with CV risks, as much as LDL-C.[11]

The results of the ad hoc analysis further reinstated the effectiveness of our study drug established in the phase 3 study. The results obtained in the ad hoc analysis are suggestive of the fact that not only the study drug is effective in treatment-naïve patients but also it can be safely used in patients switching from other antihypertensive and lipid-lowering therapies. Interestingly, a slight increase in BP was observed in patients in the normal hypertension group. However, the majority of these patients achieved their BP targets, and their BP at 12 weeks was not within the defined range of hypertension. Hence, slight increase in BP would not be considered a finding of any clinical significance.

In the multiple logistic regression analysis, the odds of treatment failure to achieve the target BP were higher in patients with BMI $\geq$ 25 kg/m^2. This finding was not surprising, considering that obesity has been consistently associated with hypertension and increased cardiovascular risk.[21,38] Studies have also suggested that obese patients with concomitant hypertension and hyperlipidemia are less likely to achieve BP and lipid control.[11,39] Furthermore, the odds of treatment failure increased with an increase in the baseline hypertension stage. This tendency was also observed in a similar observational study.[21] In addition, the odds of treatment failure to achieve the target LDL-C level were greater in patient group classified as very high-risk group than in the low-risk group. An observational study with a similar design showed correlation between the severity of hyperlipidemia and reduced treatment success rate, and the odds of treatment failure increased with the increased severity of hyperlipidemia.[21] Further, BMI $\geq$ 25 kg/m^2 and higher hypertension stage at the baseline were associated with treatment failure to achieve the target BP and LDL-C simultaneously. Patients already treated with antihypertensive and/or lipid-lowering medications also had an increased risk of treatment failure compared with those who were treatment-naïve at baseline. However, these findings should be interpreted with caution, as the majority enrolled in this study were already taking combinations of antihypertensive and lipid-lowering medications at baseline. One possible explanation for this finding is that in patients already receiving treatment for hypertension and/or dyslipidemia, the likelihood of polypharmacy is supposed to be greater than in those who were treatment-naïve, resulting in decreased drug adherence. Medication adherence is crucial for successful treatment of chronic diseases. A similar observational study conducted by Ihm et al, who investigated the efficacy and safety of an FDC containing irbesartan and atorvastatin, showed that the number of concomitant medications was one of the risk factors associated with poor treatment success rate of achieving both BP and LDL-C targets.[21] Unfortunately, drug compliance with the study drug was not investigated in our study. Therefore, well-controlled studies are needed to corroborate these findings.

In terms of safety, the reported incidence rates of AEs following the administration of ARB and statin combinations varied across studies. The incidence rate in our study was slightly lower than that reported in a previous phase 3 clinical study conducted using the study drug and in other studies on the combined use of ARBs and statins.[21–26] However, the incidence rate in this study was comparable to that observed in a post-marketing surveillance study, in which the safety and effectiveness of the study drug were assessed in more than 600 subjects for up to 24 weeks [unpublished data]. Therefore, the findings of our study further support the safety of the study drug.

In the multiple logistic regression analysis, females were more likely to experience AEs. However, the incidence rates of ADRs in males and females were similar and therefore, it would be difficult to draw any clinically meaningful conclusion from these findings. Furthermore, to our knowledge, differences in the safety of rosuvastatin and valsartan have not been reported previously. In the case of a family history of premature CAD, patients with an unknown family history had greater odds of experiencing AEs; however, due to inclusion of a small number of patients, it is difficult to support any claims with this finding.

Our study had some limitations. First, it was an open-label, single-arm, non-comparative, non-confirmatory study. Because we had no control group for comparison, the effectiveness and safety of the study drug could not be compared with those who received no treatment or other treatments. Nonetheless, the study included a large number of subjects to identify any previously unrecognized AEs, and the data obtained provided sufficient evidence for the effectiveness and safety of the study drug. Moreover, this study design had the advantage of being reflective of real-world clinical settings. Second, this study included only Asian patients; therefore, there is a possibility of racial disparity. Further studies that include other racial and ethnic groups are required before generalizing the results of our study. Third, as this was not a controlled trial, other factors, such as the use of concomitant medications and therapies, may have introduced bias and

affected the outcomes of our study. Overall, the present results support the effectiveness and safety of the study drug; however, some of the results obtained in this study must be interpreted with caution.

Conclusion

Despite these limitations, we concluded that the study drug containing rosuvastatin and valsartan, when administered for up to 12 weeks in a real-world clinical setting, was effective in lowering BP and LDL-C levels in patients with concomitant hypertension and hyperlipidemia. High metabolic profiles, including BMI, BP, and LDL-C level, were identified as risk factors that could affect the effectiveness of the study drug. Moreover, there were no new findings that would raise questions about the safety of the study drug in real-world setting. Therefore, the study drug is suggested as a good alternative to increase convenience and compliance in patients with concomitant hypertension and hyperlipidemia, particularly in those taking multiple medications.

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Disclosure

The authors report no conflicts of interest in this work.

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