VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 5, 815–823
DOI: 10.5603/CJ.a2020.0167

ISSN 1897–5593
eISSN 1898–018X

Effect of FIXed-dose combination of ARb and statin on adherence and risk factor control: The randomized FIXAR study

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Abstract

Background: *The efficacy of fixed-dose combinations (FDCs) in improving adherence and risk factor control for cardiovascular disease has not been reported consistently. Here, we compared adherence and efficacy between an olmesartan/rosuvastatin FDC and the usual regimen.*

Methods: *In this 6-month, open-label, randomized, active-control study, we screened 154 patients; of these, 150 were randomly assigned to receive either olmesartan/rosuvastatin FDC or the usual regimen with separate angiotensin receptor blockers and statins. In total, 135 patients completed the study (median age: 68 years; male: 68.9%). The primary outcome was patients' adherence; the secondary outcomes were changes in blood pressure (BP) and lipid parameters.*

Results: *During follow-up, adherence in both groups was high and similar between the groups (98.9% and 98.3% in the FDC and usual regimen groups, respectively, p = 0.328). Changes in systolic (–8 and –5 mmHg, respectively, p = 0.084) and diastolic BP (–5 and –2 mmHg, p = 0.092) did not differ significantly, although they were numerically greater in the FDC group. Changes in low-density lipoprotein cholesterol (LDL-C) were greater in the FDC group (–13 and –4 mg/dL, respectively, p = 0.019), whereas changes in other lipid parameters were similar between the groups. The test drugs were well tolerated, showing no difference in safety between the groups.*

Conclusions: *Patients' adherence was excellent and similar in the groups, whereas the reduction in the LDL-C level was greater in the FDC group. We provide comprehensive information on the adherence and efficacy of an FDC compared to the usual regimen in Korean patients with high cardiovascular risk.*
(Cardiol J 2022; 29, 5: 815–823)

Key words: hypertension, hypercholesterolemia, drug therapy, renin–angiotensin system, rosuvastatin calcium

Introduction

Statins are currently the standard of care for cardiovascular prevention [1] and are commonly prescribed with antihypertensive agents for high-risk patients. The European guidelines classify patients with severe hypertension as a high-risk group, for whom active lipid-lowering therapy is recommended [2]. The American guidelines include blood pressure (BP) when calculating an individual's cardiovascular risk using a pooled cohort equation [3]. Thus, the presence of hypertension in a patient may increase the need for statin-based therapy. In the last two decades, the

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Received: 25.02.2020 Accepted: 8.11.2020 Early publication date: 1.12.2020

use of combination or concomitant therapies with antihypertensives and lipid-lowering agents has increased in Korea [4].

Renin–angiotensin system (RAS) blockers are recommended for patients with ischemic heart disease plus hypertension, diabetes mellitus, heart failure, or chronic kidney disease. In addition, they are recommended for patients with multi-site vascular diseases [5]. The use of RAS blockers is based on the results of studies, including the HOPE [6] and EUROPA [7] studies, which showed the benefit of RAS blockers in secondary cardiovascular prevention. In addition, considering their efficacy and safety, angiotensin receptor blockers (ARBs) and statins are frequently co-prescribed in clinical trials and real-world practice [8, 9].

Patients' adherence to a treatment regimen is known to be negatively affected by its complexity; thus, it can be improved by simplification of regimens [10]. Previous studies compared a fixed-dose combination (FDC) of acetylsalicylic acid, a statin, and an angiotensin-converting enzyme inhibitor (ACEI) with a regimen of individual drugs. Several studies reported that an FDC can be helpful in increasing patients' adherence [11–13]. Furthermore, a recent study in low- and middle-income countries found that an FDC is cost-effective in secondary cardiovascular disease prevention [14]. Conversely, the UMPIRE study demonstrated that an FDC was effective in controlling BP and low-density lipoprotein cholesterol (LDL-C) level [11]. However, several studies found no differential effect of FDCs and usual regimens in terms of control of risk factors [12, 13, 15]. Moreover, data on the effects of FDCs in East Asian patients are extremely limited.

Considering these results, the current FIXAR study aimed to compare the adherence of two groups of patients receiving an FDC consisting of olmesartan and rosuvastatin or the usual regimen. The usual regimen included individual drugs of any ARBs and statins that have comparable efficacy with that of the FDC. Secondly, we compared changes in BP and lipid parameters, including the LDL-C level. Drug tolerability in the study population was also assessed.

Methods

Study participants

Men and women aged 20–80 years who required antihypertensive and lipid-lowering therapies were eligible for the study. Patients already under pharmacological treatment for hypertension and high blood cholesterol were initially screened. The need for pharmacological treatment was determined based on the guidelines of the 2013 Korean Society of Hypertension [16] and the Korean Society of Lipid and Atherosclerosis [17]. Briefly, the inclusion criteria were as follows: patients with BP ≥ 140/90 mmHg or patients already under antihypertensive treatment. Furthermore, the patients had one of the following conditions: 1) atherosclerotic cardiovascular disease; 2) diabetes, carotid artery stenosis with ≥ 50% luminal narrowing, or aortic aneurysm and LDL-C level ≥ 100 mg/dL; 3) two or more cardiovascular risk factors and LDL-C level ≥ 130 mg/dL; or 4) no risk factors or one risk factor and LDL-C level ≥ 160 mg/dL. The exclusion criteria were patients 1) with uncontrolled hypertension (systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg); 2) with uncontrolled diabetes mellitus (hemoglobin A1c ≥ 9% or fasting blood glucose ≥ 160 mg/dL); 3) with high-grade heart failure or clinically significant arrhythmia or who experienced cardiovascular or cerebrovascular events within 3 months of screening; and 4) with a history of chronic liver disease, chronic kidney disease (glomerular filtration rate < 60 mL/min/1.73 m^2), or systemic inflammatory disease or those receiving systemic anti-inflammatory treatment; 5) with additional lipid-lowering agents other than the study drugs; as well as 6) pregnant or breast-feeding women or women with child-bearing potential not receiving contraception. All participants provided written informed consent.

Study design

This was a 6-month, open-label, randomized, active-control study (ClinicalTrials.gov ID: NCT04061824). The institutional review board of Severance Hospital, Seoul, Korea approved the protocol (No. 4-2015-1122). At the screening visit, patients were interviewed regarding their medical history, and they underwent a physical examination and laboratory assessment. Participants who met the inclusion criteria were randomly assigned in a 1:1 ratio to receive one of the following two regimens: 1) an FDC of olmesartan/rosuvastatin (20 mg/5 mg, 20 mg/10 mg, 20 mg/20 mg, or 40 mg/20 mg); or 2) the usual regimen with ARBs and statins. The drug doses given to the participants of the FDC group were determined according to the potency of the ARBs and statins previously received by the participants (i.e. before enrollment). After randomization, the participants were followed up at the end of the 3rd and 6th months for outcome evaluation. Although other medications, including

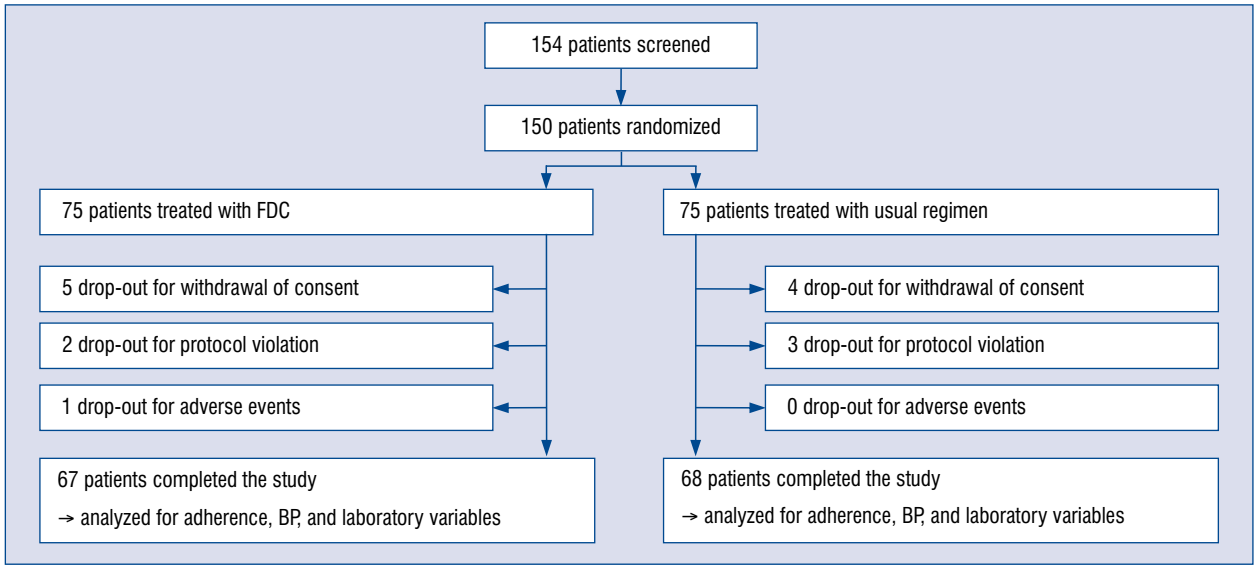

Figure 1. Study profile showing the numbers of patients who participated or dropped out; BP — blood pressure; FDC — fixed-dose combination.

antiplatelet, anti-hypertensive, or anti-diabetic agents, were allowed in both groups, patients who changed drugs or doses during the study period were excluded from analysis.

Adherence was estimated by direct measurement via pill count. Patients were instructed to return all surplus medications at the follow-up visits. Adherence (%) was calculated as: the number of pills dispended/the number of pills prescribed × 100. In addition, BP was measured, and fasting blood samples were collected at randomization and at the end of the 6th month. BP was measured by the same person at a regular time using a validated electronic sphygmomanometer (HEM-7080 IT; Omron Healthcare, Kyoto, Japan). Laboratory parameters, including lipid profiles, were measured at these time points. Samples were analyzed within 4 h of collection by a local laboratory certified by the Korean Society of Laboratory Medicine. Tolerability was assessed from adverse event reports, history taking, physical examinations, and laboratory evaluations.

Statistical analysis

The primary outcome was drug adherence during the study period. The secondary outcomes included changes in systolic and diastolic BP as well as total cholesterol, triglyceride, high-density lipoprotein-cholesterol (HDL-C), and LDL-C levels. A minimum of 62 participants per treatment group were required, assuming a power of 0.80, to determine the superiority of the FDC to the usual regimen in terms of the primary outcome. A 5 ± 10% difference in adherence between the groups was defined as significant. Assuming a 10% dropout rate, at least 68 individuals per group were recruited. The primary and secondary outcomes were analyzed in the population that underwent follow-up. Tolerability was assessed in all patients who were administered the study agents more than once. Differences in categorical variables between the groups were examined using the χ^2 test, whereas those in continuous variables were assessed using Student's t-test. The paired t-test was used to evaluate differences before and after treatment in each group. Differences were considered significant at p values < 0.05 (two-sided). All data were analyzed using SAS software 9.3 (SAS Korea, Seoul, Korea)

Results

Baseline characteristics

In total, 154 patients were screened; of these, 150 were subsequently randomized (Fig. 1). At screening, 4 patients did not meet the inclusion criteria and were excluded. Of the 150 randomized participants, 135 completed the study, whereas 15 patients dropped out for the following reasons: 9 due withdrawal of consent, 5 due to protocol violation, and 1 due to adverse events. The clinical characteristics of the patients are shown in Table 1. The median age was 68 years, and 93 (68.9%)

Table 1. Clinical characteristics of the study participants.

	FDC (n=67)	Usual regimen (n = 68)	P
Age [years]	68 (59, 73)	68 (60, 72)	0.923
Male	46 (68.6%)	47 (69.1%)	0.954
Medical history:			
Hypertension	67 (100%)	68 (100%)	1.000
Diabetes mellitus	22 (32.8%)	18 (26.4%)	0.418
Hypercholesterolemia	62 (92.5%)	61 (89.7%)	0.563
Coronary artery disease	41 (61.1%)	42 (61.7%)	0.946
Peripheral artery disease	5 (7.4%)	3 (4.4%)	0.453
Body mass index [kg/m^2]	24.8 (23.7, 26.8)	24.7 (23.3, 26.9)	0.956
Systolic BP [mmHg]	129 (119, 140)	129 (116, 140)	0.606
Diastolic BP [mmHg]	77 (69, 85)	75 (68, 84)	0.865
Lipid profile [mg/dL]:			
Total cholesterol	153 (136, 168)	151 (128, 177)	0.904
Triglyceride	117 (91, 149)	114 (86, 171)	0.979
HDL-C	47 (40, 55)	47 (40, 56)	0.760
LDL-C	79 (65, 90)	76 (61, 98)	0.604

Data are presented as median (interquartile range) or number (%); FDC — fixed-dose combination; BP — blood pressure; HDL-C — high--density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol

patients were male. Forty (29.6%) patients had diabetes mellitus, and 83 (61.5%) had a history of coronary artery disease. The median systolic BP was 129 mmHg, and the LDL-C level was 78 mg/dL at randomization. Demographic variables did not differ significantly between the groups. The doses of olmesartan and rosuvastatin used in the FDC group and ARBs and statins in the usual regimen group are shown in Table 2.

Primary and secondary outcomes

At the 6-month follow-up, patients' adherence to the regimens was not significantly different between the two groups (98.9% and 98.3% in the FDC and usual regimen groups, respectively, p = 0.328). The median change in systolic BP did not differ significantly between the two groups, although it was numerically greater in the FDC group than in the usual regimen group (–8 mmHg and –5 mmHg, respectively, p = 0.084). Similarly, the change in diastolic BP was similar in the two groups (–5 mmHg and –2 mmHg, respectively, p = 0.092). However, the median change in the LDL-C level was greater in the FDC group than in the usual regimen group (–13 mg/dL and –4 mg/dL, respectively, p = 0.019). The changes in the other lipid parameters were not different between the two groups (Table 3).

Tolerability

The proportion of patients with adverse events in the FDC and usual regimen groups was similar (21 [31.3%] and 18 [26.4%] patients, respectively, p = 0.573). The test drugs were well tolerated during the study, and the number of patients with serious adverse events was not different between the groups (3 [4.4%] in both groups, p = 1.000). The relatively common adverse events observed in the study population included dizziness, upper gastrointestinal symptoms, upper respiratory tract infection symptoms, headache, and myalgia, in order of frequency (Table 4).

Discussion

The major findings of our study included the following: 1) Patients' adherence was higher than 98% in the FDC and usual regimen groups and did not differ between the two groups. 2) The changes in systolic and diastolic BP were not significantly different between the two groups, although they were numerically greater in the FDC group. 3) The LDL-C level was reduced to a greater extent in the FDC group than in the usual regimen group. 4) Tolerability of the study regimens in the two groups was similar during the study. Our study provides comprehensive information comparing

Table 2. Doses of angiotensin receptor blockers (ARBs) and statins used in patients in the fixed-dose combination (FDC) and usual regimen groups, who completed the study.

FDC	Number of patients (n = 67)	Usual regimen	Number of patients (n = 68)
Olmesartan 20 mg/ /rosuvastatin 5 mg	12 (17.9)	Equivalent regimens:	13 (19.1)
		Candesartan 8 mg and atorvastatin 10 mg	3
		Candesartan 8 mg and pravastatin 40 mg	1
		Candesartan 8 mg and simvastatin 20 mg	1
		Fimasartan 60 mg and pitavastatin 2 mg	1
		Olmesartan 20 mg and atorvastatin 10 mg	1
		Olmesartan 20 mg and rosuvastatin 5 mg	2
		Telmisartan 40 mg and rosuvastatin 5 mg	2
		Valsartan 80 mg and pitavastatin 2 mg	1
		Valsartan 80 mg and pravastatin 40 mg	1
Olmesartan 20 mg/ /rosuvastatin 10 mg	25 (37.3)	Equivalent regimens:	26 (38.2)
		Candesartan 8 mg and rosuvastatin 10 mg	6
		Fimasartan 30 mg and rosuvastatin 10 mg	1
		Fimasartan 30 mg and simvastatin 40 mg	1
		Losartan 50 mg and fluvastatin 80 mg	1
		Olmesartan 20 mg and rosuvastatin 10 mg	9
		Telmisartan 40 mg and rosuvastatin 10 mg	3
		Valsartan 80 mg and pitavastatin 4 mg	1
		Valsartan 80 mg and rosuvastatin 10 mg	3
		Valsartan 80 mg and atorvastatin 20 mg	1
Olmesartan 20 mg/ /rosuvastatin 20 mg	19 (28.4)	Equivalent regimens:	20 (29.4)
		Candesartan 8 mg and atorvastatin 40 mg	1
		Candesartan 8 mg and rosuvastatin 20 mg	1
		Losartan 50 mg and atorvastatin 40 mg	1
		Olmesartan 20 mg and rosuvastatin 20 mg	4
		Telmisartan 40 mg and atorvastatin 40 mg	1
		Telmisartan 40 mg and rosuvastatin 20 mg	2
		Valsartan 80 mg and atorvastatin 40 mg	1
		Valsartan 80 mg and rosuvastatin 20 mg	9
Olmesartan 40 mg/ /rosuvastatin 20 mg	11 (16.4)	Equivalent regimens:	9 (13.2)
		Candesartan 16 mg and rosuvastatin 20 mg	1
		Losartan 100 mg and rosuvastatin 20 mg	1
		Olmesartan 40 mg and rosuvastatin 20 mg	3
		Telmisartan 80 mg and atorvastatin 40 mg	1
		Valsartan 160 mg and atorvastatin 40 mg	1
		Valsartan 160 mg and rosuvastatin 20 mg	2

Data are presented as number (%)

the usual regimen and an FDC comprising an ARB and a statin in Korean patients with high cardiovascular risk.

We found that patients' adherence to the study regimens, including ARBs and statins, as well as the FDC, was higher than that in most previous studies. In a meta-analysis of 5 prior studies, the adherence rates were 93.0% and 92.8% in the FDC and control groups, respectively [18]. Similarly, a meta-analysis of 9 studies by Huffman et al. [19] reported a 15-month adherence of 86% and 65% for the FDC and control groups, respectively. Con-

Table 3. Other anti-hypertensive agents used in patients in the fixed-dose combination (FDC) and usual regimen groups, who completed the study.

Regimen	FDC (n = 67)	Usual regimen (n = 68)
Beta-blocker	18 (26.9%)	22 (32.4%)
CCB	17 (25.4%)	14 (20.6%)
Diuretics	2 (3.0%)	2 (2.9%)
Beta-blocker and CCB	3 (4.5%)	5 (7.4%)
Beta-blocker and diuretics	0 (0%)	2 (2.9%)
CCB and diuretics	1 (1.5%)	1 (1.5%)
Beta-blocker, CCB, and diuretics	2 (3.0%)	1 (1.5%)
Others	1 (1.5%)	0 (0%)

Data are presented as number (%); CCB — calcium channel blocker

Table 4. Primary and secondary outcome variables.

	FDC (n = 69)	Usual regimen (n = 73)	P
Primary outcome variables:			
Adherence [%]	98.9 (96.1, 100.0)	98.3 (95.6, 100.0)	0.328
Secondary outcome variables:			
Systolic BP [mmHg]	–8 (–18, 1)	–5 (–15, 9)	0.084
Diastolic BP [mmHg]	–5 (–12, 2)	–2 (–10, 6)	0.092
Total cholesterol [mg/dL]	–11 (–27, 1)	–5 (–21, 8)	0.195
Triglyceride [mg/dL]	6 (–32, 37)	0 (–29, 21)	0.193
HDL-C [mg/dL]	1 (–4, 5)	1 (–5, 5)	0.878
LDL-C [mg/dL]	–13 (–25, –1)	–4 (–16, 7)	0.019

Data are presented as median (interquartile range); FDC — fixed-dose combination; BP — blood pressure; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol

Table 5. Adverse events.

	FDC (n = 75)	Usual regimen (n = 75)	P
Patients with adverse events	21 (31.3%)	18 (26.4%)	0.573
Patients with serious adverse events	3 (4.4%)	3 (4.4%)	1.000
Frequency of each adverse event:			
Dizziness	8	2	
Upper GI symptoms	6	4	
URI symptoms	4	5	
Headache	4	3	
Myalgia	5	1	
Edema	2	2	
Skin problems	1	2	
Minor bleeding	0	3	
Others	9	15	

Data are presented as number (%); FDC — fixed-dose combination; GI — gastrointestinal; URI — upper respiratory tract infection

versely, a recent study conducted in Iran revealed that the adherence to an FDC consisting of acetylsalicylic acid, a statin, and an ACEI or hydrochlorothiazide was 80.5% [20]. A study by Selak et al. [12] showed that the 12-month adherence to an FDC including acetylsalicylic acid, statin, and an ACEI was 81%, whereas that to the usual regimen was 46%. In addition, the 15-month adherence was 86% and 65% in users of the FDC and usual regimen, respectively, in the UMPIRE study [11]. In the Kanyini GAP study, the 18-month adherence was 70% and 47% in the FDC and control groups, respectively [13]. Patients' adherence to regimens can be affected by the follow-up duration [21], patient's age [22], underlying disease, number of drugs [22], and adverse events associated with the drugs. A meta-analysis by Webster et al. [21] revealed that adherence to a polypill was higher at earlier follow-up time points than at later follow-up time points. The adherence in our study was higher than that in other studies, and it may be related to the short follow-up duration and relatively advanced age of the participants. Furthermore, we used ARBs as antihypertensive agents; thus, the higher safety profile of ARBs than that of ACEIs might have influenced patients' adherence. Although the reason for the high adherence rate in the usual regimen group in our study is not completely understood, it might be associated with the factors mentioned above.

In our study, the changes in the LDL-C level were greater in the FDC group than in the usual regimen group. A recent meta-analysis reported that achievement rates of BP and LDL-C level targets were higher in patients receiving a polypill than in those receiving the usual regimens [23]. In other studies, the reduction in BP and LDL-C level was also greater among FDC users [11]. In particular, patients who were undertreated or exhibited poor adherence at the baseline obtained greater benefit from FDCs [21, 24]. However, as mentioned in the introduction, FDCs or the usual regimen did not show significant differences in controlling the risk factors in many studies [12, 13]. It is not clear why, in our study, the LDL-C level was reduced to a greater extent in the FDC group than in the usual regimen group, despite similar adherence in the two groups. We permitted the use of diverse statins in the usual regimen group, whereas only rosuvastatin was used in the FDC group. Therefore, differences in individual responses to diverse statins in the usual regimen group might have partially caused the differential results. For example, statins such as atorvastatin 20 mg and simvastatin 40 mg are considered to have lipid-lowering efficacy similar to that of rosuvastatin 10 mg. However, these regimens have been found to elicit slightly greater LDL-C reductions in some studies [25, 26]. Therefore, this modestly higher effect of rosuvastatin, compared to other statins with similar efficacy, might have induced greater LDL-C reduction in the patients receiving FDC of olmesartan/rosuvastatin in this study. However, further investigation is needed to fully explain this finding.

In the current study, the rates of patients experiencing adverse events were not different between the two groups, although it was numerically higher in the FDC group than in the other group. In an analysis of 9 prior studies, this rate was higher in the FDC group (30% and 24% in the FDC and usual regimen groups, respectively) [19]. These rates are consistent with those in our study. In addition, a study analyzing 9 randomized controlled trials revealed a modestly higher rate of adverse events in the FDC group [27]. However, the differential safety profile between FDCs and the usual regimen was not consistent in these previous studies. A meta-analysis involving 5 studies identified no significant difference in the rates of adverse events between the FDC and usual regimen groups [18].

Limitations of the study

Our study had some limitations. First, we did not fully assess concomitantly administered pharmacological agents. Because a large proportion of the study population had coronary or peripheral artery disease, they might have received additional drugs, such as antiplatelet agents. Concomitant administration of additional drugs might have reduced the single-pill effect in the FDC group. Second, our study was conducted in a tertiary hospital, and most participants were well-treated at baseline. Thus, the adherence in the two groups was high, and the inter-group difference might have been minimized. Third, the follow-up duration was 6 months, which is shorter than those in previous studies. This might have attenuated any potential difference in the primary and secondary outcomes between the two groups. Finally, our study was open label. Despite our best attempts to prevent it, potential bias caused by the study design cannot be completely ruled out. Nevertheless, it is noteworthy that the current study was well performed to investigate our original study objective, and, for the first time, to our knowledge, we showed comparison data of the efficacy of an FDC and the usual regimen of hypertension in Korean patients with multiple risk factors.

Conclusions

In conclusion, patients' adherence to the test regimens was excellent and similar in the two groups. The LDL-C level was reduced to a greater extent in the FDC group than in the usual regimen group, whereas changes in BP and other lipid parameters did not differ between the groups. Our study provides comprehensive information on the efficacy of an FDC compared with that of the usual regimen in Korean patients with high cardiovascular risk.

Acknowledgments

This research was financially supported by Daewoong Pharmaceutical Co., Ltd. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication. We are grateful to Surae Kim R.N. for her excellent assistance with clinical data collection and patient care.

Conflict of interest: None declared

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