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ORIGINAL ARTICLE

Low-density lipoprotein cholesterol reduction and target achievement after switching from statin monotherapy to statin/ezetimibe combination therapy: Real-world evidence

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Abstract

What is known and objectives: This study investigated the additional low-density lipoprotein cholesterol (LDL-C) reductions and target (LDL-C < 100 mg/dL) achievement rates in patients after switching from statin monotherapy to statin/ezetimibe combination therapy, in clinical practice.

Methods: This retrospective study used data recovered from the electronic medical record systems of two tertiary care medical centres for patients treated between 2015 and 2017. Patients prescribed statin/ezetimibe combination therapy after switching from statin monotherapy were enrolled. The observed LDL-C reductions and the percentage of patients achieving LDL-C levels of <100 mg/dL, after 3 months of treatment, were assessed relative to baseline values.

Results and discussion: A total of 4252 patients with prescriptions for statin/ezetimibe combination therapy were enrolled. Changing from statin monotherapy to the combination therapy resulted in additional LDL-C level reductions of 31.0-41.0% (all intensity groups, $P < .01$). Similarly, 88.3-91.1% of the enrolled patients successfully achieved LDL-C levels of <100 mg/dL (all intensity groups, $P < .01$). A subgroup analysis of patients with baseline LDL-C levels ≥ 100 mg/dL showed that switching from moderate- or high-intensity statin monotherapy to a rosuvastatin/ezetimibe combination showed greater LDL-C reductions than did switching to an atorvastatin/ezetimibe combination, within the same statin intensity groups.

What is new and conclusion: The present study provides real-world evidence of the LDL-C reduction benefits associated with statin/ezetimibe combinations in the clinical practice setting. The results also demonstrate that if statin monotherapy does not effectively help patients reach their target LDL-C goals, changing to a statin/ezetimibe combination prescription may show enhanced LDL-C-lowering effects and improve the likelihood of achieving LDL-C targets, in real practice.

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1 | WHAT IS KNOWN AND OBJECTIVE

Atherosclerotic cardiovascular disease, including ischaemic heart disease, cerebrovascular disease and atherosclerosis, is the second most common cause of death, after neoplasms,[1] with a mortality in 2017, of 119.6 per 1 000 000 persons.[2] Dyslipidaemia, characterized by high levels of low-density lipoprotein cholesterol (LDL-C), is a well-established major risk factor for atherosclerotic disease.[3] There is evidence from randomized trials of lipid-lowering drugs that lowering LDL-C levels can reduce the risk of cardiovascular or cerebrovascular diseases.[4]

According to the National Cholesterol Education Program (NCEP) Adult Treatment Panel, European Society of Cardiology and European Atherosclerosis Society, and American College of Cardiology/American Heart Association (ACC/AHA) guidelines, there is a recommendation that more intense LDL-C management be implemented to achieve desired targets.[5-7] Many recent studies have already reported that statins are the most cost-effective drug for preventing cardiovascular disease.[8-11] Based on these studies, statins are considered to be the first-line treatment lipid-lowering therapeutics for the primary and secondary prevention of circulatory disease.[3,6,7] Worldwide, statins are commonly prescribed, including in Korea[11,12] where prescriptions for atorvastatin (56.07%) and rosuvastatin (23.28%) have increased over the past decade.[13]

Although intensive lipid-lowering therapy is emphasized in several guidelines, the proportion of patients reaching their target LDL-C goal remains low.[14] Moreover, the Centralized Pan-Asian Survey of the Under treatment of Hypercholesterolemia (CEPHEUS) study reported that only 31.5% of very high-risk patients treated with statin therapy reached their target LDL-C goals (<70 mg/dL).[15] Therefore, the prescription of high-intensity statin therapy or a combination therapy that includes ezetimibe has increased. Ezetimibe, a non-statin drug, reduces the absorption of dietary and biliary cholesterol by inhibiting its transport across the intestinal wall; this is accomplished by ezetimibe blocking the function of the duodenal Niemann-Pick C-like protein 1L1.[16] Several previous studies have compared the effects of the various statins,[17-19] and the powerful effects of statin/ezetimibe combinations have been demonstrated in randomized controlled trials (RCTs). However, few studies have investigated the additional LDL-C effects or improvements in target attainment after switching from statin monotherapy to statin/ezetimibe in real-world clinical settings.[20,21] These studies demonstrated that switching to statin/ezetimibe combination therapy was superior to statin monotherapy in terms of achieving the target goal in patients with coronary heart disease (CHD) and CHD risk equivalent. We aimed to assess these effects in real-world patients who were switched from statin monotherapy to a statin/ezetimibe combination outside of a controlled clinical study, regardless of their risk factors.

2 | METHODS

2.1 | Study population and design

This retrospective study used data from an electronic medical record (EMR) system. Patients who were prescribed statin/ezetimibe combination therapy, between 1 January 2015 and 31 December 2017, at two hospital outpatient clinics (Catholic University of Korea's St. Mary's Hospital and Seoul National University Hospital) in Seoul, Korea, were enrolled. Demographic, laboratory and prescription data were reviewed.

2.2 | Statin/ezetimibe combinations

In this study, we selected ezetimibe/atorvastatin (Atozet, Merck and Co., Korea) and ezetimibe/rosuvastatin (Rosuzet, Hanmi, Pharm Co., Korea) therapies. Six statin/ezetimibe combinations were assessed: atorvastatin (10 mg) with ezetimibe (10 mg) [AtoZ_10], atorvastatin (20 mg) with ezetimibe (10 mg) [AtoZ_20], atorvastatin (40 mg) with ezetimibe (10 mg) [AtoZ_40], rosuvastatin (5 mg) with ezetimibe (10 mg) [RosuZ_5], rosuvastatin (10 mg) with ezetimibe (10 mg) [RosuZ_10], and rosuvastatin (20 mg) with ezetimibe (10 mg) [RosuZ_20].

2.3 | Definition of data extraction items and study design

The index date (visit 0) was defined as the date when the initial statin/ezetimibe combination was prescribed. The type of statin prescribed, prior to the index date, was also reviewed and classified as a high-, moderate- or low-intensity statin, based on ACC/AHA definitions.[22] The high-intensity statins included atorvastatin (40 mg) and rosuvastatin (20 mg), and the moderate-intensity statins included atorvastatin (10 or 20 mg), fluvastatin (80 mg), pitavastatin (2 or 4 mg), pravastatin (40 mg), simvastatin (20 or 40 mg) and

TABLE 1 Baseline characteristics of patients prescribed statin monotherapy (n = 5907)

Variables	AtoZ_10 + RosuZ_5	AtoZ_10	RosuZ_5	*P* value	AtoZ_20 + RosuZ_10	AtoZ_20	RosuZ_10	*P* value	AtoZ_40 + RosuZ_20	AtoZ_40	RosuZ_20	*P* value
Number	2836	2060	776		2243	1030	1213		828	177	651	
Age, years	58.9 ± 12.4	58.3 ± 12.6	60.8 ± 11.5	<.001*	61.4 ± 12.3	60.7 ± 13.0	62.0 ± 11.6	.015*	61.4 ± 12.2	58.8 ± 12.6	62.1 ± 12.0	.002*
Sex, male (%)	1476 (52.1)	1083 (52.6)	393 (50.6)	.359	1284 (57.2)	590 (57.3)	694 (57.2)	.974	521 (62.9)	123 (69.5)	398 (61.1)	.041*
Height, cm	163.2 ± 9.0	163.3 ± 9.0	163.0 ± 8.7	.583	163.0 ± 8.8	163.0 ± 8.8	163.0 ± 8.9	.872	163.9 ± 9.1	164.7 ± 8.2	163.7 ± 9.4	.240
Weight, Kg	66.4 ± 13.0	66.5 ± 13.4	66.4 ± 11.7	.910	67.0 ± 12.5	66.8 ± 13.2	67.2 ± 11.9	.502	68.4 ± 13.4	68.8 ± 14.2	68.3 ± 13.2	.742
BMI, Kg/m^2	24.94 ± 3.8	24.9 ± 3.9	25.0 ± 3.2	.493	25.1 ± 3.5	25.0 ± 3.7	25.2 ± 3.2	.287	25.3 ± 3.7	25.2 ± 4.4	25.4 ± 3.5	.793
SBP, mmHg	129 ± 20	128 ± 20	132 ± 20	.028*	126.8 ± 19.4	125 ± 20	129 ± 19	.052	128.4 ± 18.2	127 ± 17	130 ± 19	.245
DBP, mmHg	76 ± 14	75 ± 14	78. ± 13	.062	74.2 ± 13.5	74 ± 15	75 ± 12	.453	76.5 ± 12.9	75 ± 13	78 ± 13	.147
Statin change	2475 (87.3)	1791 (86.9)	684 (88.1)	.392	2022 (90.2)	892 (86.6)	1130 (93.2)	<.001*	801 (96.7)	163 (92.1)	638 (98.0)	<.001*
Type of statin				<.001*				<.001*				.008*
Low	63 (3.5)	41 (3.3)	22 (3.8)		16 (0.9)	9 (1.3)	7 (0.7)		3 (0.4)	1 (0.8)	2 (0.3)	
Moderate	1622 (89.0)	1115 (89.6)	507 (87.9)		1402 (82.0)	512 (74.5)	890 (87.0)		430 (59.7)	59 (47.2)	371 (62.2)	
High	136 (7.5)	88 (7.1)	48 (8.3)		292 (17.1)	166 (24.2)	126 (12.3)		288 (39.9)	65 (52.0)	223 (37.4)	
BUN, mg/dL	20.4 ± 14.8	21.5 ± 16.3	17.4 ± 8.7	<.001*	18.6 ± 10.5	20.1 ± 13.0	17.2 ± 7.3	<.001*	17.8 ± 9.6	23.0 ± 15.7	16.4 ± 6.4	<.001*
Cr, mg/dL	1.4 ± 1.9	1.5 ± 2.1	1.00 ± 0.7	<.001*	1.1 ± 1.2	1.3 ± 1.6	1.0 ± 0.7	<.001*	1.1 ± 0.8	1.4 ± 1.3	1.0 ± 0.6	<.001*
GFR, mL/min/1.73 m^2	73.4 ± 26.7	71.3 ± 28.0	79.3 ± 21.8	<.001*	76.7 ± 24.5	73.5 ± 27.3	79.5 ± 21.2	<.001*	77.8 ± 23.5	69.8 ± 30.7	80.0 ± 20.7	<.001*
AST, U/L	28 ± 27	27 ± 26.0	29 ± 28	.237	29 ± 23	28 ± 24	29 ± 21	.244	27 ± 15	26 ± 12	27 ± 16.0	.259
ALT, U/L	30 ± 29	30 ± 28.9	31 ± 29	.578	31 ± 29	31 ± 35	31 ± 24	.679	31 ± 40	35 ± 73	30 ± 25	.409
HbA1c, %	6.7 ± 1.4	6.71 ± 1.37	6.80 ± 1.30	.245	6.8 ± 1.4	6.78 ± 1.46	6.88 ± 1.42	.212	6.75 ± 1.37	7.02 ± 1.51	6.69 ± 1.32	.037*
TC, mg/dL	195 ± 52	198 ± 53	187 ± 51	<.001*	197 ± 53	199 ± 59	196 ± 48	.324	207 ± 58	215 ± 61	205 ± 57	.063
TG, mg/dL	166 ± 119	169 ± 120	158 ± 115	.027*	165 ± 117	169 ± 122	163 ± 112	.242	160 ± 136	178 ± 130	156 ± 137	.048*
HDL-C, mg/dL	51.9 ± 15	52 ± 15	52 ± 15	.685	51 ± 15	50 ± 16	52 ± 14	.006*	51 ± 15	49 ± 15	52 ± 15	.042*
LDL-C, mg/dL	111 ± 41	113 ± 41	106 ± 41	<.001*	116 ± 43	116 ± 47	116 ± 40	.895	128 ± 45	131 ± 46	127 ± 44	.233

Note: Data are presented as means ± standard errors or as distribution inclusion percentages.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AtoZ, atorvastatin + ezetimibe, RosuZ, rosuvastatin + ezetimibe; BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

*Statistical difference between groups ($P < .05$).

rosuvastatin (5 or 10 mg). The low-intensity statins included fluvastatin (40 mg) and pravastatin (10 or 20 mg).

Demographic data, including patient age, sex, calculated body mass index, systolic blood pressure (BP) and diastolic BP, were extracted. Laboratory findings, such as levels of blood urea nitrogen, creatinine, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), LDL-C, aspartate aminotransferase, alanine aminotransaminase and glycated haemoglobin (HbA1c), were also extracted. All measurements were performed using an automated blood chemistry analyser (Hitachi 747; Hitachi, Tokyo, Japan). HbA1c percentages were determined using high-performance liquid chromatography and Diabetes Control and Complications Trial-aligned methods (Tosoh-G8; Tosoh, Tokyo, Japan). We also extracted comorbidity data, such as heart failure (I50, I11.0, I13.0, I24.8), E10-15 (diabetes mellitus), I60-69 (cerebrovascular diseases), C (cancer) and I20-25 (ischaemic heart diseases), using the International Classification of Diseases (ICD)-10 classifications. We reviewed each patient's thyroxine and warfarin prescription histories as they affect serum statin concentrations. Visit 1 was defined as the visit that occurred, on average, 3 months after the index date. The data, described above, were extracted from visit 1. If more than one test value existed, the value chosen was the one that was closest to the 3-month point. An LDL-C reduction was defined as the difference between the index and visit 1 values. The LDL-cholesterol reduction rate was calculated as follows:

$$\text{LDL-C reduction rate (\%)} = \text{mean per cent change (\%)}$$
$$= 100 \times (\text{visit 0} - \text{visit 1})/\text{visit 0}.$$

2.4 | Direct chart review and data quality management

After extracting the data, a data quality management process was conducted in a standardized way, according to the data table specifications. Within the EMR data, there are various representations of unstructured laboratory data that are not exactly represented numerically (eg, >1995 mg/dL, <10 mg/dL or <3 IU/U). To increase the data reliability, the relevant data were manually reviewed and compared with the original data.

2.5 | Ethical consideration

The data used in this study were stored in encrypted files by each hospital investigator, accessible only by the responsible researchers. When data from the two hospitals were needed for statistical analysis, patient anonymity was preserved by removing the security and registration numbers. Since only a randomized number was accessible to the responsible researchers at each hospital, the researchers or analysts from the other hospital could not confirm the actual patient number. When a direct chart review was required, only the responsible researchers at each hospital could access the chart. As such, this study did not directly deal with personal patient information. Additionally, because this retrospective study used accumulated data from closed files and involved strict data encryption, the rights and welfare of the patients were not affected. Further, this study did not involve any possible physical or mental harm to any patient. Thus, informed consent was not required; the study was approved by the institutional review boards of the Catholic University of Korea and the Seoul National University Hospital (IRB no. KC18REDE0188).

2.6 | Statistical analysis

Continuous variables are expressed as means and standard deviations, whereas categorical variables are expressed as medians and percentages. The associations between the different statins and their 3-month LDL-C reductions (absolute difference and reduction percentage) were evaluated using independent *t* tests. The ratios of LDL-C normal ranges (<100 mg/dL) from different types of statins were calculated using chi-square tests. All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC); *P*-values <.05 were considered to be statistically significant.

3 | RESULTS

A total of 5907 patients received prescriptions for AtoZ and RosuZ, within the study period. Among those patients, 609 reverted to statin monotherapy during the study period and were excluded. Among the remaining patients, 1046 were initially prescribed an ezetimibe/statin combination therapy, without having a record of prior statin treatment. However, one of the limitations of this type of EMR study is the difficultly in distinguishing between patients who had received statin prescriptions from other hospitals and those who truly never had been prescribed statins; regardless, these patients were also excluded. Thus, a total of 4252 patients, confirmed to have been previously prescribed statin monotherapy, were enrolled.

3.1 | Baseline characteristics of study subjects

Table 1 shows the baseline characteristics of the patients, prior to beginning ezetimibe/statin combination therapy; 2836 of the 5907 (48.0%) patients received AtoZ_10 or RosuZ_5, 2243 (38.0%) received AtoZ_20 or RosuZ_10, and 828 (14.0%) received AtoZ_40 and RosuZ_20. Prior to starting the statin/ezetimibe treatment, the mean age of the patients receiving AtoZ_10 or RosuZ_5 was 58.9 ± 12.4 years, 61.4 ± 12.3 years in the AtoZ_20 or RosuZ_10 group, and 61.4 ± 12.2 years in the AtoZ_40 or RosuZ_20 group; in all groups, males were predominant. In the AtoZ_10 or RosuZ_5 group, 63 patients (3.5%) were previously treated with low-intensity statins, 1622 with moderate-intensity statins and 136 with

high-intensity statins. In the AtoZ_20 or RosuZ_10 group, the majority of patients (82.9%) were previously prescribed moderate-intensity statins, 0.9% low-intensity statins, and 17.1% were previously prescribed high-intensity statins. In the AtoZ_40 or RosuZ_20 group, 3 (0.4%) patients were originally low-intensity statins, 430 (59.7%) received moderate-intensity statins, and 288 (39.9%) were originally prescribed high-intensity statins.

Prior to starting combination therapy, the mean TC levels were 195 ± 52.4 mg/dL in the AtoZ_10 or RosuZ_5 group, 197 ± 53 mg/dL in the AtoZ_20 or RosuZ_10 group, and 207 ± 58 mg/dL in the AtoZ_40 or RosuZ_20 group. There were no differences between the AtoZ-10 and RosuZ_5 groups, with respect to TC, TG and HDL-C levels before starting their indicated combination therapies. At the index visit, the mean TG level was highest in the AtoZ_10 or RosuZ_5 group, the mean HDL-C levels were similar for the three groups, and the highest LDL-C was observed in the AtoZ_40 or RosuZ_20 (128 ± 45 mg/dL) group.

3.2 | Effect of combination therapy on LDL-C levels

Figure 1 shows effect of the combination therapy on LDL-C levels. Between baseline and 3 months of combination therapy, the additional LDL-C level reductions and target goal achievements were significantly increased following implementation of combination therapy. In the AtoZ_10 or RosuZ_5 group, there was an additional 31.0% reduction ($P < .01$) in the LDL-C level after 3 months of combination therapy and the percentage of patients achieving their LDL-C target (<100 mg/dL) increased from 35.3% to 88.3% ($P < .01$). Similarly, in the AtoZ_20 or RosuZ_10 group, the LDL-C levels declined by 36.4% ($P < .01$) and 90.1% of patients reached their LDL-C goal ($P < .01$). In the AtoZ_40 or RosuZ_20 group, LDL-C levels declined by an additional 41.0% ($P < .01$) and 87.5% of the patients achieved their LDL-C target, up from 21.9% at baseline ($P < .01$).

3.3 | Relative LDL-C reductions according to the intensity of prior statin monotherapy

We analysed the LDL-C level reductions that occurred after switching to a combination therapy from high-, moderate- or low-intensity statin monotherapy (Figure 2). For patients switching from a low-intensity statin therapy to either AtoZ_10 or RosuZ_5, an additional LDL-C reduction of 40.9% was observed for those switching to AtoZ_10 and 49.2% for those switching to RosuZ_5 (Figure 2A). Those switching from a moderate-intensity statin therapy to AtoZ_10 showed a further LDL-C reduction of 32.8%; those switching to RosuZ_5 showed a further reduction of 29.3% ($P < .01$) (Figure 2A). In the cases of patients switching from a moderate-intensity statin monotherapy to AtoZ_20 (36.1%) or RosuZ_10 (38,7%, $P < .01$), significant reductions were also observed (Figure 2B). Additional LDL-C level reductions were also observed for patients switching from high-intensity statin therapies to AtoZ_20 (27.6%) or RosuZ_10 (30.6%, $P < .01$) (Figure 2B). For all patients previously treated with statin monotherapies, patients switching to RosuZ_10 exhibited greater LDL-C declines than those switching to AtoZ_20. Additional LDL-C reductions were observed in patients who changed from a moderate-intensity statin monotherapy to AtoZ_40 (37.3%) or RosuZ_20 (45.8%, $P < .01$) (Figure 2C). In our results, patients switching to RosuZ generally showed greater LDL-C reductions than did those switching to AtoZ.

3.4 | LDL-C level changes in patients with baseline LDL-C levels above 100 mg/dL

Sub-analyses were performed for the 2881 patients who had LDL-C levels > 100 mg/dL before being prescribed a statin/ezetimibe therapy (Table 2). In the AtoZ_20 and RosuZ_10 groups, there were no significant differences in the LDL-C level reductions or target achievement rates when the prescription was changed from low-intensity statin monotherapy to the combination therapy. A total

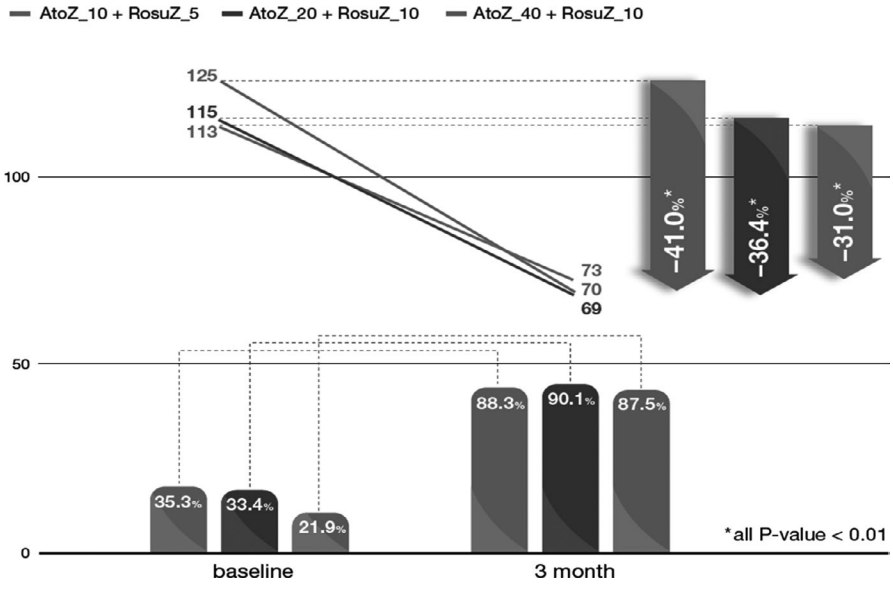

FIGURE 1 Additional LDL-cholesterol reduction when changing prescription with ezetimibe-statin combination therapy

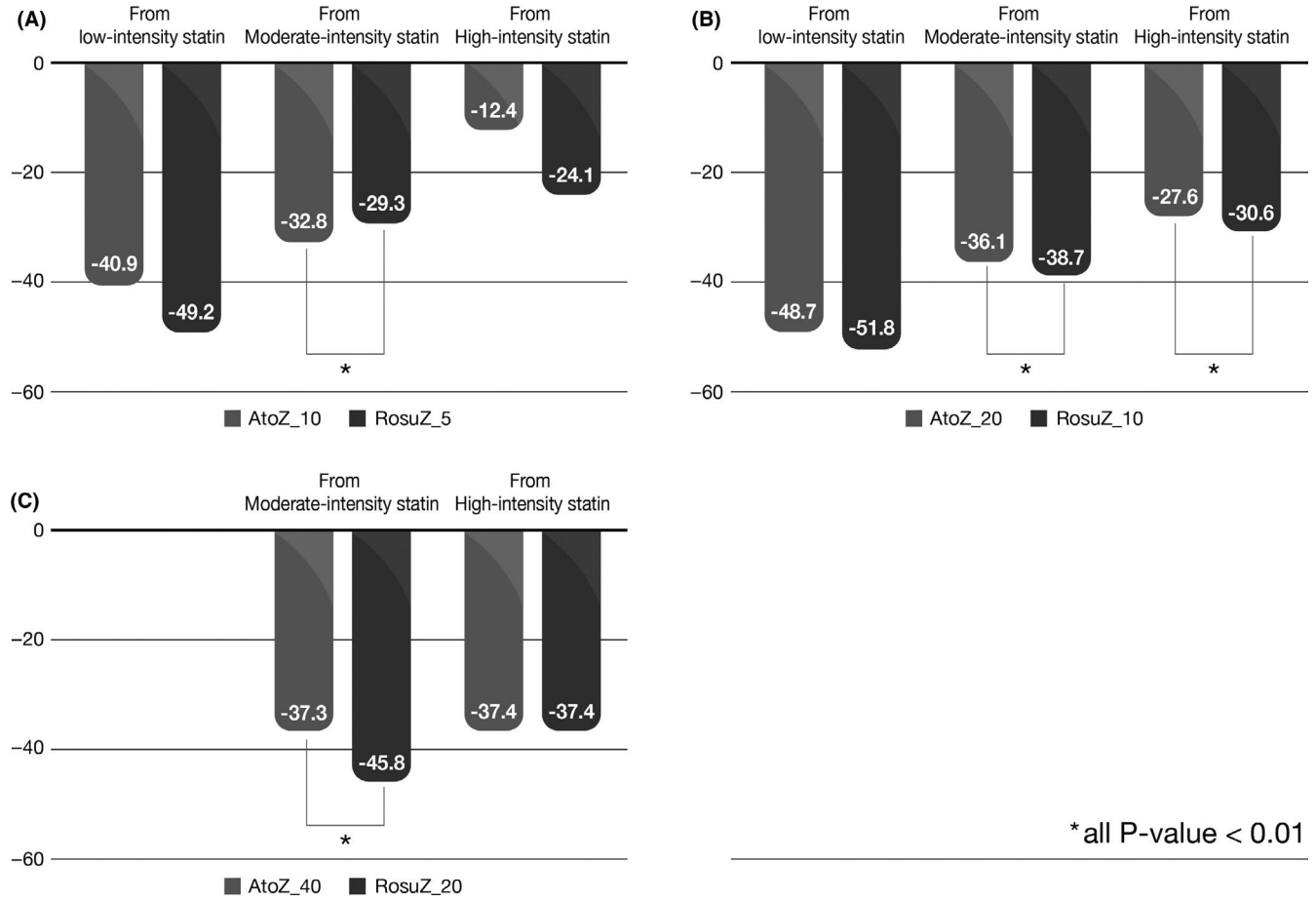

FIGURE 2 Relative LDL-C reductions according to the intensity of prior statin monotherapy

of 2398 patients changed from moderate-intensity statin monotherapy to a combination therapy. There were no significant differences in the results between the AtoZ_10 and RosuZ_5 groups or between the AtoZ_20 and RosuZ_10 groups. However, patients in the RosuZ_10 and RosuZ_5 groups tended to demonstrate greater LDL-C reductions and target achievement rates than those in the AtoZ_20 and AtoZ_10 groups (Table 2). Patients in the group that switched from moderate-intensity statin monotherapy to RosuZ_20 showed significantly greater LDL-C reductions than did those in the AtoZ_40 group (48.0 ± 1.1 vs 40.1 ± 3.0%, $P = .014$).

A total of 422 patients, previously prescribed high-intensity statin monotherapy, were changed to a combination therapy. The associated LDL-C reductions were not significantly different between patients in the AtoZ_10 and RosuZ_5 groups. Similarly, the efficacies of AtoZ_40 and RosuZ_20 were similar. However, those in the RozuZ_10 group (47.3 ± 2.8%) showed significantly greater LDL-C reductions than those in the AtoZ_20 group (38.7 ± 2.7, $P = .036$).

4 | DISCUSSION

This retrospective study used EMR-based data to investigate the additional LDL-C reductions observed in patients switching from statin monotherapies to statin/ezetimibe combination therapies. The RCT studies employed tightly controlled conditions to confirm the intrinsic LDL-C-lowering effects of the statin/ezetimibe combinations. However, expecting LDL-C reductions, in actual practice, that are similar to those in the RCTs is unrealistic. Factors such as clinical practice and out-of-hospital data such as side effects, cost and tablet size affect patient compliance and influence real-world evidence (RWE).

Clinical practice evidence suggests that LDL-C is a leading cause of cardiovascular disease and that intensive LDL-C-lowering therapy reduces the rate of cardiovascular disease.[5,6,23] However, despite these recommendations, the number of patients achieving their target LDL-C level is suboptimal. Previous studies investigated the disparity between the guidelines and clinical practice found that the statin prescription should vary according to the patient's risk stratification.[24]

The present study found that changing from statin monotherapy to a statin/ezetimibe combination was more effective at providing LDL-C-lowering effects than statin monotherapy. Several studies investigated the effects of adding ezetimibe to atorvastatin, rosuvastatin or simvastatin monotherapy[25-28] and consistently showed that such combination therapy might improve the management of patients who failed to reach their LDL-C target

TABLE 2 Association between low-density lipoprotein (LDL)-cholesterol changes and statin therapy, according to baseline LDL-cholesterol levels ≥ 100 mg/dL (n = 2881)

	AtoZ_10	RosuZ_5	*P* value	AtoZ_20	RosuZ_10	*P* value	AtoZ_40	RosuZ_20	*P* value
From low-intensity statin (n = 61)									
Number, n	30	16		7	5		1	2	
Baseline, mg/dL	140 ± 6	135 ± 6	.590	171 ± 41	132 ± 11	.379			
After 3 months mg/dL	75 ± 4	66 ± 5	.172	65 ± 12	53 ± 5	.426			
Additional LDL-C reduction rate (%)	44.5 ± 3.3	50.8 ± 3.5	.239	59.2 ± 4.4	58.7 ± 15.3	.942			
Target achievement rate < 100 mg/dL, n (%)	25 (83.3%)	15 (93.8%)	.649	6 (85.7%)	5 (100.0%)	>.999			
From moderate-intensity statin (n = 2398)									
Number, n	795	276		332	641		43	311	
Baseline, mg/dL	134 ± 1	130 ± 1	.030*	137 ± 2	132 ± 1	.025*	137 ± 4	139 ± 2	.604
After 3 months mg/dL	81 ± 1	77 ± 1	.012*	78 ± 1	75 ± 1	.134	83 ± 5	71 ± 2	.015*
Additional LDL-C reduction rate (%)	38 0.2 ± 0.7	39.8 ± 1.1	.246	41.9 ± 1.0	42.5 ± 0.7	.614	40.1 ± 3.0	48.0 ± 1.1	.014*
Target achievement rate < 100 mg/dL, n (%)	659 (82.9%)	234 (84.8%)	.468	282 (84.9%)	561 (87.5%)	.262	33 (76.7%)	273 (87.8%)	.048*
From high-intensity statin (n = 422)									
Number, n	38	24		96	58		52	154	
Baseline, mg/dL	134 ± 5	144 ± 11	.440	139 ± 4	138 ± 4	.850	138 ± 5	135 ± 3	.716
After 3 months mg/dL	74 ± 5	76 ± 4	.762	83 ± 4	69 ± 3	.004*	81 ± 4	77 ± 2	.294
Additional LDL-C reduction rate (%)	43.6 ± 3.7	44.2 ± 3.7	.903	38.7 ± 2.7	47.3 ± 2.8	.036	38.4 ± 2.5	42.0 ± 1.6	.250
Target achievement rate < 100 mg/dL, n (%)	32 (84.2%)	21(87.5%)	>.999	68 (70.8%)	53 (91.4%)	.003*	43 (82.7%)	121 (78.6%)	.524

Note:: Data are presented as means ± standard errors or as distribution inclusion percentages.

Abbreviations: AtoZ, atorvastatin + ezetimibe; LDL-C difference = initial visit LDL-C – follow-up visit LDL-C; LDL-C reduction rate, difference (%) = mean per cent change (%) = 100 * (initial visit – follow-up visit)/initial visit; RosuZ, Rosuvastatin + ezetimibe.

*Statistical difference between groups ($P < .05$).

using statin monotherapy. Similar to these previous studies, our results also showed additional LDL-C-lowering effects of 12.4-45.8% after switching from a statin monotherapy to a statin/eremite combination therapy. Whereas a doubling of the statin dose is associated with additional 4-6% reductions in LDL-C levels,[29] the LDL-C-lowering effect, in the present study, was more significant following a switch to statin/ezetimibe therapy. The present results showed that the percentage of patients reaching their target LDL-C goal (<100 mg/dL) was >82% in all of the statin/ezetimibe groups. According to Pan-Asian CEPHEUS study, 49.4% of patients achieved their recommended LDL-C level and 54.8% of high-risk patients attained their target LDL-C level using statin monotherapy.[15] One Korean study, involving 808 patients with stable artery disease and acute coronary syndrome, reported that 40.0% of patients with stable artery disease and 23.7% of those with acute coronary syndrome were under their LDL-C targets, after switching to the combination therapy.[30] Therefore, a statin/ezetimibe combination may be an alternative choice for the treatment of dyslipidaemia.

In the present study, among patients who switched from moderate- or high-intensity statin monotherapies to a combination, RosuZ showed more potent LDL-C-lowering effects (LDL-C level reduction and per cent of patients achieving their LDL-C targets) than AtoZ. Multiple studies have reported the lipid-lowering efficacy of moderate- and high-intensity statin, especially comparing atorvastatin with rosuvastatin.[18,19,29,31] However, there have been conflicting results regarding the cardiovascular outcomes. Our results showed the superiority of the rosuvastatin/ezetimibe combination, relative to the atorvastatin/ezetimibe combination. These results were concordant with a previous study that showed that a rosuvastatin/ezetimibe combination was more effective at reducing LDL-C levels than a simvastatin/ezetimibe combination.[32] Thus, rosuvastatin/ezetimibe combinations may be expected to have the strongest LDL-C-lowering effects, relative to the dose.

The previously mentioned studies reported the different effects of high-dose statin monotherapy relative to low-dose statin and ezetimibe combination therapy. However, the efficacies of fixed-dose combinations have not been reported, except in one study. Kim et al compared the effects of a fixed-dose rosuvastatin/ezetimibe combination with rosuvastatin monotherapy and reported that the fixed-dose combination showed greater LDL-C reductions than the monotherapy (43% vs 54%).[28] Hence, the additional LDL-C-lowering effects obtained by adding ezetimibe to a statin monotherapy are expected. However, our study examined real-world practice and also demonstrated improved LDL-C reductions when the combination therapy was prescribed. In addition to the evidence from ezetimibe combination RCTs, our study demonstrates the LDL-C-lowering benefits of ezetimibe/statin combinations in clinical practice.

The present study had several limitations. First, the study was retrospective in nature and was based on EMR data. Because of the nature of the study, the absence of information regarding patient adherence lessens our confidence in the absolute extent of LDL-C level reductions following a switch to a combination therapy. Moreover, adverse effects were not studied. The advantage of this EMR-based study is that it provided RWE, and is useful for evaluating the clinical situation because it reflects actual practice.[33] Second, we evaluated the percentages of patients achieving target LDL-C levels of <100 mg/dL without classifying their risk factors. Nevertheless, approximately 82% of patients achieved LDL-C levels of <100 mg/dL after switching to the combination therapy, regardless of their statin monotherapy dosage.

In general, when statin monotherapy has not allowed a patient to attain their target LDL-C goal, the addition of ezetimibe therapy is well-known to provide more potent LDL-C-lowering effects than increasing the statin monotherapy dosage. In addition to the RCT evidence of the benefits of statin/ezetimibe combination therapy, our study demonstrated the ability of combination therapy to provide additional LDL-C reduction benefits, in real-world practice.

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CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

ETHICS APPROVAL STATEMENT

This study was approved by the institutional review boards of the Catholic University of Korea and the Seoul National University Hospital (IRB no. KC18REDE0188).

DATA AVAILABILITY STATEMENT

All the data generated and/or analysed during the current study are included in this article and are available from the corresponding author on reasonable request.

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