Original Research

A Paradigm Shift in Dyslipidemia Management in Primary Care: A 12-Month Cohort Study

Jun Hwa Hong, MD, PhD[1,*]; Ung Jeon, MD[2,*]; Won-Yong Shin, MD, PhD[2]; Weon Kim, MD, PhD[3]; Kayeon Seong, RN, PhD[1]; Sang-Ho Park, MD, PhD[2]; Hee-dong Kim, MD[2]; Joong-Wha Chung, MD[4]; and Jaehyuk Choi, MD, PhD[5]

[1]Department of Internal Medicine, Eulji University Hospital, School of Medicine, Daejeon, Korea; [2]Division of Cardiology, Department of Internal Medicine, School of Medicine, Soonchunhyang University Cheonan Hospital, Cheonan, Korea; [3]Division of Cardiovascular, Department of Internal Medicine, Kyung Hee University Hospital, Kyung Hee University, Seoul, Korea; [4]Department of Internal Medicine, Chosun University School of Medicine, Kwangju, Korea; and [5]Division of Cardiology, Department of Internal Medicine, College of Medicine, Hallym University Dongtan Sacred Heart Hospital, Dongtan, Korea

ABSTRACT

Purpose: LDL-lowering therapy is beneficial to reduce the risk of cardiovascular disease (CVD). Higher statin doses lower LDL-C levels and prevent CVD; however, they increase adverse events, such as muscle-related adverse events and new-onset diabetes mellitus (DM). Ezetimibe combined with statin therapy improves LDL-C–lowering levels and tolerability in patients with established CVD. We aimed to analyze the efficacy and safety of a fixed-dose rosuvastatin and ezetimibe (R+E) combination therapy in intermediate-risk patients with hypercholesterolemia and no DM after 12 months of visiting a primary physician.

Methods: This multicenter, open-label, single-arm, prospective observational study involved 5717 patients from 258 primary health care centers in Korea enrolled between 2016 and 2018. Patients had no DM or previous CVD but had cardiovascular risk factors and were taking a statin or a fixed-dose combination of E (10 mg) + R (5, 10, or 20 mg). We analyzed 700 patients using propensity score matching.

Findings: A fixed-dose R+E combination therapy significantly reduced LDL-C in 5/10 mg R+E (29.35%), 10/10 mg R+E (36.19%), and 20/10 mg R+E (41.83%) compared with statin monotherapy (19.09%) at 12-month follow-up ($P = 0.017$). Compared with statin monotherapy, HDL-C levels increased in 5/10 mg R+E (mean change at 12 months; $P = 0.004$), and triglyceride levels decreased in 10/10 mg R+E (mean change at 12 months; $P = 0.033$). The fixed-dose R+E combination therapy was associated with fewer adverse events and a neutral effect on glucose deterioration compared with statin monotherapy at 12 months of follow-up.

Implications: In a possible paradigm shift, a fixed-dose R+E combination therapy may be beneficial for primary cardiovascular prevention with potent LDL-lowering efficacy and tolerability; however, further large prospective studies are needed. (*Clin Ther.* 2022;44:698–709.)

Keywords: cardiovascular diseases, dyslipidemia, ezetimibe, glycated hemoglobin A, rosuvastatin.

INTRODUCTION

The prevalence of hypercholesterolemia (defined as a total cholesterol [TC] level ≥240 mg/dL or the use of lipid-lowering drugs) increased markedly from 8.8% in

*These authors contributed equally to this work.

Accepted for publication March 3, 2022
https://doi.org/10.1016/j.clinthera.2022.03.004
0149-2918/$ - see front matter

2007 to 18.0% in 2018, according to the 2007-2018 Korea National Health and Nutrition Examination Survey and National Health Insurance Service data.[1] In 2018, 45.6% of men and 31.3% of women older than 20 years were diagnosed with dyslipidemia when defined as satisfying 1 of the following criteria: serum lowLDL-C level ≥160 mg/dL, serum HDL level <40 mg/dL, and serum triglyceride (TG) level ≥200 mg/dL. Considering cardiovascular risk factors, such as hypertension, smoking, and cardiovascular family history, the cutoff level of LDL to define dyslipidemia is lower and the prevalence of dyslipidemia may be considerably higher. Despite advances in dyslipidemia treatment modalities, its prevalence in Korea has continuously increased from 2010 to 2015.[2]

LDL-lowering therapy is essential for the secondary and primary prevention of cardiovascular disease (CVD). Statin therapy is the first choice for LDL-lowering treatment. Ezetimibe was approved by the US Food and Drug Administration in 2002 and is a new class of cholesterol-lowering agents that inhibit cholesterol absorption in the intestine.[3] Ezetimibe monotherapy lowers LDL-C by approximately 18%.[4] However, greater cholesterol-lowering efficacy is achieved with coadministration of statins, with 21% to 30% additional LDL-C lowering efficacy compared with statin therapy.[5,6] Combination therapy of statin and ezetimibe not only has a greater LDL-C–lowering effect than statin monotherapy[7] but also produces additional cardiovascular risk reduction in several studies, such as in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial.[8]

Statin therapy also produces cardiovascular benefits in patients with cardiovascular risk factors without established atherosclerotic vascular disease. Treatment with rosuvastatin (10 mg/d) lowered cardiovascular events by approximately 24% (hazards ratio [HR] = 0.76; 95% CI, 0.64–0.88) in intermediate-risk patients according to the Heart Outcomes Prevention Evaluation 3 trial.[9] In that study, some adverse events (AEs), such as cataract surgery ($P = 0.02$) and muscle-related symptoms ($P = 0.005$) were reported, although there was no significant excess development of diabetes mellitus (DM) and cancers. A higher statin dose treatment of 20 mg of rosuvastatin in apparently healthy persons reduced primary major cardiovascular events by approximately 44% (HR = 0.46; 95% CI, 0.46–0.69) in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin study.[10] However, administration of 20 mg of rosuvastatin increased the incidence of newly diagnosed DM by 25% (20 mg of rosuvastatin, 3%; placebo, 2.4%; $P = 0.01$). In primary cardiovascular prevention, greater LDL-C lowering results in a better clinical outcome. Despite the definite benefits of statin treatment, high-dose statin therapy has been associated with AEs, such as the development of DM and muscle symptoms. In this study, we aimed to analyze the efficacy and safety of fixed-dose rosuvastatin and ezetimibe (R+E) combination therapy in intermediate-risk patients without DM and with dyslipidemia during a 12-month follow-up period.

METHODS

Study Design

This multicenter, open-label, single-arm, prospective observational study involved 5717 enrolled patients between 2016 and 2018 from 258 primary health care centers. The clinical trial protocol and method of obtaining informed consent were approved by the Korean Food and Drug Administration and the local ethics review boards of each hospital. The study was conducted in accordance with the ethics principles of the current Declaration of Helsinki, and patients signed informed consent documents before any relevant laboratory tests being conducted.

Study Population

Patients who met the following eligibility criteria for dyslipidemia of the Korean Society of Lipid and Atherosclerosis were enrolled: (1) LDL-C level >100 mg/dL in previous statin users, (2) LDL-C level >130 mg/dL with >2 risk factors, and (3) LDL-C level >160 mg/dL with 1 or no risk factors. Five risk factors to stratify the need for lipid-lowering agents without established CVD were as follows: (1) age (men, ≥45 years; women, ≥55 years); (2) family history of early-onset coronary artery disease; (3) hypertension; (4) history of smoking; and (5) low HDL-C level (<40 mg/dL). Intermediate-risk patients were defined as an annual risk of major cardiovascular events of approximately 1%. All the participants in this study cohort were of Asian ethnicity (domestic Korean). Primary physicians could decide to prescribe moderate-intensity statins or statins and ezetimibe combination therapy in statin-naive patients with dyslipidemia. They could change the statin-to-statin and ezetimibe

combination in previous statin users for further LDL lowering.

Patients were eligible for this study if they met the following inclusion criteria to rule out DM at the first visit: (1) no history of a diagnosis of type 2 DM, (2) no history of prescribed glucose-lowering agents, and (3) no typical DM symptoms (polyuria, polydipsia, and unexplained weight loss). Exclusion criteria in this study were (1) known DM, (2) pregnant or lactating women, and (3) those receiving corticosteroid treatment. The follow-up visits were at 6 and 12 months after enrollment. At each visit, all participants were examined by physicians on prescribed days and on observed days concerning additional medicine and any symptoms (myalgia, muscle weakness, or nausea). Blood tests were performed to determine lipid profiles in the early morning, 8 hours after midnight fasting. To discriminate between newly diagnosed DM, glycated hemoglobin (HbA_{1c}), fasting blood glucose, and, if possible, 2-hour blood glucose levels after a 75-g oral glucose tolerance test were examined. Additional visits were permitted based on physicians' decisions or if the patients wished to evaluate the efficacy and tolerability of the medication.

Outcome Measurements

The primary end points of this study were mean change absolute decrease in LDL-C levels from baseline to after 12 months of treatment with statin or fixed-dose R+E combination therapy. The secondary end points were mean change and absolute decrease in LDL-C levels from baseline to 6 months using statin treatment or fixed-dose R+E combination therapy. The mean change and absolute decrease in TG, HDL-C, and TC from baseline to 6 months and at 12 months were also evaluated. Tolerability was assessed based on the incidence of AEs and development of new-onset type 2 DM in terms of the following: HbA_{1c} level $\geq$6.5%, fasting blood glucose level after 8 hours of fasting $\geq$126 mg/dL, 2-hour blood glucose level after a 75-g oral glucose tolerance test $\geq$200 mg/dL, or typical DM symptoms (polyuria, polydipsia, and unexplained weight loss), with random blood glucose levels $\geq$200 mg/dL.

Statistical Analysis

All statistical analyses were performed using R software, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). This observational study used 1-to-3 propensity score matching to minimize confounding bias. In total, 700 patients (statin monotherapy group, n = 175; fixed-dose R+E combination therapy group, n = 525) were selected using the propensity score, which was adjusted for age, sex, body mass index (BMI), prior medical history, the status of preceding drugs for dyslipidemia, duration of dyslipidemia, smoking status, and alcohol consumption status.

The primary end point was calculated for each group (statin monotherapy and fixed-dose R+E combination therapy) as the difference between baseline and 12 months in LDL-C levels using a paired *t* test. Moreover, we used a 2-sample *t* test to examine whether there was a significant reduction in LDL-C levels between patients in the statin group and in the fixed-dose R+E combination groups. Furthermore, we performed ANOVA among 3 specified fixed-dose R+E combination groups according to rosuvastatin doses (5, 10, and 20 mg).

Similarly, we calculated the primary end points and computed the secondary end points using paired *t* and 2-sample *t* tests and ANOVA. However, we added a comparison between baseline and 6 months, and we assessed not only LDL-C but also HDL-C, TG, and TC levels.

In the case of AEs, we standardized AEs according to MedDRA (version 19.0) and prioritized preferred term and system organ class. We calculated the number of patients with AEs and AE cases with these proportions using AE classes. AE classes include AEs, serious AEs, adverse drug reactions (ADRs), and serious ADRs. We used the Fisher exact test for the contingency table because the expected values were <5. In addition, we presented the number of patients with AEs and the proportion of each group in terms of the result, severity, appropriate measures, treatment status, and relation to drugs with AEs and measured the relative risk of new-onset DM and AEs in the entire sample.

RESULTS

Baseline Characteristics

In total, 700 patients were included in the analysis with propensity score matching. Patients were divided into statin monotherapy (n =175) and fixed-dose R+E combination therapy (5/10 mg, n = 280; 10/10 mg, n = 196; 20/10 mg, n = 49) groups. Mean (SD) age was similar in both statin monotherapy (61.06 [11.03] years) and fixed-dose R+E combination

Table I. Baseline characteristics of participants.

Characteristic	Statin (n = 175)	R+E (n = 525)	5/10 mg R+E (n=280)	10/10 mg R+E (n=196)	20/10 mg R+E (n=49)	F/χ^2	*P*
Age, mean (SD), y	61.06 (11.03)	60.58 (11.02)	60.85 (10.85)	61.04 (10.95)	57.16 (11.94)	1.831	0.140
Sex, No. (%)							
Male	88 (12.6)	271 (38.7)	132 (18.9)	113 (16.1)	26 (3.7)	5.240	0.155
Female	87 (12.4)	254 (36.3)	148 (21.1)	83 (11.9)	23 (3.3)		
Current smoker, No. (%)	25 (14.3)	77 (14.7)	37 (13.2)	31 (15.8)	9 (18.3)	3.124	0.425
BMI, mean (SD), kg/m^2	25.21 (3.52)	25.20 (3.19)	24.98 (3.05)	25.33 (3.41)	25.98 (2.96)	1.465	0.223
LDL-C, mg/dL	109.51 (40.64)	118.13 (49.23)	117.01 (49.76)	118.57 (49.06)	122.82 (47.53)	1.675	0.171
HDL-C, mg/dL	53.19 (11.10)	50.88 (12.73)	50.88 (12.88)	50.85 (13.04)	51.03 (10.66)	1.523	0.207
TG, mg/dL	149.33 (78.93)	169.46 (95.52)	166.52 (88.64)	176.36 (108.13)	158.63 (77.94)	2.803	0.039
TC, mg/dL	186.56 (45.95)	193.42 (54.90)	193.01 (54.92)	193.34 (55.32)	196.09 (54.09)	0.785	0.503

BMI = body mass index; R+E = fixed-dose rosuvastatin and ezetimibe combination therapy; TC = total cholesterol; TG = triglyceride.

therapy groups (60.58 [11.02] years), although the 20/10 mg R+E group was relatively younger but without significant difference. The sex ratio in all groups was 1:1 for men and women. The mean (SD) BMI of all patients was 25.21 (3.27) kg/m^2, and no significant differences were found among the groups. Baseline mean (SD) LDL-C levels for each group were 109.51 (40.64) mg/dL in the statin monotherapy group and 118.13 (49.23) mg/dL in the fixed-dose R+E combination therapy groups. Baseline TC, HDL-C, and TG levels were not significantly different between the groups, except for the TG level in the 10/10 mg R+E group, which was higher than that of the statin monotherapy group (176.36 [108.13] mg/dL vs 149.33 [78.93] mg/dL; $P < 0.005$) (Table I).

Primary Outcomes

Statin monotherapy lowered mean (SD) LDL-C levels to approximately 20.90 (42.09) mg/dL (19.09%) from baseline after 12 months. Patients treated with fixed-dose R+E combination therapy (all dose sum) had lower mean (SD) LDL-C levels of approximately 39.13 (45.15) mg/dL (33.12%) from baseline after 12 months. The LDL-lowering efficacy of the fixed-dose R+E combination therapy was dose dependent (5/10 mg R+E, 34.34 [45.49] mg/dL[29.35%]; 10/10 mg R+E, 42.91 [43.58] mg/dL [36.19%]; and 20/10 mg R+E, 51.37 [46.51] mg/dL [41.83%]; $P = 0.017$) (Table II and Figure 1). Target LDL achievement of <100 mg/dL was similar in the statin monotherapy group (64.63%) and in the fixed-dose R+E combination therapy groups (69.11%) ($P = 0.5212$). Fixed-dose R+E combination therapy also had the following dose-dependent target LDL achievement rates: 59.76% in the 5/10 mg R+E group, 76.72% in the 10/10 mg R+E group, and 88.24% in the 20/10 mg R+E group. Target LDL achievement of <70 mg/dL had significant differences in the statin monotherapy group (19.51%) and the fixed-dose R+E combination therapy groups (35.35%) ($P = 0.009$). Fixed-dose R+E combination therapy reached <70 mg/dL with dose-dependent efficacy (5/10 mg R+E,

Table II. LDL-C and percent change from baseline after treatment of statin or R+E.

Group	Baseline, Mean (SD)	12 Months					
		Mean (SD)	*P*	Mean (SD) Change	Change, %	2-Sample *t* Test *P*	ANOVA *P*
Statin (n = 175)	109.51 (40.64)	88.60 (24.68)	<0.001	−20.90 (42.09)	−19.09		
R+E (n = 525)	118.13 (49.23)	79.00 (31.49)	<0.001	−39.13 (45.15)	−33.12	<0.001	
5/10 mg R+E (n = 280)	117.01 (49.76)	82.66 (33.27)	<0.001	−34.34 (45.49)	−29.35	0.001	0.017
10/10 R+E (n = 196)	118.57 (49.06)	75.66 (28.31)	<0.001	−42.91 (43.58)	−36.19	<0.001	
20/10 mg R+E (n = 49)	122.82 (47.53)	71.45 (30.92)	<0.001	−51.37 (46.51)	−41.83	<0.001	

R+E = fixed-dose rosuvastatin and ezetimibe combination therapy.

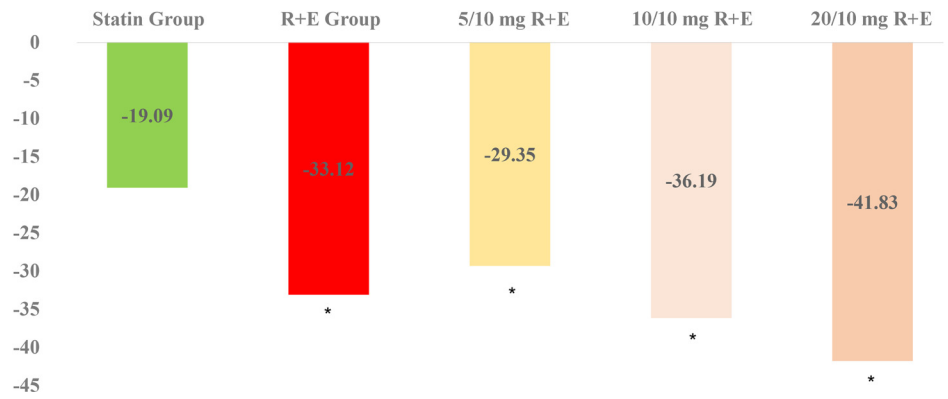

Figure 1. LDL-lowering efficacy at 12 months with statin or fixed-dose combination of rosuvastatin and ezetimibe (R+E) treatment. Asterisk indicates 2-sample *t* test $P < 0.001$ versus statin group.

29.27%; 10/10 mg R+E, 38.79%; and 20/10 mg R+E, 52.94%), and significant differences were identified in 10/10 mg R+E group ($P = 0.0062$) and 20/10 mg R+E group ($P = 0.0007$) compared with statin monotherapy (Table III and Supplemental Figure 1).

Secondary Outcomes

The mean (SD) LDL-lowering efficacy of R+E combination therapy (−33.00 [43.40] mg/dL) was also higher than statin monotherapy (−19.92 [41.02] mg/dL) at 6 months of follow-up. Mean (SD) HDL-C levels did not change significantly with statin monotherapy (0.07 [9.89] mg/dL, $P = 0.9246$ at 6 months; −1.03 [9.38] mg/dL, $P = 0.1477$ at 12 months). Fixed-dose R+E combination therapy significantly increased mean (SD) HDL-C levels at 12-month follow-up (1.24 [10.99] mg/dL, $P = 0.08$ at 12 months). The increase in HDL-C was shown predominantly in the 5/10 mg R+E group (3.71% at 12 months, $P = 0.0035$). Fixed-dose R+E combination therapy lowered serum TG levels approximately 11.0% compared with 6% in statin monotherapy. TG-lowering efficacy was prevalent in the 10/10 mg R+E (15.29%, $P = 0.048$) and 20/10 R+E mg (23.88%,

Table III. LDL-C achievement rate after 12 months of treatment of statin or R+E.

Group	Baseline >100, No.	12 Months					
		≤100, No.	Reach, %	χ^2 Test *P*	≤70, No.	Reach, %	χ^2 Test *P*
Statin (n = 175)	82	53	64.63		16	19.51	
R+E (n = 525)	314	217	69.11	0.521	111	35.35	0.009
5/10 mg R+E (n = 280)	164	98	59.76	0.547	48	29.27	0.136
10/10 mg R+E (n = 196)	116	89	76.72	0.089	45	38.79	0.006
20/10 mg R+E (n = 49)	34	30	88.24	0.019	18	52.94	0.001

R+E = fixed-dose rosuvastatin and ezetimibe combination therapy.

P = 0.0148) groups at 6 months and in the 10/10 mg R+E (16.38%, *P* = 0.0333) group at 12 months (Table IV Figures 2A and B).

Tolerability Outcome

HbA_{1c} and fasting glucose levels were monitored in 33 of 175 patients (18.86%) with statin monotherapy and in 149 of 525 patients (28.38%) with fixed-dose R+E combination therapy. Statin monotherapy did not increase HbA_{1c} (−0.09% [0.23%], *P* = 0.1498) and fasting glucose (0.54 [12.02] mg/dL, *P* = 0.7263) levels at 6 and 12 months. All doses of fixed-dose R+E combination therapy produced no significant change in HbA_{1c} (−0.05% [0.29%], *P* = 0.0853) and fasting glucose (0.37 [13.08] mg/dL, P = 0.7030) levels; however, at 12 months, 5/10 mg R+E therapy was associated with significantly lower HbA_{1c} (−0.10% [0.25%], *P* = 0.0021) levels, although no change in fasting glucose was observed (Supplemental Table I).

New-onset DM was evaluated through measuring HbA_{1c}, fasting glucose and random glucose levels, and newly diagnosed reports. During the 12-month study period, the incidence of new-onset DM in statin monotherapy was 0.64% (n = 5). The incidence of new-onset DM did not differ between the fixed-dose R+E combination groups (0.47%, n = 23), although the highest incidence was observed in the 20/10 mg R+E (1.81%, n = 6) group (Supplemental Table II).

Elevated liver enzyme levels were reported in 3 patients (1.71%) in the statin monotherapy group and in 2 patients (0.38%) in the fixed-dose R+E combination therapy group, which were unrelated to dose. Concerns of musculoskeletal and connective tissue disorders, including myalgia, were reported in 4 patients (2.28%) in the statin monotherapy group and in 8 patients (1.52%) in the fixed-dose R+E combination groups, which were unrelated to dose.

Composite ADRs and serious ADRs did not differ significantly between the statin monotherapy group and the fixed-dose R+E combination groups. Moreover, no patients stopped taking medication because AEs, as summarized in Table V, with detailed data shown in Supplemental Table III.

DISCUSSION

This propensity-weighted, real-world analysis compared the cholesterol-lowering efficacy and tolerability of a fixed-dose R+E combination therapy with statin monotherapy in Korean patients with non-DM dyslipidemia. A fixed-dose R+E combination therapy lowered LDL-C more than statin monotherapy without increasing AEs or deterioration in glycemic control status. The lowest dose of R+E combination (5/10 mg) therapy was most preferentially prescribed by primary care physicians. The 5/10 mg R+E dose had more potent LDL-C lowering than statin monotherapy and was the most tolerable in terms of glycemic control, with improvement in HbA_{1c} levels and no increase in new-onset DM up to the end of the 12-month follow-up period.

In this real-world analysis of R+E combination therapy, LDL-C–lowering efficacy was relatively lower than that in randomized controlled studies. In a

Table IV. Lipid profiles changes from baseline at 6 months and 12 months with statin or R+E.

Group	Baseline, Mean (SD)	6 Months					12 Months				
		Mean (SD)	Paired *t* Test *P*	Mean Change	2-Sample *t* Test *P*	ANOVA *P*	Mean (SD)	Paired *t* Test *P*	Mean Change	2-Sample *t* Test *P*	ANOVA *P*
				LDL-C, mg/dL							
Statin (n = 175)	109.51 (40.64)	89.59 (26.26)	<0.001	-19.92 (41.02)			88.60 (24.68)	<0.001	-20.90(42.09)		
R+E (n = 525)	118.13 (49.23)	85.14 (36.07)	<0.001	-33.00 (43.40)	<0.001		79.00 (31.49)	<0.001	−39.13 (45.15)	<0.001	
5/10 mg R+E (n = 280)	117.01 (49.76)	90.76 (35.98)	<0.001	-26.25 (41.00)	0.110	<0.001	82.66 (33.27)	<0.001	−34.34 (45.49)	0.001	0.017
10/10 mg R+E (n = 196)	118.57 (49.06)	81.14 (36.45)	<0.001	-37.43 (43.94)	<0.001		75.66 (28.31)	<0.001	−42.91 (43.58)	<0.001	
20/10 mg R+E (n = 49)	122.82 (47.53)	69.01 (27.69)	<0.001	-53.81 (45.46)	<0.001		71.45 (30.92)	<0.001	−51.37 (46.51)	<0.001	
		HDL-C, mg/dL									
Statin (n = 175)	53.19 (11.10)	53.26 (11.23)	0.925	0.07 (9.89)			52.15 (11.82)	0.148	−1.03 (9.38)		
R+E (n = 525)	50.88 (12.73)	51.74 (12.61)	0.029	0.86 (9.00)	0.351		52.12 (13.06)	0.010	1.24 (10.99)	0.008	
5/10 mg R+E (n = 280)	50.88 (12.88)	51.50 (12.39)	0.244	0.62 (8.95)	0.547	0.717	52.76 (13.34)	0.007	1.89 (11.69)	0.004	0.356
10/10 mg R+E (n = 196)	50.85 (13.04)	51.84 (12.77)	0.142	0.98 (9.32)	0.363		51.35 (13.29)	0.509	0.50 (10.55)	0.140	
20/10 mg R+E (n = 49)	51.03 (10.66)	52.75 (13.39)	0.145	1.71 (8.09)	0.236		51.56 (10.32)	0.653	0.53 (8.15)	0.256	
		TG, mg/dL									
Statin (n = 175)	149.33 (78.93)	138.94 (65.01)	0.061	−10.39 (72.99)			139.80 (65.26)	0.096	−9.53 (75.20)		
R+E (n = 525)	169.46 (95.52)	152.28 (80.35)	<0.001	−17.18 (85.46)	0.309		151.22 (78.14)	<0.001	−18.24 (90.43)	0.209	

(*continued on next page*)

Table IV. (*continued*)

Group	Baseline, Mean (SD)	6 Months					12 Months				
		Mean (SD)	Paired *t* Test *P*	Mean Change	2-Sample *t* Test *P*	ANOVA *P*	Mean (SD)	Paired *t* Test *P*	Mean Change	2-Sample *t* Test *P*	ANOVA *P*
5/10 mg R+E (n = 280)	166.52 (88.64)	159.81 (84.34)	0.191	−6.71 (85.73)	0.625	0.008	155.35 (77.62)	0.034	−11.17 (87.90)	0.832	0.108
10/10 mg R+E (n = 196)	176.36 (108.13)	149.40 (78.55)	<0.001	−26.96 (87.43)	0.048		147.47 (82.86)	<0.001	−28.88 (98.75)	0.033	
20/10 mg R+E (n = 49)	158.63 (77.94)	120.76 (51.85)	<0.001	−37.88 (66.94)	0.015		142.62 (59.26)	0.083	−16.01 (63.21)	0.545	
		TC, mg/dL									
Statin (n = 175)	186.56 (45.95)	164.57 (29.39)	<0.001	−21.99 (46.72)			162.71 (29.99)	<0.001	−23.85 (48.03)		
R+E (n = 525)	193.42 (54.90)	158.86 (41.46)	<0.001	-34.56 (48.60)	0.003		154.24 (36.94)	<0.001	−39.18 (50.36)	<0.001	
5/10 mg R+E (n = 280)	193.01 (54.92)	165.65 (40.37)	<0.001	-27.37 (48.16)	0.239	<0.001	160.51 (38.02)	<0.001	−32.50 (50.71)	0.068	0.002
10/10 mg R+E (n = 196)	193.34 (55.32)	154.27 (42.84)	<0.001	-39.08 (46.67)	0.001		148.45 (34.41)	<0.001	−44.90 (48.44)	<0.001	
20/10 mg R+E (n = 49)	196.09 (54.09)	138.49 (32.51)	<0.001	-57.61 (50.26)	<0.001		141.56 (33.95)	<0.001	−54.53 (50.72)	<0.001	

R+E = fixed-dose rosuvastatin and ezetimibe combination therapy; TC = total cholesterol; TG = triglyceride.

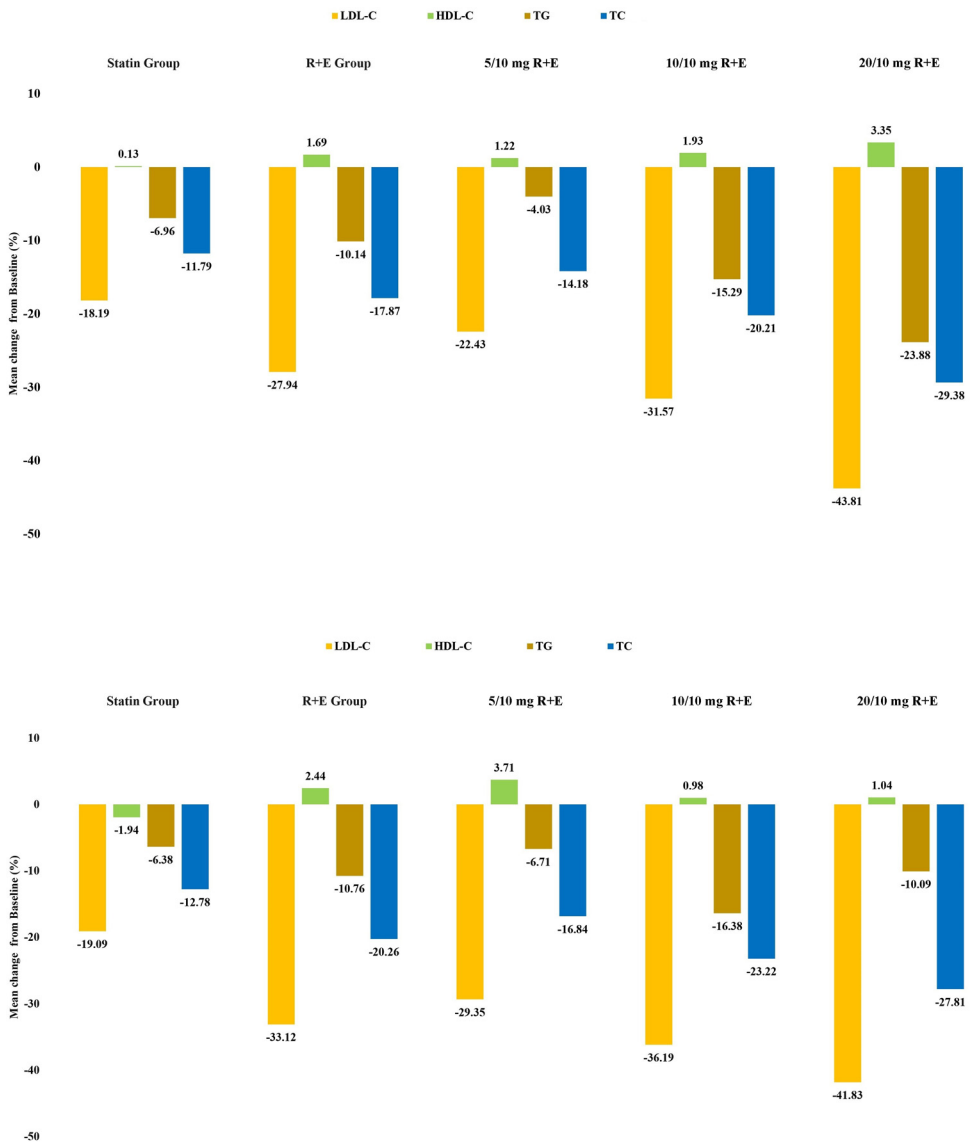

Figure 2. Change in LDL-C, HDL-C, triglyceride (TG), and total cholesterol (TC) levels at 6 months (A) and 12 months (B) with statin or fixed-dose combination of rosuvastatin and ezetimibe (R+E) treatment.

multicenter, randomized study of R+E (Multicenter Randomized Study of Rosuvastatin and Ezetimibe), R+E combination therapy lowered LDL-C levels approximately 59% from baseline to drug-naive primary hypercholesterolemia in Korea. The combination of the lowest dose (5/10 mg) of R+E lowered LDL-C levels approximately 56%, from a mean of 148 to 66 mg/dL at 8 weeks. The difference in LDL-C–lowering efficacy was approximately 10.9% between rosuvastatin monotherapy and R+E combination therapy.[11] In the Ildong Rosuvastatin & Ezetimibe randomized controlled trial, R+E combination therapy also lowered LDL-C levels approximately 57% from baseline to primary hypercholesterolemia in Korea. The 5/10 mg R+E combination therapy had a similarly high LDL-C–lowering efficacy of 51.8% from a mean of 160.7 to 76.9 mg/dL at 8 weeks, and the LDL-lowering efficacy difference was 11.3% compared with 5-mg rosuvastatin monotherapy. The participants who were previous statin users had stopped statin use during

Table V. Adverse events at 12 months.

	Statin Group (n = 175)		R+E (n = 525)		5/10 mg R+E (n = 280)		10/10 mg R+E (n = 196)		20/10 mg R+E (n = 49)	
	No. (%)	No. of Events	No. (%)	No. of Events	n (%)	No. events	No. (%)	No. of Events	No. (%)	No. of Events
Adverse events	19 (10.90)	28	27 (5.14)	50	9 (3.21)	9	14 (7.14)	36	4 (8.16)	5
Fisher exact test *P*			0.013		0.002		0.273		0.791	
Serious adverse events	3 (1.71)	3	1 (0.19)	1	0 (0.00)	0	1 (0.51)	1	0 (0.00)	0
Fisher exact test *P*			0.050		0.056		0.347		>0.99	
Adverse drug reactions	0 (0.00)	0	11 (2.10)	11	5 (1.79)	5	5 (2.55)	5	1 (2.04)	1
Fisher exact test *P*			0.074		0.162		0.063		0.219	
Serious adverse drug reactions	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
Fisher exact test *P*			>0.99		>0.99		>0.99		>0.99	

R+E = fixed-dose rosuvastatin and ezetimibe combination therapy.

4 weeks of the run-in period; thus, baseline LDL-C levels were somewhat high.[12] In our real-world analysis, previous statin users changed to other statins or a fixed-dose R+E combination therapy immediately after visiting primary care without a statin-free period. Thus, the baseline LDL-C level (statin monotherapy, 109.51 mg/dL; fixed-dose combination of R+E, 118.13 mg/dL) was lower than that in randomized controlled studies. Although the LDL-C–lowering efficacy of R+E was lower (33.12%), the reached mean LDL-C level at 12 months was 79 mg/dL, and the difference with statin monotherapy was 14.03%. Considering drug adherence in real-world data and no statin washout period, fixed-dose R+E combination therapy had consistent LDL-C efficacy compared with statin monotherapy.

Representative statin-associated AEs are myopathy, myalgia, hepatic enzyme elevation, and increased new-onset DM. Although the benefit of statin treatment for the prevention of cardiovascular events outweighs the disadvantages,[13] the most common cause of discontinued statin therapy is statin-associated AEs.[14] Statin-associated AEs are more prevalent in high-dose statin use or high-intensity statin use than in low-dose or low-potency use.[15]

Ezetimibe is a synthetic 2-azetidinone that acts through inhibiting sterol absorption in the intestine. Ezetimibe monotherapy reduced LDL-C levels by a mean of 17% in 2 randomized controlled trials of patients with primary hypercholesterolemia.[16,17] Although it has a low LDL-lowering potency (<30% reduction), ezetimibe monotherapy is consistently tolerable, and the incidence of muscle-related AEs is relatively low (<1%). In the Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3 study, patients who were statin intolerant and who presented with muscle symptoms or muscle enzyme elevation when taking >2 statins were tolerant when switching therapy to 10 mg/d of ezetimibe or 420 mg/mo of evolocumab.[18] Although the exact mechanism remains unknown, ezetimibe and PCSK9i are very tolerable to patients with hypercholesterolemia and a higher rate of muscle-related AEs due to statin therapy, irrespective of low

LDL levels. PCSK9i is also new therapeutic strategy with potent LDL-C–lowering efficacy and tolerability to statin-intolerant patients. Considering the injectable therapy and cost, the ezetimibe and statin combination therapy is preferable strategy. The addition of ezetimibe to statin therapy also did not aggravate muscle-related AEs despite the higher LDL-lowering efficacy of an additional 17% to 25% lowering compared with statin monotherapy.[19]

Statin therapy, which varies depending on potency, dose, and lipophilicity, is associated with increased insulin resistance, fasting glucose, and the incidence of new-onset DM in clinical studies, especially in patients with baseline DM risk factors (higher fasting glucose, BMI, TG, and history of hypertension).[20] In contrast to statin therapy, ezetimibe monotherapy improved insulin resistance in patients with non-DM metabolic syndrome[21] and lowered fasting glucose and HbA_{1c} levels in patients with type 2 DM.[22] Although there is a paucity of large clinical trials evaluating the tolerability of new-onset DM with statin and ezetimibe combination therapy, 1 study reported that the addition of ezetimibe to statins did not increase fasting glucose levels compared with statin monotherapy during 96 weeks in patients with non-DM hypercholesterolemia.[23] In a retrospective study that followed up patients for a mean of 7 years, moderate-intensity statin and ezetimibe combination therapy neutralized the increased prevalence rate for new-onset DM compared with high-intensity statin therapy in patients with pre-DM hypercholesterolemia.[24]

This study has several limitations. The baseline characteristics were not enough to explain all the cardiovascular risks being instructed in real-world analysis. Because we did not allocate the kinds of statin and statin doses, the differences of statin potency might affect the LDL-lowering efficacy and tolerability in the statin monotherapy group. In addition, the adherence for statin and R+E combination therapy was not evaluated in this study. The variant adherence of medications might be associated with low absolute reduction of LDL-C in R+E combination therapy compared with other randomized controlled trials.

CONCLUSIONS

Fixed-dose R+E combination therapy resulted in high cholesterol-lowering efficacy, tolerable muscle-related AEs, and a neutral effect on glucose metabolism (and even lower HbA_{1c} levels with 5/10 mg R+E combination therapy) compared with statin monotherapy in real-world clinical situations. Additional large clinical studies are recommended to further validate these findings in relation to CVD prevention. In a possible paradigm shift, a fixed-dose R+E combination therapy may be beneficial for primary cardiovascular prevention with potent LDL-lowering efficacy and tolerability.

ACKNOWLEDGMENTS

All authors were involved in the conception, design of the study, and analysis or interpretation of the data. Jun Hwa Hong and Ung Jeon were involved in drafting the manuscript. All authors approved the final version of the manuscript, including the authorship list.

FUNDING SOURCES

The research was supported by Hanmi Pharmaceutical Co Ltd (Seoul, Republic of Korea). The sponsor supported the supply of the investigational products, laboratory tests, and clinical research coordinator expenses.

DECLARATION OF INTEREST

None.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2022.03.004.

REFERENCES

1. Korea Centers for Disease Control and Prevention. *Korea Health Statistics 2018: Korea National Health and Nutrition Examination Survey (KNHANES VII-3)*. Ministry of Health and Welfare; 2020.
2. Jeong JS, Kwon HS. Prevalence and Clinical Characteristics of Dyslipidemia in Koreans. *Endocrinology and metabolism (Seoul, Korea)*. 2017;32:30–35.
3. Earl J, Kirkpatrick P. Ezetimibe. *Nature Reviews Drug Discovery*. 2003;2:97–98.
4. Dujovne CA, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. *Am J Cardiol*. 2002;90:1092–1097.
5. Pearson TA, et al. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. *Mayo Clin Proc*. 2005;80:587–595.

6. Hildemann SK, et al. Dual cholesterol inhibition with ezetimibe/simvastatin in pre-treated hypercholesterolaemic patients with coronary heart disease or diabetes mellitus: prospective observational cohort studies in clinical practice. *Curr Med Res Opin*. 2007;23:713–719.
7. Strilchuk L, et al. An overview of rosuvastatin/ezetimibe association for the treatment of hypercholesterolemia and mixed dyslipidemia. *Expert Opin Pharmacother*. 2020;21:531–539.
8. Cannon CP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med*. 2015;372:2387–2397.
9. Yusuf S, et al. Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. *N Engl J Med*. 2016;374:2021–2031.
10. Ridker PM, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195–2207.
11. Kim KJ, et al. Effect of fixed-dose combinations of ezetimibe plus rosuvastatin in patients with primary hypercholesterolemia: MRS-ROZE (Multicenter Randomized Study of ROsuvastatin and eZEtimibe). *Cardiovasc Ther*. 2016;34:371–382.
12. Hong SJ, et al. A Phase III, Multicenter, Randomized, Double-blind, Active Comparator Clinical Trial to Compare the Efficacy and Safety of Combination Therapy With Ezetimibe and Rosuvastatin Versus Rosuvastatin Monotherapy in Patients With Hypercholesterolemia: I-ROSETTE (Ildong Rosuvastatin & Ezetimibe for Hypercholesterolemia) Randomized Controlled Trial. *Clin Ther*. 2018;40:226–241 e4.
13. Newman CB, et al. Statin Safety and Associated Adverse Events: A Scientific Statement From the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2019;39:e38–e81.
14. Zhang H, et al. Discontinuation of statins in routine care settings: a cohort study. *Annals of internal medicine*. 2013;158:526–534.
15. Silva M, et al. Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. *Clin Ther*. 2007;29:253–260.
16. Dujovne CA, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. *The American Journal of Cardiology*. 2002;90:1092–1097.
17. Knopp RH, et al. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. *European Heart Journal*. 2003;24:729–741.
18. Nissen SE, et al. Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial. *Jama*. 2016;315:1580–1590.
19. Davidson MH, et al. Striated Muscle Safety of Ezetimibe/Simvastatin (Vytorin). *The American Journal of Cardiology*. 2006;97:223–228.
20. Navarese EP, et al. Meta-Analysis of Impact of Different Types and Doses of Statins on New-Onset Diabetes Mellitus. *The American Journal of Cardiology*. 2013;111:1123–1130.
21. Nakamura A, et al. Impact of decreased insulin resistance by ezetimibe on postprandial lipid profiles and endothelial functions in obese, non-diabetic-metabolic syndrome patients with coronary artery disease. *Heart and Vessels*. 2019;34:916–925.
22. Nozue T, Michishita I, Mizuguchi I. Effects of ezetimibe on glucose metabolism in patients with type 2 diabetes: A 12-week, open-label, uncontrolled, pilot study. *Curr Ther Res Clin Exp*. 2010;71:252–258.
23. Toth PP, et al. Ezetimibe Does Not Increase Fasting Glucose Levels More Than Statins Alone in Non-Diabetic, Hypercholesterolemic Patients. *Journal of the American College of Cardiology*. 2015;65:A1633.
24. Barkas F, et al. Statin therapy with or without ezetimibe and the progression to diabetes. *J Clin Lipidol*. 2016;10:306–313.

Address correspondence to: Won-Yong Shin, MD, PhD, Division of Cardiology, Department of Internal Medicine, School of Medicine, Soonchunhyang University Cheonan Hospital, Soonchunhyang 6 gil 31, Dongnam-gu, Cheonan, Chungcheongnam-do, 31151, Republic of Korea. E-mail: shinwonyong@naver.com.