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A Retrospective Study of LDL-Cholesterol in Koreans on Atorvastatin/Ezetimibe or Atorvastatin Monotherapy

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Abstract

Purpose: To investigate low-density lipoprotein cholesterol (LDL-C) goal attainment rates in patients with hypercholesterolemia treated with atorvastatin/ezetimibe or atorvastatin monotherapy.

Methods: This was a multicenter, noninterventional, retrospective, chart review study of Korean patients with hypercholesterolemia who were statin-naïve and prescribed atorvastatin/ezetimibe or atorvastatin monotherapy during an observational period, from January 2014 to July 2017, and followed up for 12–18 weeks. Patients were propensity score matched to reduce treatment selection bias. Outcomes included LDL-C goal attainment rate at week 12, defined by risk groups according to Korean Society of Lipidology and Atherosclerosis guidelines; and change in lipid parameters from the index date to week 12.

Results: A total of 969 patients were enrolled in the study: atorvastatin/ezetimibe, n = 349; atorvastatin monotherapy, n = 620. Following propensity matching (n = 316 in each group), respective LDL-C goal attainment rates for atorvastatin/ezetimibe and atorvastatin monotherapy groups were 86% and 75%, respectively (p = 0.0004). Atorvastatin/ezetimibe produced significantly larger reductions at week 12 in mean LDL-C (−50.3% vs −42.7%), total cholesterol (−36.8% vs −30.7%) and non-high-density lipoprotein cholesterol (non-HDL-C; −47.3% vs −39.8%) levels compared to atorvastatin monotherapy (all p < 0.0001).

Conclusion: More patients achieved LDL-C goal attainment with atorvastatin/ezetimibe than with atorvastatin monotherapy, and atorvastatin/ezetimibe was associated with significantly larger reductions in mean LDL-C, total cholesterol and non-HDL-C levels than atorvastatin monotherapy, in Korean patients with hypercholesterolemia in a real-world clinical practice.

Keywords: Hypercholesterolemia; Low-Density Lipoprotein C; Atorvastatin/Ezetimibe; Atorvastatin Monotherapy; Korean patients

Introduction

The Global Burden of Disease 2015 study estimated that during that year there were 422.7 million cases of cardiovascular disease (CVD) and 17.92 million CVD deaths worldwide [1]. Although there has been a dramatic decline in the age-standardized CVD death rate between 1990 and 2015 in all high-income and some middle-income countries, many regions showed a gradual reduction or no change in CVD mortality during this period [1]. In Korea, despite a significant decrease in the total CVD mortality

rate, deaths from ischemic heart disease have increased over a 30-year period (1983–2012) [2].

Hypercholesterolemia is widely recognized as a strong risk factor for CVD and lowering low-density lipoprotein cholesterol (LDL-C) is a primary goal of therapy. Statins (HMG CoA reductase inhibitors) are the most effective LDL-C lowering drugs and are recommended in current blood cholesterol management guidelines [3].

A recent study of more than 12,000 adults who participated in the 2010–2012 Korea National Health and Nutrition Survey (KNHANES), reported an age-standardized prevalence for dyslipidemia of 39.6% [4], which was defined using NCEP ATP III criteria as hyper-LDL-cholesterolemia or hypertriglyceridemia [5]. In addition, the 2015 KNHANES found that approximately one-fifth of Korean adults aged ≥30 years had hypercholesterolemia, defined as serum total cholesterol level ≥240 mg/dL or the use of lipid-lowering medications [6].

Despite the availability of statins, many patients with stable or acute coronary heart disease (CHD) fail to achieve LDL-C targets. Recent results from the Dyslipidemia International Study II (DYSIS II) of patients in the Asia-Pacific region showed that 69% of patients with stable CHD failed to achieve LDL-C <70 mg/dL, and 77% of patients with acute coronary syndrome (ACS) failed to achieve their LDL-C targets [7]. In Korean patients in the DYSIS II study, 57% of CHD patients and 62% of ACS patients failed to achieve their LDL-C targets after 4 months of treatment [8, 9].

Concomitant administration of ezetimibe and a statin achieves more effective LDL-C reduction than statin monotherapy without increasing the risk of side effects from increased statin doses. A randomized clinical trial in 628 patients with primary hypercholesterolemia showed a greater reduction in LDL-C for combined atorvastatin/ezetimibe than for atorvastatin monotherapy [10]. More recently, data from the landmark IMPROVE-IT trial, in high-risk post-ACS patients, showed that ezetimibe 10 mg/simvastatin 40 mg significantly reduced LDL-C levels and the rate of long-term cardiovascular events compared with simvastatin 40 mg monotherapy [11].

There is currently a lack of evidence for the effectiveness of atorvastatin/ezetimibe as a primary treatment for hypercholesterolemia in the real-world clinical practice setting in Korea. The objective of the current study was to investigate LDL-C goal attainment rates in statin-naïve patients with hypercholesterolemia treated with atorvastatin/ezetimibe or atorvastatin monotherapy in real-world clinical practice in Korea.

Methods

Study Design

This was a multicenter, noninterventional, retrospective, chart review study of patients with hypercholesterolemia treated with a combination of atorvastatin/ezetimibe or atorvastatin monotherapy. Medical records from patients enrolled at 12 sites in Korea were reviewed during the observational period, from January 2014 to July 2017, and those who were statin-naïve and initiated atorvastatin/ezetimibe or atorvastatin monotherapy within this period were enrolled. Patients were followed up for 12–18 weeks from the index date (date of starting treatment), with data collection beginning in August 2017. Data for lipid parameters were collected within 4 weeks prior to the index date and at 12–18 weeks from the index date.

Inclusion and exclusion criteriaStudy Design

AAdult statin-naïve patients with hypercholesterolemia aged ≥19 years at the time of starting treatment with atorvastatin/ezetimibe (10/10 mg or 10/20 mg) or atorvastatin monotherapy (10 mg or 20 mg), between January 2014 and July 2017, were included in the study. Patients were also required to receive treatment with atorvastatin/ezetimibe or atorvastatin monotherapy for at least 12 weeks by July 2017, and have lipid profile results (LDL-C, total cholesterol, triglyceride, and high-density lipoprotein cholesterol [HDL-C]) available at both the index date and at 12 weeks from treatment initiation.

Main exclusion criteria were: patients who had received statin treatment, other than atorvastatin, during the 12-week follow-up period; a very high triglyceride level (≥500 mg/dL) or low LDL-C level (<70 mg/dL) at the index date; patients with severe acute liver disease or severe renal failure; and patients who were prescribed atorvastatin/ezetimibe or atorvastatin for an unapproved indication.

Efficacy analyses

The primary efficacy outcome was the LDL-C goal attainment rate at week 12. This outcome was defined by LDL-C goals in risk groups according to the 2015 Korean Society of Lipidology and Atherosclerosis (KSLA) guidelines [12] as follows: very high risk <70 mg/dL, high risk <100 mg/dL, moderate risk <130 mg/dL, and low risk <160 mg/dL.

Secondary efficacy outcomes were the percentage change in LDL-C, HDL-C, total cholesterol, triglyceride and non-HDL-C levels from the index date to week 12.

The goal attainment rate and changes in lipid parameters were assessed on both unmatched and propensity score matched treatment groups (see Statistical Analysis).

An exploratory analysis of the goal attainment rate and change in lipid parameters was performed in hypercholesterolemia patients with concurrent diabetes.

Statistical analysis

Continuous data were summarized using descriptive statistics (number of subjects, mean, standard deviation [SD], median, minimum, maximum) and compared using Student's t-test. Categorical data were summarized using frequency and percentage and compared by the chi-squared test. For the difference in LDL-C goal attainment rate between two treatment groups, statistical significance was determined using the chi-squared test.

Results for the rate of change in lipid parameters were expressed as least square mean (LSM) and standard error (SE) for each treatment, and LSM difference with SE and 95% CI. Differences

between the two treatment groups for lipid parameters were calculated by analysis of covariance (ANCOVA) with adjusting baseline characteristics (unmatched groups) and paired t-tests (matched groups).

All statistical analyses were performed as two-tailed tests at a 5% significance level and carried out using SAS Software version 9.4 or higher.

Propensity score matching was conducted to reduce treatment selection bias in the two treatment groups due to confounding variables including age, sex, center, baseline LDL-C, risk classification, statin dosage, diabetes and other comorbidities. The propensity score was calculated using a logistic regression model using 1:1 nearest neighbor greedy algorithm [13], with baseline lipid parameters, risk classification defined by the 2015 KSLA guidelines [12] and diabetes used as covariates in propensity score matching and ANCOVA.

Determination of Sample Size

Sample size was calculated from estimation of goal attainment rates, the proportion of dyslipidemia patients with diabetes, and the proportion of discarded patients following propensity score matching.

The goal attainment rates in two randomized controlled trials which compared statin monotherapy with statin/ezetimibe combination therapy were 73% versus 85% [10] and 68% versus 86% [14], respectively. For calculation of the sample size, we conservatively estimated goal attainment rates of 70% and 85% for statin monotherapy and statin/ezetimibe combination therapy, respectively. Sample size calculation, using PASS 12® software, showed that a minimum of 242 patients (121 in each group) would attain 80% power at a 5% significance level for a two-tailed test of the null hypothesis that the two treatment groups had similar goal attainment rates.

The proportions of dyslipidemia patients who had concurrent diabetes in the ACTFAST-2 [15], ATGOAL [16], and IMPROVE_IT [17] studies were reported as 27–44%. Assuming that the proportion of dyslipidemia patients who had concurrent diabetes was 27%, the calculated number of dyslipidemia patients needed for enrollment (in order to include 242 patients with concurrent diabetes) was 898.

The proportion of discarded patients after propensity score matching was conservatively estimated to be 30%. On this basis, the final sample size was calculated as 1,284 patients (642 per group).

Results

Following screening, 51 subjects (n = 21, atorvastatin/ezetimibe group; n = 30, atorvastatin monotherapy group) were excluded due to: failure to meet inclusion/exclusion criteria in 32 subjects (n = 18 atorvastatin/ezetimibe group; n = 14, atorvastatin monotherapy group), lipid test at week 12 performed more than 3 days after the last administration of the study drug in 14 subjects (n = 3, atorvastatin/ezetimibe group; n = 11 atorvastatin monotherapy group), dose modification during the study in 2 subjects (n = 2, atorvastatin monotherapy group), and 3 subjects who were non-Korean (n = 3, atorvastatin monotherapy group).

A total of 969 subjects (349 subjects in the atorvastatin/ezetimibe group and 620 subjects in the atorvastatin monotherapy group) were enrolled in this study, all of whom were included in analyses.

Demographic and baseline characteristics

Demographic and baseline characteristics of subjects in the study population are summarized in Table 1. The mean (SD) age of all subjects was 59.0 (11.8) years, of whom 47.3% were male. Subjects had a mean (SD) body mass index of 24.9 (3.4) kg/m2 and approximately half of all patients were non-smokers (53.6%) and non-drinkers (46.1%). Significant differences between the atorvastatin/ezetimibe and atorvastatin groups were found for mean systolic blood pressure (SBP; 129.1 versus 125.7 mmHg) and diastolic blood pressure (DBP; 78.3 versus 75.9 mmHg) (each p = 0.003). However, SBP and DBP were not used as covariates for risk propensity score matching as hypertension was included as a major risk factor in risk classification.

There was also a statistically significant inter-group difference in the risk level of subjects (p = 0.034). The proportion of subjects with very high risk (LDL-C goal <70 mg/dL) was higher in the atorvastatin/ezetimibe group compared with the atorvastatin group (29.8% versus 26.0%); lower in high (LDL-C goal <100 mg/dL; 24.9% versus 31.3%) and intermediate risk subjects (LDL-C goal <130 mg/dL; 20.1% versus 23.2%); and higher in low risk subjects (LDL-C goal <160 mg/dL; 25.2% versus 19.5%) (Table 1).

Data regarding past medical history were available for 60.1% of subjects (n = 582). The most common condition (categorized by System Organ Class) was a history of cardiac disorders (n = 116; 12.0%), followed by gastrointestinal disorders (n = 102; 10.5%), and endocrine disorders (excluding diabetes, n = 96; 9.9%) and neoplasms benign, malignant and unspecified (including cysts and polyps) (n = 96; 9.9%) (Table 1).

By Preferred Term, the most common disorder was gastroesophageal reflux disease (GERD) (n = 46; 4.8%), followed by atrial fibrillation (n = 45; 4.6%), and hypothyroidism (n = 37; 3.8%) (Table 1).

A total of 775 subjects (80.0%) had a risk of CVD, of which hypertension was the most common (n = 523; 54.0%), followed by diabetes (n = 355; 36.6%), and CHD (n = 227; 23.4%) (Table 1).

Table 1: Demographic and baseline characteristics of subjects in the study population (prior to propensity score matching).

Parameter	Atorvastatin/ezetimibe	Atorvastatin monotherapy	Total
n (%)	349 (36.0)	620 (64.0)	969 (100)
Age (years): mean (SD)	58.5 (11.8)	59.4 (11.7)	59.0 (11.8)
Sex, male: n (%) female: n (%)	162 (46.4) 187 (53.6)	296 (47.7) 324 (52.3)	458 (47.3) 511 (52.7)
Body Mass Index (kg/m2): mean (SD) ^	25.1 (3.5)	24.8 (3.4)	24.9 (3.4)
Smoking Status, n (%)			
Non-Smoker	186 (53.3)	333 (53.7)	519 (53.6)
Smoker	46 (13.2)	58 (9.4)	104 (10.7)
Ex-Smoker	28 (8.0)	73 (11.8)	101 (10.4)
Unknown	89 (25.5)	156 (25.2)	245 (25.3)
Drinking Status, n (%)			
Non-Drinker	163 (46.7)	284 (45.8)	447 (46.1)
Drinker	87 (24.9)	159 (25.7)	246 (25.4)
Unknown	99 (28.4)	177 (28.6)	276 (28.5)
Systolic blood pressure (mmHg): mean (SD) *	129.1 (17.0)	125.7 (15.9)	126.9 (16.3)
Diastolic blood pressure (mmHg): mean (SD) *	78.3 (11.8)	75.9 (10.9)	76.8 (11.3)
Risk Level, n (%) †			
Very high risk (LDL-C goal <70 mg/dL)	104 (29.8)	161 (26.0)	265 (27.4)
High risk (LDL-C goal <100 mg/dL)	87 (24.9)	194 (31.3)	281 (29.0)
Intermediate risk (LDL-C goal <130 mg/dL)	70 (20.1)	144 (23.2)	214 (22.1)
Low risk (LDL-C goal <160 mg/dL)	88 (25.2)	121 (19.5)	209 (21.6)
Medical history: n (%)	171 (49.0)	411 (66.3)	582 (60.1)
Cardiac disorders: n (%)	12 (3.4)	104 (16.8)	116 (12.0)
Atrial fibrillation: n (%)	4 (1.2)	41 (6.6)	45 (4.6)
Gastrointestinal disorders: n (%)	30 (8.6)	72 (11.6)	102 (10.5)
Gastroesophageal reflux disease: n (%)	13 (3.7)	33 (5.3)	46 (4.8)
Endocrine disorders: n (%)	24 (6.9)	72 (11.6)	96 (9.9)
Hypothyroidism: n (%)	10 (2.9)	27 (4.4)	37 (3.8)
Neoplasms benign, malignant and unspecified (including cysts and polyps): n (%)	26 (7.5)	70 (11.3)	96 (9.9)
Cardiovascular Risk: n (%)	273 (78.2)	502 (81.0)	775 (80.0)
Hypertension: n (%)	191 (54.7)	332 (53.6)	523 (54.0)
Diabetes: n (%)	116 (33.2)	239 (38.6)	355 (36.6)
Coronary Heart Disease: n (%)	89 (25.5)	138 (22.3)	227 (23.4)
Family history of premature coronary artery disease: n (%)	18 (5.2)	22 (3.6)	40 (4.1)

^Body Mass Index (BMI): n = 305, atorvastatin/ezetimibe group; n = 563, atorvastatin monotherapy group; n = 868, total.

*Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP): n = 319 atorvastatin/ezetimibe; n = 550, atorvastatin; n = 869, total. Significant inter-group difference in SBP (p = 0.003) and DBP (p = 0.003).

† Significant inter-group difference in risk level (p = 0.034).

Propensity score matching

The propensity scores of the two treatment groups were more similar after matching (Table 2). Before matching, mean (SD) scores in the atorvastatin/ezetimibe and atorvastatin monotherapy groups were 0.399 (0.131) and 0.338 (0.101), respectively. After matching, the respective scores were 0.373 (0.106) and 0.373 (0.105).

Table 2: Propensity score matching.

Propensity score	Atorvastatin/ezetimibe (N = 349)	Atorvastatin monotherapy (N = 620)
Unmatched: mean (SD)	0.399 (0.131)	0.338 (0.101)
n	349	620
Matched: mean (SD)	0.373 (0.106)	0.373 (0.105)
n	316	316

Efficacy analyses

Rates of LDL-C goal attainment before and after propensity matching are summarized in Table 3. Goal attainment rates were 83% and 79% in unmatched atorvastatin/ezetimibe (n = 349) and atorvastatin monotherapy (n = 620) groups, respectively. Following propensity matching (n = 316 in each group), the goal attainment rate was significantly higher in the atorvastatin/ezetimibe group than in the atorvastatin monotherapy group (86% and 75%, p=0.0004).

Significant differences between the two treatment groups were found for LDL-C, total cholesterol and non-HDL-C levels ($p < 0.0001$ for all), with atorvastatin/ezetimibe producing larger reductions in mean lipid levels than atorvastatin monotherapy (Table 4). These differences were identified in both unmatched (using ANCOVA) and propensity matched (using paired t-tests) groups. Mean percentage changes from the index date to week 12 in propensity matched atorvastatin/ezetimibe and atorvastatin monotherapy groups were −50.3% and −42.7%, respectively, for LDL-C; −36.8% and −30.7% for total cholesterol; and −47.3% and −39.8% for non-HDL-C. There were no significant inter-group differences for HDL-C or triglycerides.

In hypercholesterolemia patients with diabetes, LDL-C goal attainment rates in unmatched atorvastatin/ezetimibe (n = 116) and atorvastatin monotherapy (n = 239) groups were 0.77 (95% CI, 0.69–0.84) and 0.79 (95% CI, 0.74–0.85), respectively. In propensity matched groups (n = 103 for each), respective rates were 0.82 (95% CI, 0.74–0.89] and 0.74 (95% CI, 0.65–0.82).

No significant differences between the treatment groups in hypercholesterolemia patients with diabetes were found for change from baseline for any lipid parameter (LDL-C, HDL-C, non-HDL-C, total cholesterol or triglyceride) in unmatched or propensity matched groups. Mean percentage changes in propensity matched atorvastatin/ezetimibe and atorvastatin monotherapy groups (n = 103) were −47.0% and −45.3%, respectively, for LDL-C; −0.6% and 0.2% for HDL-C; −42.9% and −41.6% for non-HDL-C; −34.3% and −32.4% for total cholesterol; and −10.7% and −12.8% for triglyceride.

Table 3: LDL-C goal attainment rate before and after propensity matching

	Atorvastatin/ezetimibe	Atorvastatin monotherapy
Week 12 (Unmatched): n	349	620
Goal attainment incidence: n	290	487
Goal attainment rate: ratio [95% CI]	0.83 [0.79–0.87]	0.79 [0.75–0.82]
Week 12 (Matched): n	316	316
Goal attainment incidence: n	272	237
Goal attainment rate: ratio [95% CI]	0.86 [0.82–0.90]	0.75 [0.70–0.80]

Table 4: Percentage change in lipid parameters from the index date to week 12 in unmatched and propensity matched treatment groups.

	Unmatched						
	Atorvastatin/ ezetimibe (N = 349)	Atorvastatin monotherapy (N = 620)	Atorvastatin/ ezetimibe (N = 349)	Atorvastatin monotherapy (N = 620)	Atorvastatin/ ezetimibe (N = 349)	Atorvastatin monotherapy (N = 620)	P value *
	Index date: mean (SD)		Week 12: mean (SD)		Percentage change from index date to week 12: mean (SD)		
LDL-C	157.5 (38.7)	142.2 (30.0)	73.6 (25.9)	83.4 (23.9)	−51.2 (19.7)	−40.2 (16.7)	<0.0001
HDL-C	52.1 (13.3)	51.1 (12.9)	51.7 (13.8)	50.9 (13.7)	0.3 (17.6)	0.8 (18.0)	0.881
Non-HDL-C	185.1 (40.9)	169.7 (34.9)	92.8 (30.7)	103.7 (27.4)	−48.1 (19.0)	−37.6 (16.6)	<0.0001
Total cholesterol	237.3 (43.4)	220.7 (37.7)	144.5 (31.8)	154.6 (29.3)	−37.7 (15.3)	−29.0 (13.0)	<0.0001
Triglyceride	172.1 (88.6)	146.4 (75.6)	126.7 (71.3)	121.4 (71.7)	−16.1 (48.9)	−7.8 (59.9)	0.56
	Propensity matched						
	Atorvastatin/ ezetimibe (N = 316)	Atorvastatin monotherapy (N = 316)	Atorvastatin/ ezetimibe (N = 316)	Atorvastatin monotherapy (N = 316)	Atorvastatin/ ezetimibe (N = 316)	Atorvastatin monotherapy (N = 316)	P value ^
	Index date: mean (SD)		Week 12: mean (SD)		Percentage change from index date to week 12: mean (SD)		
LDL-C	151.1 (33.6)	151.4 (29.8)	72.4 (25.7)	85.8 (25.0)	−50.3 (19.9)	−42.7 (15.0)	<0.0001
HDL-C	51.9 (13.3)	51.6 (12.7)	51.6 (13.9)	51.8 (13.8)	0.4 (17.7)	1.5 (19.1)	0.468
Non-HDL-C	179.7 (37.8)	177.0 (31.9)	91.9 (30.6)	105.2 (29.0)	−47.3 (19.2)	−39.8 (15.7)	<0.0001
Total cholesterol	231.6 (40.1)	228.6 (34.5)	143.5 (31.5)	157.0 (29.9)	−36.8 (15.3)	−30.7 (12.3)	<0.0001
Triglyceride	173.2 (90.6)	145.4 (70.1)	128.4 (72.8)	122.6 (76.7)	−15.3 (50.0)	−9.5 (40.6)	0.098

* ANCOVA, controlling for the effects of baseline values and risk level; ^ Paired t-test

Discussion

The current retrospective, real-world chart review study of statin-naive patients with hypercholesterolemia showed that a combination of atorvastatin and ezetimibe was superior to atorvastatin alone in achieving LDL-C goals after 12 weeks of treatment. Treatment groups were propensity matched to reduce selection bias due to confounding variables including age, sex, baseline LDL-C, risk classification, diabetes and other comorbidities. The primary efficacy outcome – the goal attainment rate – was significantly higher in the atorvastatin/ezetimibe group than in the atorvastatin monotherapy group (p = 0.0004). These results are consistent with those reported in randomized controlled trials (RCTs) of patients with hypercholesterolemia, with atorvastatin/ezetimibe producing significantly higher LDL-C goal attainment rates than atorvastatin alone [18–20].

Hypercholesterolemia is a key risk factor for CVD and, despite the wide availability of lipid-lowering therapy, few very high-risk (e.g. stable CHD or hospitalized for an ACS) patients achieve LDL-C target levels. Data from the international, observational, cross-sectional DYSIS II study showed that fewer than one-third of patients with stable CHD achieved an LDL-C level <70 mg/dL, despite all patients being at very high CV risk [21], and these findings were replicated within Asian DYSIS II cohorts [8, 9, 22]. Other cross-sectional and real-world evidence clearly demonstrates that many CHD patients with dyslipidemia remain inadequately treated with most patients on statin therapy not achieving treatment targets [23–28]. Collectively, these findings indicate huge potential to improve cardiovascular outcomes using more intensive lipid-lowering therapy.

In the current real-world study, atorvastatin/ezetimibe also produced statistically significantly greater decreases in LDL-C, total cholesterol, and non-HDL-C levels compared with atorvastatin monotherapy. Significant differences were found by ANCOVA tests on unmatched data and paired t-tests for propensity matched data. These results demonstrate the greater LDL-C-lowering effect of atorvastatin/ezetimibe than atorvastatin monotherapy. Results obtained from RCTs for patients with hypercholesterolemia have consistently shown that

atorvastatin/ezetimibe produced significantly greater reductions in LDL-C and triglycerides than atorvastatin monotherapy, with significant improvement in other lipid profiles reported less consistently during comparisons of the two treatment modalities [10, 18–20].

A 12-week RCT in patients with primary hypercholesterolemia reported that atorvastatin/ezetimibe significantly reduced LDL-C, total cholesterol, triglycerides and non–HDL-C, and significantly increased HDL-C compared with atorvastatin alone [10] although, in a 12-month extension, significant differences between the two treatment groups were only found for reductions in LDL-C, total cholesterol and triglyceride levels [18]. A combination of atorvastatin plus ezetimibe significantly reduced levels of LDL-C, triglycerides, and non-HDL-C at 4 weeks in patients with heterozygous familial hypercholesterolemia compared to atorvastatin alone [19].

In a RCT of hypercholesterolemic patients with CHD, a combination of atorvastatin plus ezetimibe led to significantly greater reductions in LDL-C, total cholesterol, triglycerides and non-HDL-C, and significantly increased HDL-C, at 6 weeks compared to atorvastatin/placebo [20]. In the current study, subgroup analysis of hypercholesterolemic patients with diabetes failed to show any significant differences between atorvastatin/ezetimibe and atorvastatin monotherapy in achieving LDL-C goals or improving lipid parameters. These analyses were limited by the failure to enroll the planned number of diabetic patients in the atorvastatin/ezetimibe group with consequent reductions in power.

Limitations of this observational study, which is based on a retrospective chart review, include potential bias caused by confounding effects due to the lack of randomization. These effects are likely to be minimized following propensity matching of patients but cannot be ruled out entirely. In the current study, we matched the atorvastatin/ezetimibe and atorvastatin groups on recognized CV risk factors. Consequently, half of the atorvastatin group were excluded and the results are only applicable to patients with the characteristics of the atorvastatin/ezetimibe group rather than being generalizable to all patients. When we conducted propensity score matching, baseline LDL levels were significantly different between the two groups before matching. Thus, many patients with low baseline LDL levels in the atorvastatin group were excluded in the matching process. This represents a limitation of the study and is also a problem for other comparative studies in which patients are not randomized. Due to the shorter time period of market availability for atorvastatin/ezetimibe than atorvastatin, the number of enrolled patients in the combination treatment group was lower than planned, reducing the power of the study, most notably in the diabetic patient subgroup, as discussed above.

Despite these limitations, this study provides a meaningful comparison of LDL-C goal attainment rates with atorvastatin/ezetimibe and atorvastatin monotherapy in Korean patients with hypercholesterolemia in a real-world clinical practice setting, complementing existing evidence obtained from RCTs. Atorvastatin/ezetimibe, a dual fixed-dose combination tablet for the primary treatment of hypercholesterolemia had greater efficacy than atorvastatin alone. This study is expected to serve as a useful reference for the establishment of dyslipidemia treatment guidelines in Korean patients.

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Compliance with Ethical Standards

Conflict of Interest

NA

Ethical Approval

Approval was obtained by all study sites from the appropriate institutional review board (IRB) or ethics review committee (ERC) for the finalised protocol and other study documents. The study was conducted in accordance with Good Pharmacoepidemiology Practice (GPP) guidelines and national and/or regional laws and regulations for the protection of subjects participating in biomedical studies.

As this was a retrospective chart review study using data extracted from medical records, no on-site visit by patients was required, and no direct patient identifiers (e.g. name or medical record number) were collected. In addition, the study neither provided drugs nor collected biological samples. Consequently, a waiver of patient consent was granted by IRBs.

Abbreviations

DBP:	Diastolic blood pressure
HDL-C:	High-density lipoprotein cholesterol
KNHANES:	Korea National Health and Nutrition Survey
KSLA:	Korean Society of Lipidology and Atherosclerosis
LDL-C:	Low-density lipoprotein cholesterol
SBP:	Systolic blood pressure

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