ORIGINAL ARTICLE

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Early efficacy and safety of statin therapy in Korean patients with hypercholesterolemia: Daegu and Gyeongbuk Statin Registry

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Background/Aims: To date, prospective data are limited on efficacy and safety profiles of statin therapy in Korean hypercholesterolemic patients. Hence, the aim of this study was to evaluate the practice patterns of statin therapy and its efficacy and safety through the prospective Daegu and Gyeongbuk statin registry.

Methods: Statin naïve patients who were prescribed statins according to the criteria of Korean Guidelines for Management of Dyslipidemia were enrolled. Clinical and laboratory evaluations were performed at baseline and at week 8, where the efficacy was assessed with the same guidelines.

Results: Of 908 patients, atorvastatin and rosuvastatin were most frequently prescribed statins (63.1% and 29.3%, respectively). High intensity statins (atorvastatin 40 mg or rosuvastatin 20 mg) were prescribed in 24.7% of all patients and in 79.5% of high and very high risk groups. The total and low density lipoprotein (LDL) cholesterol levels decreased from 203.7 ± 43.0 to 140.6 ± 28.6 mg/dL and 134.4 ± 35.7 to 79.5 ± 21.3 mg/dL, respectively. The achievement rate of the LDL target goal was 98.6% in low risk, 95.0% in moderate risk, 88.1% in high risk, and 42.1% in very high risk patients (59.7% in overall). There was no significant difference in the efficacy between atorvastatin and rosuvastatin. Adverse events were observed in 12.0% of patients and led to 1.4% of treatment cessation.

Conclusions: The efficacy of the usual starting dose of statins in daily practice was relatively insufficient for Korean hypercholesterolemic patients with high or very high risks. Short-term adverse events of statin therapy were not common in Korean patients with a low discontinuation rate.

Keywords: Dyslipidemias; Cholesterol; Hydroxymethylglutaryl-CoA reductase inhibitors

INTRODUCTION

Recently, the prevalence of cardiovascular disease has increased with the aging population and lifestyle changes in Korea [1,2]. The prevalence of hypercholesterolemia, which is a well-known risk factor for cardiovascular disease in patients over 30 years old, has increased from 8.0% in 2005 to 15.7% in 2014, as reported by the Ministry of Health and Welfare in Korea [2]. Statins are effective for the primary and secondary prevention of cardiovascular

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disease by reducing the cholesterol biosynthesis mainly in the liver, through the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase [3-9]. Although statins are usually well tolerated in most patients, several adverse effects including liver and muscle toxicities have been reported in the previous studies [1,3,7,9-15]. There are few prospective data on the efficacy and safety of statin therapy in Korean patients. The aim of this study was to evaluate the practice patterns of statin therapy and its efficacy and safety in patients with dyslipidemia through the prospective Daegu and Gyeongbuk statin registry (DG Statin Registry).

METHODS

Patient enrollment

The DG Statin Registry was designed as a prospective observational study enrolling 1,000 patients who were statin-naïve and indicated for statin therapy in Daegu Metropolitan City and Gyeongbuk province of Korea from December 2011 to January 2015. The study was approved by each Institutional Review Committee (DSMC 2011-11-286) and conducted in accordance with the guidelines of the ethics committee at each participating institution. Written informed consent was obtained from all patients.

Inclusion criteria were statin naïve patients who were 30 years or older, in need to use statin therapy, and agreed to a follow-up visit and evaluation after 8 weeks (± 2 weeks) of statin therapy with informed consent. The exclusion criteria were as follows: (1) an unexplained rise in the creatine phosphokinase (CPK) of > 3 times the upper limit; (2) alanine aminotransferase (ALT)/aspartate transaminase (AST) values > 1.5 times the upper limit at baseline; (3) a history of severe or unstable medical or psychological disease, affecting the patient's participation or general condition; and (4) a history of drug or alcohol abuse.

All statins (atorvastatin [ATV], rosuvastatin [RSV], simvastatin, pitavastatin, and fluvastatin) available in the market were registered, and the type of statin prescribed was entirely at the discretion of the individual physician. At the time of the final analysis, the patients' grouping was classified according to the Korean Guidelines for Management of Dyslipidemia [1], and the statin intensity was classified according to the 2013 American College of Cardiology/American Heart Association cholesterol guidelines [12].

Measurements and statistical analyses

A basic history taking, baseline characteristics, and blood tests were obtained before beginning the statin therapy. A follow-up history taking, and blood tests were repeated at week 8 of the therapy. Patients were requested to fast and avoid any alcohol consumption or cigarette smoking for > 12 hours before the blood test. The efficacy endpoint was defined as the achievement of the target low density lipoprotein cholesterol (LDL-C) level according to the risk categories of the Korean Guidelines for Management of Dyslipidemia and National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines. The secondary efficacy endpoint was the percent change in the lipid parameters including the LDL-C, high density lipoprotein cholesterol (HDL-C), triglyceride, and total cholesterol (TC) levels from baseline to the following outpatient admission.

The safety endpoint was assessed with the incidence of adverse events reported primarily from treatment-related events during the study period. Certain events were classified as safety events of interest, requiring completion of a special electronic case report form. These included an abnormal liver function test classified as an ALT or AST of > 1.5 times the upper limit, hepatitis with an ALT or AST of > 3 times the upper limit, myalgia including weakness, general weakness, myopathy, and other muscle symptoms, myopathy as a creatine kinase of > 2 times the upper limit, and any other complaint of symptoms by the patient after therapy.

Statistical analyses were performed with the SPSS software version 23.0.0.0 (IBM Corp., Armonk, NY, USA). Data were reported as frequencies and percentages for dichotomous and categorical variables, and as the mean ± standard deviation for continuous variables. Dichotomous and categorical variables were assessed using chi-square tests and Fisher's exact tests, and continuous variables were assessed using Student's *t* tests or the Wilcoxon rank-sum tests, as appropriate, with a significance level of the *p* value of < 0.05.

Table 1. Baseline characteristic

Characteristic	Value
All patients	908
Demographic	
Age, yr	63.9 ± 11.6
Male sex	560 (61.7)
BMI, kg/m²	24.5 ± 3.3
Smoking	475 (52.3)
Family history of premature CHD	7 (0.8)
Comorbidity	
Hypertension	501 (55.2)
Diabetes mellitus	216 (23.8)
Coronary artery disease	605 (68.1)
Stroke	46 (5.1)
Peripheral arterial disease	5 (0.6)
Carotid disease	5 (0.6)

Values are presented as mean ± SD or number (%).
BMI, body mass index; CHD, coronary heart disease.

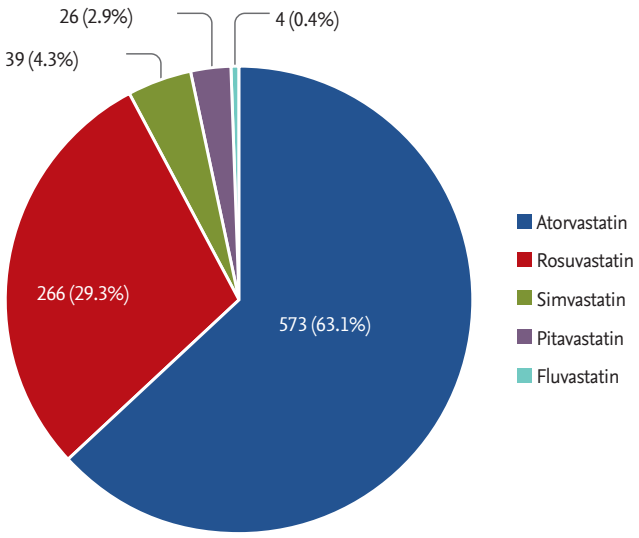

Figure 1. Type of statin. Data are presented as the number (percentage).

RESULTS

From December 2012 to January 2015, 1,000 individuals were initially screened. Ninety-two patients were excluded as follows: 31 due to loss to follow-up, three due to failure to meet the inclusion criteria (elevated baseline liver enzyme), and 58 due to inadequate data. Hence, total of 908 eligible patients were included in the final analysis.

The mean age of the study group was 63.9 ± 11.6 years (61.7% men), and the mean body mass index was 24.5 ± 3.3 kg/m². There were 23.8% of the patients with diabetes mellitus and 68.1% with obstructive (≥ 50% stenosis) or non-obstructive (< 50% stenosis) coronary artery disease (Table 1). The types of prescribed statins were as follows (Fig. 1): ATV in 63.1%, RSV in 29.3, simvastatin in 4.23%, pitavastatin in 2.9%, and fluvastatin in 0.4%.

According to the criteria of the Korean Guidelines for Management of Dyslipidemia [1], the risk levels were stratified into 68.1% as a very high risk group, 6.6% as a high risk group, 16% as a moderate risk group, and 9.4% as low-risk group. High-intensity statins (ATV 40 mg or RSV 20 mg) were prescribed in 24.7% of all patients and were prescribed for 79.5% of high and very high risk patients. Nearly 73% of high and very high risk patients were initially prescribed at least one moderate or high intensity statin (Fig. 2A).

If the patients were classified only by the LDL-C levels regardless of their risks, 5.9% were classified as the very high LDL-C group (≥ 190 mg/dL), 14.3% as the high LDL-C group (160 to 189 mg/dL), 29.0% as the borderline high LDL-C group (130 to 159 mg/dL), 32.8% as the near optimal LDL-C group (100 to 129 mg/dL), and 18% as the optimal LDL-C group (< 100 mg/dL). Of the patients with a high or very high LDL-C level, moderate intensity statins were used for about 55% and high intensity statins for more than 30% (Fig. 2B).

Efficacy

The mean baseline TC level was 203.7 ± 43.0 mg/dL, and mean follow-up TC level 140.6 ± 28.6 mg/dL ($p < 0.001$). The HDL-C levels were significantly elevated after the statin therapy (47.7 ± 11.3 to 49.0 ± 11.6 mg/dL, $p < 0.001$) and the LDL-C levels were significantly reduced after the statin therapy (134.4 ± 35.7 to 79.5 ± 21.3 mg/dL, $p < 0.001$) (Table 2). The distribution of the TC and LDL-C at baseline and at follow-up is shown in Fig. 3.

The overall achievement of the target LDL-C level was 59.7% in the DG registry. The achievement rates were 98.6% in the low risk, 95.0% in the moderate risk, 88.1% in the high risk, and 42.1% in the very high risk patients (Fig. 4). To sum it up, the patients in the high and very

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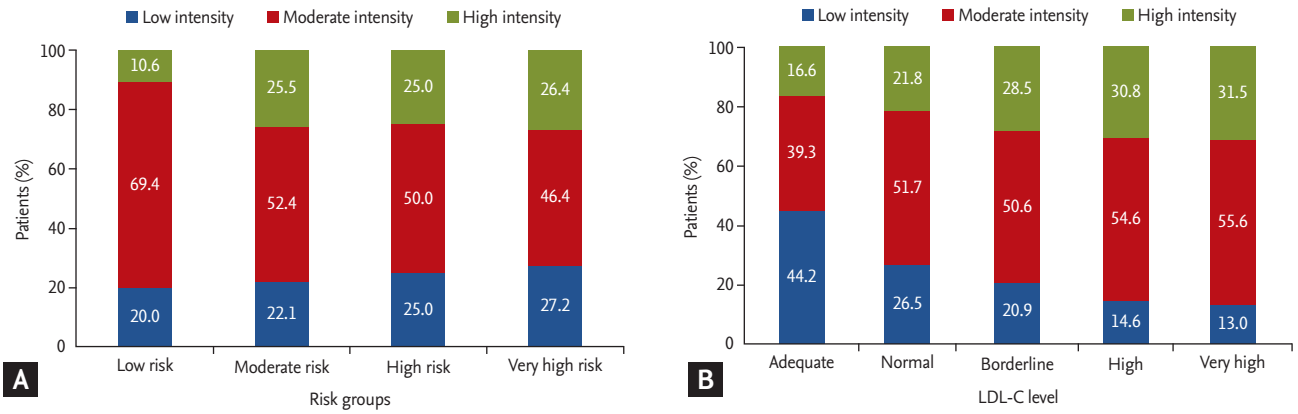

Figure 2. The distribution of the statin therapy according to the (A) risk group. (B) Low density lipoprotein cholesterol (LDL-C). (B) The LDL-C was classified into five groups: adequate < 100 mg/dL, normal 100 to 129 mg/dL, borderline 130 to 159 mg/dL, high 160 to 189 mg/dL, and very high > 190 mg/dL.

Table 2. Laboratory data

Characteristic	Baseline	Follow-up	*p* value
Lipid profile			
Total cholesterol, mg/dL	203.7 ± 43.0	140.6 ± 28.6	< 0.001
HDL-C, mg/dL	47.7 ± 11.3	49.0 ± 11.6	< 0.001
LDL-C, mg/dL	134.4 ± 35.7	79.5 ± 21.3	< 0.001
TG, mg/dL	146.6 ± 103.6	122.2 ± 63.4	< 0.001
Non-HDL-C, mg/dL	153.7 ± 41.0	75.1 ± 44.5	< 0.001
AST, U/L	25.5 ± 9.4	25.8 ± 13.6	0.592
ALT, U/L	23.9 ± 11.7	27.7 ± 21.6	< 0.001
BUN, mg/dL	17.3 ± 7.4	16.5 ± 7.8	< 0.001
Creatinine, mg/dL	0.91 ± 0.67	0.94 ± 0.98	0.159
CPK, U/L	116.7 ± 65.0	116.9 ± 157.5	0.643
LDH, U/L	371.3 ± 93.0	383.8 ± 135.3	0.288
hs-CRP, mg/dL	0.55 ± 1.70	0.24 ± 0.94	< 0.001
FBS, mg/dL	122.0 ± 41.4	115.3 ± 35.8	<0.001
Non-DM, mg/dL (n = 692)	107.1 ± 22.0	104.2 ± 18.8	0.037
DM, mg/dL (n = 216)	155.7 ± 53.6	140.4 ± 49.9	0.019

Values are presented as mean ± SD.
HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; AST, aspartate transaminase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; CPK, creatine phosphokinase; LDH, lactate dehydrogenase; hs-CRP, high-sensitivity C-reactive protein; FBS, fasting blood sugar; DM, diabetes mellitus.

high risk groups had a lower achievement of the target LDL-C level. Additionally, an achievement rate of more than 30% of the LDL-C reduction was 81.9%, 76.7%, 80.9%, and 72.3% for the low risk, moderate risk, high risk, and very high risk groups, respectively. Overall, 74.6% of the patients achieved a 30% or greater reduction in the LDL-C level.

In addition, despite the short-term follow-up, there was a significant reduction in the high-sensitivity C-reactive protein level after the statin therapy from 0.55 ± 1.70 to 0.24 ± 0.94 mg/dL ($p < 0.001$).

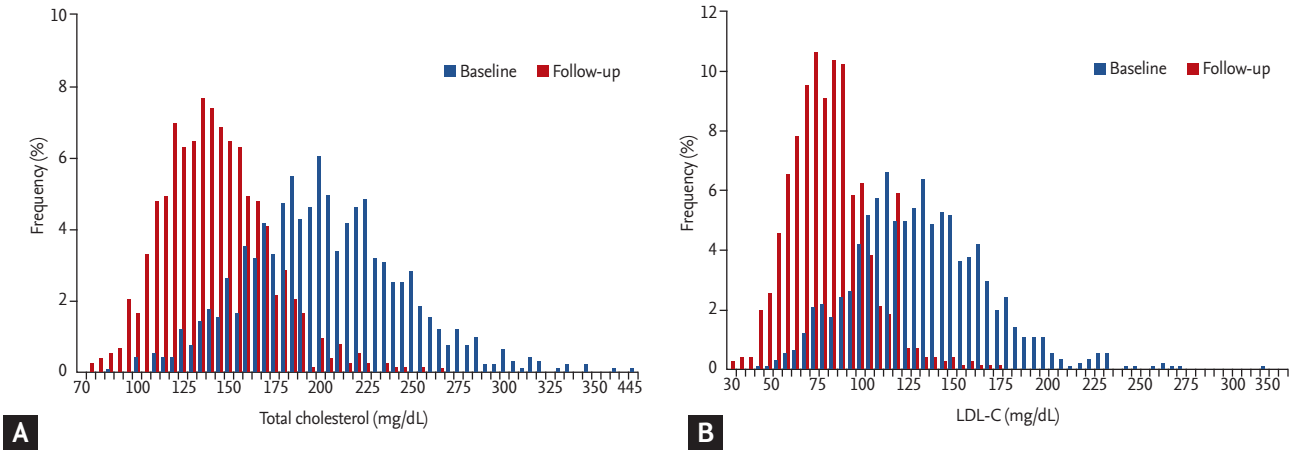

Figure 3. Change in the (A) total cholesterol and (B) low density lipoprotein cholesterol (LDL-C). Data are presented as the number.

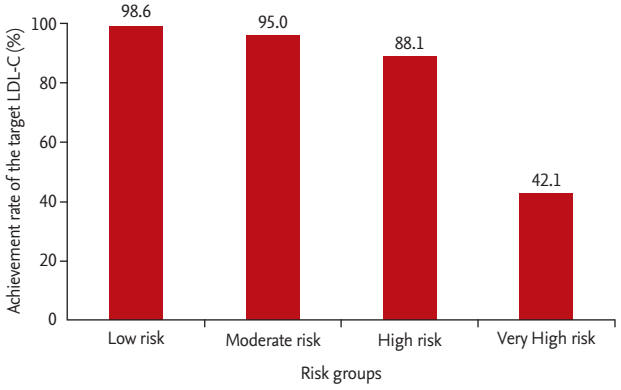

Figure 4. Changes in the low density lipoprotein cholesterol (LDL-C) levels in each risk group.

Safety

No clinically significant elevations were observed in the follow-up laboratory tests (AST, ALT, lactate dehydrogenase, CPK, and glucose level) at week 8 (Table 2). The incidence of treatment-related adverse events occurring during the study period was 12.0% (109 patients). Transient elevation of the liver enzymes was reported in 40 patients (4.4%) and hepatitis in six patients (0.7%). Myalgia was reported in 38 patients (4.1%) and myopathy in 11 patients (1.2%). The other adverse events are described in Table 3. There were 13 reports (1.4%) of serious adverse events that required cessation of the statin treatment including serious myopathy, intolerable myalgia, and an excessive increase in the liver enzymes (≥ 5 times over the upper normal limit).

Comparison between atorvastatin and rosuvastatin

As depicted in Fig. 5, the doses of ATV and RSV, which are the two most prescribed statins, increased proportionally to the baseline LDL-C levels. The mean LDL-C values at week 8 were similar across the dosage groups, despite the differences in the baseline level. ATV 10 mg and RSV 5 mg reduced the LDL-C by 31.3% and 33.9% (p = 0.397), ATV 20 mg and RSV 10 mg by 39.0% and 41.2% (p = 0.331), and ATV 40 mg and RSV 20 mg by 42.1%, 42.4% (p = 0.899), respectively. The rate of achieving the target LDL-C level as a primary efficacy endpoint was 100% in both the ATV and RSV groups in the low risk patients, 96.7% and 89.7% in the moderate risk patients, 90.5% and 87.5 % in the high risk patients, and 38.3% and 52.1% in the very high risk patients, respectively. Adverse events of any type occurred in 11.6% of ATV and 13.2% of RSV patients (p = 0.787).

DISCUSSION

This study evaluated the usual treatment pattern, efficacy, and safety of statin therapy in Korean patients with dyslipidemia. The main findings were as follows. (1) In daily practice, the commonly prescribed statins were ATV and RSV. (2) The selection of the initial statin dose was dependent on the baseline LDL-C level in daily clinical practice. The statin therapy effectively modified the lipid parameters and those modifications were directly proportional to the statin dose. (3) However, the efficacy

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Table 3. Adverse effects

Characteristic	Value
Number	109/908 (12.0)
Transient elevation of liver enzymes	40 (4.4)
Hepatitis	6 (0.7)
Myalgia	38 (4.1)
Myopathy	11 (1.2)
Others	31 (3.4)
Gastrointestinal symptoms problem	15 (1.6)
Dyspnea	2 (0.2)
Ecchymosis	2 (0.2)
Acute tubulo-interstitial nephritis	1 (0.1)
Cold sweating	1 (0.1)
Cough	1 (0.1)
Dizziness	1 (0.1)
Edema	1 (0.1)
Headache	1 (0.1)
Involuntary movement	1 (0.1)
Urticaria	1 (0.1)
Bronchiolitis	1 (0.1)
Chest discomfort	1 (0.1)
Syncope	1 (0.1)

Values are presented as number (%). Abnormal liver function tests were classified as an alanine aminotransferase (ALT) or aspartate transaminase (AST) > 1.5 times the upper limit; hepatitis as an ALT or AST > 3 times the upper limit; myalgia included weakness, general weakness, myopathy, and other muscle symptoms; myopathy as a creatine kinase > 2 times the upper limit; and any other symptom complaints by the patient after therapy.

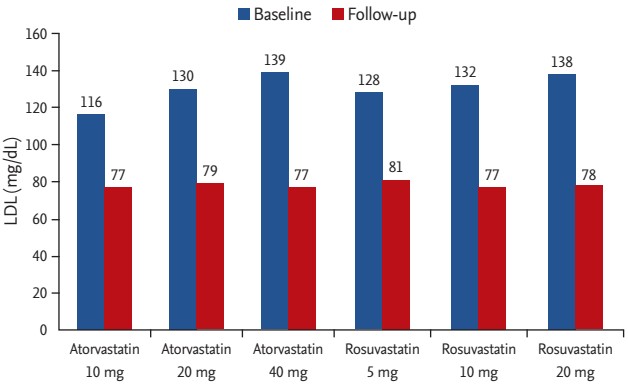

Figure 5. Baseline and follow-up low density lipoprotein (LDL) cholesterol levels according to the dose of the statin.

of the usual initial dose of statins was relatively insufficient in the higher risk Korean patients. (4) Early adverse effects of the statin therapy occurred in 12.0%, and in 1.4% the drug was discontinued. (5) There was no difference between the LDL-C lowering effects and safety issues between ATV and RSV in proportion to the dose.

The biological mechanisms and clinical benefits of statins are well known [3,4,6]. Not only do statins modify lipid profiles, but also stabilize atherosclerotic plaque by ameliorating endothelial dysfunction, reducing the inflammatory response, and diminishing the thrombogenicity [3,4,10]. Large clinical trials also demonstrated that statin therapy is an effective measure for primary and secondary prevention of cardiovascular events [15-17]. Although current Western guidelines no longer set a target LDL-C level for statin therapy [18], the 2015 Korean guidelines for the treatment of dyslipidemia recommend to first classify patients by cardiovascular risk factors, and then determine the target goal of the LDL-C level [1]. Similar to the Korean guidelines, the recent European lipid guidelines have also recommend LDL-C targets of < 70 or < 100 mg/dL in patients with a very high or high cardiovascular risks, respectively [19,20]. Recently updated Western guidelines are based on studies conducted in non-Asian populations. Despite the short-term follow-up of 8 weeks, given that a previous study has shown Asians are more susceptible to statin therapies than Caucasians [21], this study is valuable in that it investigated changes in lipid parameters and adverse events that arose from the initial statin therapy in a large cohort comprised of Korean patients

In the current registry, only 5.9% of patients started statins only based on high baseline cholesterol levels (LDL-C > 190 mg/dL). Most patients were classified to high or very high risk groups (74.7%, n = 678) according to their underlying cardiovascular risk factors such as proven atherosclerotic cardiovascular diseases or diabetes. Similar to the recent Western guidelines that recommend ATV and RSV as being highly effective for a first-line treatment for hypercholesterolemia [13], the ATV and RSV were mainly prescribed 63.1% and 29.3% of the time, respectively. Therefore, the first selected statins for the treatment of hypercholesterolemia in Koreans did not generally differ from the current Western guidelines' recommendations. As shown in Fig. 5,

various starting doses are given to patients in the routine clinical practice in Korea according to the baseline LDL-C levels and a reduction in the absolute value of the LDL-C related to a higher dose of statins, similar to the previous studies [1,22].

Another important finding was the efficacy of the initial dose of the statin. The overall achievement of the LDL-C target goal by the current Korean guidelines [1] was relatively low (59.7%) in the DG registry. Similar results were also found in the CEntralized Pan-European survey on tHE Under-treatment of hypercholeSterolemia (CEPHEUS) Pan-Asian survey in which the LDL-C goals were reached in 34.9% (LDL-C < 70 mg/dL) of patients and 55.4% (LDL-C < 100 mg/dL) of the patients with high or very high cardiovascular risks, respectively [12]. In the current study, only 45.9% of the patients in the high or very high risk groups achieved an appropriate LDL-C goal, while 96.4% of the patients in the low and moderate risk groups achieved the goal. Although moderate intensity statins and high intensity statins were prescribed 80.0% and 77.9% respectively, in the low and moderate risk groups, only 75.0% and 72.8% were prescribed in the high and very high risk groups, respectively. Proven to be highly effective, ATV or RSV was prescribed in most of the very high risk patients (96.3%). However, high-intensity statin doses were prescribed to only 26.4% of very high risk patients (29.0% of ATV or RSV). Whether the target of the statin therapy was set in the absolute value of the LDL-C or % reduction, the initial dose of statin was relatively insufficient to reach the target goal in the higher risk groups regardless of Asian's susceptibility issues to statin therapies. Unlike the guidelines for hypercholesterolemia management in the United States and Europe, the 2015 Korean Guidelines for Management of Dyslipidemia exhibit a difference in the target LDL-C level according to the risk groups [1,12,13,23]. Although the controversy over which guidelines are desirable is unclear and should be further assessed in the future, at this time it is necessary to select higher starting doses of statins for the initial treatment in patients with higher risks.

In addition to the lower prescription rate of high dose statins, the achievement of the LDL-C goal in patients with high dose statins was only 63.2%. Therefore, a non-statin therapy, including ezetimibe or a proprotein convertase subtilisin/kexin 9 (PCSK 9) inhibitor, may be considered in adjunction to patients starting on high dose statins [24-27].

The incidence of adverse events of statin therapy was relatively low at 12.0% with a discontinuation rate of 1.4% in the DG registry. The low incidence might be related to the short-term follow-up of the design of the current study. An abnormal elevation of the liver function test and myalgia were the most common adverse effects. In most cases, they were asymptomatic mild elevations of the liver enzymes, which did not cause serious liver damage, such as an increase in the bilirubin level or synthetic dysfunction. When a statin-treated patient shows elevated liver enzymes, one should not be inclined to think that the elevated liver enzymes are due to the statin therapy. Rather, the onset of increased liver enzymes should prompt the clinician to engage in a careful and systematic evaluation (history and physical examination), with consideration of all potential etiologies [14,15]. Myotoxicity is another major complication of statin therapy that is mostly presented as myalgia. In the DG registry, myalgia was reported with an occurrence of 4.1%, which was similar to the other observational cohorts [14,15]. Further, there was no statistical difference in the adverse events between ATV and RSV. Myalgia was slightly higher with RSV, but it was not statistically significant (ATV 3.4%, RSV 6.8%, $p = 0.080$). There was no difference in the occurrence of other adverse effects. As emphasized in the United States recommendations, education on adverse events will be necessary in prior to the use of these medicines [13]. It is also important to take notes of medical history during the outpatient visits after starting the medication.

The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and other studies reported an increased risk of developing diabetes mellitus in patients on statin therapy [28]. Lipophilic statins are reported to increase the risk of elevated serum glucose levels, especially with higher doses. However, in the DG registry, the serum fasting glucose level decreased after the first statin therapy. This result may be related to the design of the study with a short-term follow-up period, and the educational effects on personal will be needed to improve one's lifestyle after receiving the first statin therapy. A recent Japanese study reported that the change in the glucose level was not significant during the first 3 months, but was

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significant between 6 to 12 months, resulting in a slight rise in the hemoglobin A1c [29]. Therefore, the current study could not show the long-term effects of statins on the fasting plasma glucose level.

There are several limitations of the current study. First, this study was a region based observational study, which could result in a selection bias. Therefore, this data is not fully representative of Korean patients requiring statin treatment. This point also should be described as another limitation of this study. However, with a wide inclusion criteria, this study could directly reflect the prescription patterns of the real clinical practice and evaluate the efficacy and safety of the current statin treatment. Second, due to the design of the current study with a short-term follow-up, the long-term effects of the actual statin therapy could not be assessed. Third, because a core lab analysis was not performed, some variations between each center could have affected the results. However, all the patients were enrolled from tertiary referral centers. Therefore, the minor variations in the laboratory tests might be neglectable. Lastly, because this was an observational study and not a randomized controlled study, there is a limitation in the direct comparison of the ATV and RSV effects.

In conclusion, the most commonly prescribed statins in daily practice were ATV and RSV in up to 92% of the patients. The efficacy of the usual starting dose of statins in daily practice was relatively insufficient in high risk Korean patients. Although the adverse events of statins were not common in Korean patients, careful monitoring should be warranted.

KEY MESSAGE

1. In the real world, a reduction in the low density lipoprotein cholesterol (LDL-C) of > 30% was achieved in 74.6%. However, the achievement rate of the LDL-C target goal was insufficient (59.7%).
2. The early side effects of statins were not rare and were about 12%. However, the serious side effects that caused cessation of the statin therapy were only 1.4%, which might be an acceptable range in patients with some cautions.
3. There was no differences in the LDL-C lowering efficacy between atorvastatin and rosuvastatin, which are regarded as highly effective statins commercially.
4. The efficacy of the usual starting dose of statins in daily practice was relatively insufficient in higher risk Korean patients. Therefore, in early statin therapy, a higher dose of statins should be recommended in the patients in the higher risk groups.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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