Low-Density Lipoprotein Cholesterol Goal Attainment Rates by Initial Statin Monotherapy Among Patients With Dyslipidemia and High Cardiovascular Risk in Japan

— A Retrospective Database Analysis —

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Background: To understand the recent management status in Japan, we determined the low-density lipoprotein cholesterol (LDL-C) goal attainment (GA) rate of patients initiating statin monotherapy for dyslipidemia.

Methods and Results: Dyslipidemic patients undergoing either primary prevention with high cardiovascular risk or secondary prevention (defined by 2012 Japan Atherosclerosis Society Guidelines) were retrospectively analyzed from a hospital-based claims database. In both groups, the LDL-C levels and GA rates of patients treated with intensive or standard statin monotherapy for ≥ 4 weeks (January 2012–August 2016) were evaluated. Among 1,501,013 dyslipidemic patients, 11,695 and 9,642 were included in the primary and secondary prevention groups, respectively. A total of 94% of patients underwent statin monotherapy as the initial lipid-lowering therapy, of which most ($\geq 80\%$) took intensive statins. The proportions of patients in the primary prevention group who achieved an LDL-C goal < 120 mg/dL by intensive and standard statins were 81.1% and 61.2%, respectively, and the proportions of those who achieved a goal < 100 mg/dL in the secondary prevention group were 73.3% and 48.1%, respectively. The GA rates were similar regardless of disease complications.

Conclusions: Most patients ($> 70\%$) in both groups achieved LDL-C management goals using intensive statin monotherapy. Further treatment approaches are required for high-risk patients not achieving LDL-C goals by initial statin monotherapy. Continuous efforts are crucial for adherence and persistence of lipid-lowering therapies.

Key Words: Cardiovascular risk; Dyslipidemia; Low-density lipoprotein cholesterol; Statins

Cardiovascular disease (CVD) is the leading cause of death worldwide,¹ and the second leading cause of death after malignant neoplasms in Japan.² CVD, including coronary artery disease (CAD), peripheral arterial disease (PAD), and cerebrovascular disease, is mainly caused by arteriosclerosis, and its major risk factor is an elevated level of low-density lipoprotein cholesterol (LDL-C).³ Therefore, adequate control of LDL-C is crucial for preventing CVD in patients with dyslipidemia.

Lowering of LDL-C by statin therapy generally correlates with a reduced risk of CV events regardless of a relevant history.^{4–7} A meta-analysis of 26 trials showed that a reduction in LDL-C was associated with a decrease in the risk of major coronary events.⁸ Likewise, in Japan, a reduction in LDL-C by statin therapy significantly reduces the incidence of CAD in patients with hypercholesterolemia.⁹ Additionally, a greater reduction in CV events has been observed in

patients undergoing an intensive rather than standard statin regimen.^{10,11} Based on the evidence, major international guidelines recommend statins as the first-line therapy for dyslipidemia and optimizing the intensity and dose of statins for patients at high risk.^{12,13}

The Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic CVD published in 2012 recommend statins as the first-line drug treatment for management of LDL-C, together with lifestyle modification.¹⁴ The LDL-C management target in these guidelines is < 100 mg/dL for patients with a history of CAD (secondary prevention of atherosclerotic CVD) and < 120 mg/dL for patients at high risk of CAD (primary prevention with high CV risk). Practically, the LDL-C levels in patients at high risk for CVD may not be adequately managed in the real-world setting in Japan. In 2003, less than two-thirds of patients with hyperlipidemia achieved

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Figure 1. Study scheme. LDL-C, low-density lipoprotein cholesterol.

target LDL-C levels even under lipid-lowering therapy (LLT).¹⁵ In 2010, 56.5% of patients undergoing primary prevention with high CV risk and 24.5% of those undergoing secondary prevention reached the LDL-C goals by statin therapy among 1,720 patients at high risk for atherosclerotic CVD in the Japan Lipid Guideline Achievement Program (JL-GAP).¹⁶ In addition to the preceding studies, it is essential to assess current LDL-C management using an updated large database in a real-world population, considering the remarkable increases in the number of dyslipidemic patients in the past few decades in Japan, as revealed by a national demographic study.¹⁷

The objectives of this study were to estimate the LDL-C goal attainment (GA) rate set by the 2012 JAS guidelines and the distribution of the LDL-C levels by initial statin monotherapy in patients with dyslipidemia at high CV risk, using a large database. These findings regarding current LDL-C management will raise awareness among clinicians of the importance of further appropriate management of LDL-C.

Methods

Study Design and Data Source

This retrospective observational cohort study in Japan was performed using a hospital-based claims database constructed by Medical Data Vision Co., Ltd. (MDV, Tokyo, Japan). The database consisted of healthcare claims data and laboratory test data obtained from acute care hospitals using the diagnosis procedure combination/per-diem payment system (DPC/PDPS). As of August 2016, the database comprised approximately 15.6 million inpatients and outpatients in 270 acute care hospitals, covering 16% of Japanese hospitals that use the DPC/PDPS. The diagnoses and procedure records of this administrative database have been validated in terms of their accuracy as a substitute for clinical data.¹⁸

Study Population

Patient data from 1 January 2012 to 31 August 2016 (study period) were extracted from the database. Eligible patients were ≥20 years of age with a diagnostic history of dyslipidemia (identified by the 10th Revision of the International Classification of Diseases [ICD-10] codes). During the study period, the patients were required to have a prescription record of first statin monotherapy for a total of ≥4 weeks,^{19–21} as well as at least 1 LDL-C measurement after ≥4 weeks of the first statin monotherapy. No regimen

change (either active ingredients or dosage) was allowed from the date of initiating statin therapy (index date) through to the earliest LDL-C measurement. Statins were classified into 2 types based on the general perception accepted among Japanese clinical practice: intensive statins (atorvastatin, rosuvastatin, and pitavastatin) and standard statins (fluvastatin, pravastatin, and simvastatin).²² Within the regulatory-approved dose regimen, the LDL-C-lowering efficacies were roughly distinguished as high or low for intensive or standard statins.²³ Concomitant medications other than LLT were allowed during the study period. The detailed study scheme and patient disposition are shown in **Figure 1** and **Figure 2**, respectively.

Patients with ≥1 of the following disease complications prior to or at the index date were categorized into the primary prevention with high CV risk group: diabetes mellitus (DM), chronic kidney disease (CKD), noncardiogenic cerebral infarction, and PAD. Patients with a history of CAD, such as angina pectoris and/or myocardial infarction (MI), prior to or at the index date were categorized as the secondary prevention group. These prevention groups were defined based on the JAS guidelines.¹⁴ All diagnoses and conditions were identified using the ICD-10 codes. Patients who met the criteria for both prevention groups were categorized into the secondary prevention group.

LDL-C Levels

LDL-C levels of patients were determined at the earliest measurement from >4 to ≤52 weeks after the index date while being prescribed statin monotherapy. To estimate the GA rate, the LDL-C levels were defined for each prevention group in accordance with the JAS guidelines in 2012: <120 mg/dL for the primary prevention with high CV risk group and <100 mg/dL for the secondary prevention group.¹⁴ Additionally, the following more aggressive LDL-C thresholds were used to evaluate the GA rates for comparison with previous studies performed outside of Japan: <100 and <70 mg/dL for the primary prevention with high CV risk group and secondary prevention group, respectively.

The GA rates were further evaluated based on the patients' disease complications. Complications of interest included angina pectoris, MI, DM, CKD, PAD, and noncardiogenic cerebral infarction.

Statistical Analysis

All statistical analyses were stratified by the prevention group (primary prevention with high CV risk group and

Figure 2. Patient disposition. *Risk group categories were classified in accordance with the Japan Atherosclerosis Society guidelines.¹⁴ CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; ICD-10, 10th Revision of the International Classification of Diseases; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PAD, peripheral arterial disease.

secondary prevention group) and type of statin (intensive and standard), thus categorizing the patients into the following 4 groups: primary prevention with high CV risk receiving intensive statin therapy; primary prevention with high CV risk receiving standard statin therapy; secondary prevention receiving intensive statin therapy; and secondary prevention receiving standard statin therapy. Patient demographics and baseline characteristics were descriptively analyzed. Continuous variables are presented as means and standard deviations or medians and interquartile ranges, and categorical variables are presented as numbers and/or percentages. The LDL-C GA rates and 95% confidence intervals (CIs) were estimated based on the target goals of <120 and <100 mg/dL for the primary prevention with high CV risk and secondary prevention groups, respectively,¹⁴ using the Wilson score method.²⁴ In the exploratory analyses, the achievement rates of more aggressive LDL-C thresholds were also estimated: <100 and <70 mg/dL for the primary

prevention with high CV risk group and secondary prevention group, respectively. In addition, the LDL-C GA rates and the GA rates of the more aggressive LDL-C thresholds were further estimated and stratified by disease complications. Statistical analyses were performed using SAS Release 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Patient Demography

In total, 1,501,013 patients with a diagnostic record of dyslipidemia were identified. Of the 506,979 patients aged ≥20 years and treated with any LLT, 246,359 (48.6%) were classified into the primary prevention with high CV risk group and 232,774 (45.9%) were classified into the secondary prevention group (**Figure 2**).

Among patients treated with LLT, most were on intensive statin therapy in both the primary and secondary prevention

Table 1. Characteristics of Study Patients With Dyslipidemia and High Cardiovascular Risk in Japan

Characteristics	Primary prevention with high CV risk			Secondary prevention		
	Overall (n=11,695)	Intensive statins (n=9,567)	Standard statins (n=2,128)	Overall (n=9,642)	Intensive statins (n=8,337)	Standard statins (n=1,305)
Age (years), mean±SD	65.5±12.4	64.7±12.4	68.8±11.8	69.8±11.2	69.1±11.3	73.7±10.3
Sex, male, n (%)	5,734 (49.0)	4,790 (50.1)	944 (44.4)	6,447 (66.9)	5,739 (68.8)	708 (54.3)
BMI (kg/m ²), n	3,231	2,746	485	4,459	4,090	369
Mean±SD	24.6±4.6	24.7±4.6	24.0±4.7	24.2±4.2	24.3±4.2	23.5±3.9
Smoking status, n	3,093	2,628	465	4,190	3,847	343
Smoking, n (%)	1,267 (41.0)	1,102 (41.9)	165 (35.5)	2,184 (52.1)	2,037 (53.0)	147 (42.9)
Smoking index ^a						
Mean±SD	760.7±574.1	756.9±568.8	786.5±609.7	823.5±694.4	824.2±697.4	814.1±652.9
Median (25–75th IQR)	680 (380.0–1,000.0)	673.5 (372.0–1,000.0)	700 (400.0–960.0)	720 (420.0–1,000.0)	720 (435.0–1,000.0)	740 (350.0–1,000.0)
eGFR (mL/min/1.73 m ²), n	8,322	6,885	1,437	7,047	6,205	842
Mean±SD	67.3±25.4	67.6±25.7	66.2±23.7	63.9±23.7	64.3±23.8	60.4±22.0
History of CV event						
Angina pectoris, n (%)	–	–	–	7,925 (82.2)	6,761 (81.1)	1,164 (89.2)
MI, n (%)	–	–	–	4,202 (43.6)	3,801 (45.6)	401 (30.7)
Complications						
DM, n (%)	9,177 (78.5)	7,502 (78.4)	1,675 (78.7)	4,761 (49.4)	4,076 (48.9)	685 (52.5)
Hypertension, n (%)	8,082 (69.1)	6,557 (68.5)	1,525 (71.7)	8,032 (83.3)	6,913 (82.9)	1,119 (85.7)
CKD, n (%)	1,265 (10.8)	1,074 (11.2)	191 (9.0)	853 (8.8)	743 (8.9)	110 (8.4)
PAD, n (%)	1,194 (10.2)	975 (10.2)	219 (10.3)	1,942 (20.1)	1,660 (19.9)	282 (21.6)
Noncardiogenic cerebral infarction, n (%)	3,069 (26.2)	2,510 (26.2)	559 (26.3)	1,788 (18.5)	1,472 (17.7)	316 (24.2)

^aTo obtain the smoking index, the number of cigarettes per day was multiplied by the number of years that a patient had smoked. An index of >400 was considered as heavy smoking. BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MI, myocardial infarction; PAD, peripheral arterial disease; SD, standard deviation.

groups (n=185,779 [75.4%] and n=185,226 [79.6%], respectively), while the proportions of patients on standard statin therapy were 15–19% in these prevention groups (Figures 2,3). Of the patients who met the further study eligibility criteria, 9,567 (81.8%) were treated with intensive statins and 2,128 (18.2%) with standard statins in the primary prevention with high CV risk group. Similarly, 8,337 (86.5%) were treated with intensive statins and 1,305 (13.5%) with standard statins in the secondary prevention group.

Patients' Characteristics

The patients' characteristics are summarized in Table 1. Overall, patients in the secondary prevention group were slightly older than their counterparts (65.5±12.4 vs. 69.8±11.2 years), and patients treated with standard statins were approximately 4 years older than those treated with intensive statins in both prevention groups.

More than half (67%) of the patients in the secondary prevention group were male, whereas the sex distribution in the primary prevention with high CV risk group was almost equal (male: 44–50%). The mean body mass index was similar across all 4 groups (24–25 kg/m²).

Table 2. LDL-C GA Rates According to CV Prevention Group by Type of Statin

Primary prevention with high CV risk					
Type of statin	Patients on statin, n, (%)	LDL-C goal of <120 mg/dL		LDL-C goal of <100 mg/dL	
		Patients reaching LDL-C goal, n	GA rate % (95% CI)	Patients reaching LDL-C goal, n	GA rate % (95% CI)
Overall	11,695 (100)	9,065	77.5 (76.7–78.3)	6,156	52.6 (51.7–53.5)
Intensive statins	9,567 (81.8)	7,762	81.1 (80.3–81.9)	5,517	57.7 (56.7–58.7)
Standard statins	2,128 (18.2)	1,303	61.2 (59.1–63.3)	639	30.0 (28.2–32.0)
Secondary prevention					
Type of statin	Patients on statin, n, (%)	LDL-C goal of <100 mg/dL		LDL-C goal of <70 mg/dL	
		Patients reaching LDL-C goal, n	GA rate % (95% CI)	Patients reaching LDL-C goal, n	GA rate % (95% CI)
Overall	9,642 (100)	6,738	69.9 (69.0–70.8)	2,180	22.6 (21.8–23.5)
Intensive statins	8,337 (86.5)	6,110	73.3 (72.3–74.2)	2,054	24.6 (23.7–25.6)
Standard statins	1,305 (13.5)	628	48.1 (45.4–50.8)	126	9.7 (8.2–11.4)

CI, confidence interval; CV, cardiovascular; GA, goal attainment; LDL-C, low-density lipoprotein cholesterol.

Most patients in the secondary prevention group had a history of angina pectoris (81.1% on intensive statins, 89.2% on standard statins). The prevalence of disease complications (DM, hypertension, CKD, PAD, and non-cardiogenic cerebral infarction) was comparable between the types of statins within each prevention group. DM and hypertension were predominant in the primary and secondary prevention groups ($\approx 80\%$ and 50% in the primary prevention group and $\approx 70\%$ and 80% in the secondary prevention group, respectively).

Achievement of LDL-C Targets

The overall rates of achieving the LDL-C goals set by the guidelines were relatively higher in the primary than in the secondary prevention group. In the primary prevention

group, the GA rates for the LDL-C target <120 mg/dL were 81.1% (95% CI: 80.3–81.9) and 61.2% (59.1–63.3) in patients treated with intensive and standard statins, respectively (Table 2). In the secondary prevention group, the GA rates for the LDL-C target <100 mg/dL were 73.3% (72.3–74.2) and 48.1% (45.4–50.8) in patients treated with intensive and standard statins, respectively.

Using the more aggressive LDL-C goals, the GA rates for an LDL-C level <100 mg/dL in the primary prevention group were 57.7% (56.7–58.7) and 30.0% (28.1–32.0) in patients treated with intensive and standard statins, respectively, and the corresponding GA rates for an LDL-C level <70 mg/dL in the secondary prevention group were 24.6% (23.7–25.6) and 9.7% (8.2–11.4) in patients treated with intensive and standard statins, respectively.

Table 3. LDL-C GA Rates According to Complications by Prevention Group and Type of Statin

Primary prevention with high CV risk				
Complications^a	Patients prescribed statins, n	Patients prescribed intensive statins, n (%)	Intensive statins	
			LDL-C goal of <120 mg/dL	
			Patients reaching LDL-C goal, n	GA rate, %, (95% CI)
DM	9,177	7,502 (81.7)	6,053	80.7 (79.8–81.6)
PAD	1,194	975 (81.7)	816	83.7 (81.2–85.9)
CKD	1,265	1,074 (84.9)	890	82.9 (80.5–85.0)
Noncardiogenic cerebral infarction	3,069	2,510 (81.8)	2,145	85.5 (84.0–86.8)
Secondary prevention				
Complications^a	Patients prescribed statins, n	Patients prescribed intensive statins, n (%)	Intensive statins	
			LDL-C goal of <100 mg/dL	
			Patients reaching LDL-C goal, n	GA rates, %, (95% CI)
Angina pectoris	7,925	6,761 (85.3)	4,930	72.9 (71.8–74.0)
MI	4,202	3,801 (90.5)	2,888	76.0 (74.6–77.3)
DM	4,761	4,076 (85.6)	3,063	75.1 (73.8–76.4)
PAD	1,942	1,660 (85.5)	1,241	74.8 (72.6–76.8)
CKD	853	743 (87.1)	592	79.7 (76.6–82.4)
Noncardiogenic cerebral infarction	1,788	1,472 (82.3)	1,099	74.7 (72.4–76.8)

^aThe sum of percentages sometimes exceeded 100% because some patients had multiple complications. CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; GA, goal attainment; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral arterial disease.

(Table 3 continued the next page.)

Distributions of LDL-C Levels

The LDL-C levels were symmetrically distributed across the 4 groups (Figure 4). The mean LDL-C levels met the goals defined by the guidelines for the patients in all groups except those prescribed standard statin therapy in the secondary prevention group (101.7±26.1 mg/dL).

Of the patients who achieved the target, 47.0–77.9% in the 4 groups had LDL-C levels just below their target goals (–30 mg/dL) (data not shown). Of the patients who failed to achieve the treatment goals, the majority (72–78%) was clustered just above the treatment target (+30 mg/dL) among the 4 groups.

Achievement of LDL-C Goal by Disease Complications

Overall, no specific trend in the GA rates based on disease complications was observed. Among patients prescribed intensive statin therapy in the primary prevention with high CV risk group, the GA rate for the target of <120 mg/dL ranged from 80.7% to 85.5% and did not vary regardless of the background diseases (Table 3), despite the fact that 78.4% had DM and 26.2% had noncardiogenic cerebral infarction (Table 1). Similarly, among patients treated with intensive statins in the secondary prevention group, 81.1% and 45.6% had angina pectoris and MI, respectively (Table 1), yet the GA rates for the target of <100 mg/dL ranged from 72.9% to 79.7% (Table 3).

Discussion

In this study, we estimated the rates of achieving LDL-C management goals by initial statin monotherapy in patients

with dyslipidemia in Japan using a large-scale healthcare claims database. Overall, the rates of achieving the LDL-C goal were generally higher than in previous studies, which suggested that the implementation of active treatment by initial statins leads to appropriate LDL-C management in the majority of patients (≈70%).

Compared with previous studies, the present study found higher rates of achieving LDL-C levels for optimal management: 77.5% in primary prevention and 69.9% in secondary prevention. In a 2013 study, the LDL-C GA rate for a goal of <130 mg/dL was 80% in patients with ischemic stroke, PAD, and DM and that for a goal of <100 mg/dL was 55% and 68% in patients with other CAD and recent acute coronary syndrome, respectively.²³ Similarly, in the 2010 JL-GAP study, the LDL-C GA rate of the JAS target goals by statin monotherapy was 56.5% in the primary prevention with high CV risk group and 24.5% in the secondary prevention group.¹⁶ These gaps could be explained by differences in the target patients, treatments, statin intensity, and healthcare institutions where the data were obtained. The present study targeted dyslipidemic patients in primary prevention with high CV risk and secondary prevention groups treated at acute care hospitals and whose statin monotherapy was predominantly intensive (82–87%). On the other hand, the previous studies did not limit their target to dyslipidemic patients, included only approximately 45–67% of patients treated with statin or other LLT, and/or included patients treated at university hospitals, general hospitals, and primary care clinics. Together with these differences among the previous studies, the improvement in GA rates in our study suggested that

Intensive statins		Patients prescribed standard statins, n (%)	Standard statins			
LDL-C goal of <100 mg/dL			LDL-C goal of <120 mg/dL		LDL-C goal of <100 mg/dL	
Patients reaching LDL-C goal, n	GA rate, %, (95% CI)		Patients reaching LDL-C goal, n	GA rate, %, (95% CI)	Patients reaching LDL-C goal, n	GA rate, %, (95% CI)
4,267	56.9 (55.8–58.0)	1,675 (18.3)	1,017	60.7 (58.4–63.0)	471	28.1 (26.0–30.3)
618	63.4 (60.3–66.4)	219 (18.3)	147	67.1 (60.7–73.0)	81	37.0 (30.9–43.6)
663	61.7 (58.8–64.6)	191 (15.1)	132	69.1 (62.2–75.2)	85	44.5 (37.6–51.6)
1,652	65.8 (63.9–67.6)	559 (18.2)	371	66.4 (62.4–70.2)	198	35.4 (31.6–39.5)
Intensive statins		Patients prescribed standard statins, n (%)	Standard statins			
LDL-C goal of <70 mg/dL			LDL-C goal of <100 mg/dL		LDL-C goal of <70 mg/dL	
Patients reaching LDL-C goal, n	GA rate, %, (95% CI)		Patients reaching LDL-C goal, n	GA rates, %, (95% CI)	Patients reaching LDL-C goal, n	GA rate, %, (95% CI)
1,653	24.4 (23.4–25.5)	1,164 (14.7)	557	47.9 (45.0–50.7)	117	10.1 (8.5–11.9)
982	25.8 (24.5–27.3)	401 (9.5)	220	54.9 (50.0–59.7)	46	11.5 (8.7–15.0)
1,139	27.9 (26.6–29.3)	685 (14.4)	348	50.8 (47.1–54.5)	73	10.7 (8.6–13.2)
452	27.2 (25.1–29.4)	282 (14.5)	147	52.1 (46.3–57.9)	32	11.3 (8.2–15.6)
271	36.5 (33.1–40.0)	110 (12.9)	64	58.2 (48.8–67.0)	24	21.8 (15.1–30.4)
399	27.1 (24.9–29.4)	316 (17.7)	158	50.0 (44.5–55.5)	34	10.8 (7.8–14.7)

the LDL-C goals in the guidelines are becoming more widely recognized by physicians and that increased efforts have been made to comply with these goals from 2010 to date.

Although the majority of patients (≈ 70 – 80%) in both groups achieved the LDL-C goals in the present study, the remaining patients who did not achieve the JAS guideline goals by initial statin monotherapy required further control of their LDL-C level. This is crucial for patients on secondary prevention with a greater risk for recurrent CV events.²⁵ Based on the LDL-C goal of <70 mg/dL for secondary prevention specified in the European Society of Cardiology guidelines,²⁶ <25% of patients in this study achieved the goal even under treatment with intensive statins. The JAS guidelines were recently updated in 2017; in the update, the more aggressive treatment goal of <70 mg/dL was established for secondary prevention, especially if accompanied by familial hyperdyslipidemia, acute coronary syndrome, or DM with other high-risk factors such as noncardiogenic cerebral infarction, PAD, or CKD.²⁷ We additionally assessed GA rates in accordance with the updated guidelines,²⁷ targeting those patients. The GA rates for the LDL-C goal of <70 mg/dL were 27.3% (25.9–28.8) and 11.3% (8.6–14.5) in patients treated with intensive and standard statins, respectively (Table S1), which were similar to the GA rates in patients with secondary prevention. The GA rates were similar among patients with different disease complications, except for those with familial hyperdyslipidemia. For these patients not fully controlled by statin monotherapy, physicians should choose the most appropriate treatment to achieve the LDL-C goal, such as doubling the dosage of initial statins,²⁸ and/or adding other LLT such as ezetimibe to the initial statin,²⁹ which could be expected to result in a decreased LDL-C.

The ultimate goal of controlling LDL-C is lifetime

prevention of CV events. In our study, patients with good adherence ($\geq 80\%$) to intensive or standard statin monotherapy constituted 88.4% and 89.5% of those in the primary prevention with high CV risk group and 84.0% and 89.0% of those in the secondary prevention group, respectively (the adherence rate was estimated by the proportion of days covered based on the prescription history of initial statin monotherapy from the index date to first LDL-C measurement from >4 to ≤ 52 weeks) (Table S2). This high adherence rate could have contributed to the relatively high GA rates observed in this study. For those who achieve the LDL-C goal, maintaining an optimal LDL-C level for the long term is another challenge in CVD prevention because of the asymptomatic nature of dyslipidemia,³⁰ and its prolonged treatment period, resulting in low adherence to treatment^{31–34} and thus an increased risk of CV events.³⁵

In real-world clinical settings, it is crucial to identify the patients at high CV risk in the primary prevention group. The Japan Lipid Intervention Trial (J-LIT) study showed that LDL-C concentration ranges between 100–119 and 120–139 mg/dL were not significantly different for coronary risk in the patients with primary prevention.³⁶ A sub-analysis of the same population in the J-LIT study showed that the risk of coronary events increased in those with type 2 DM (T2DM) as complications compared with those without T2DM.³⁷ It is necessary to comprehensively manage LDL-C levels taking into consideration the CV risks and the cost-effectiveness in individual patients.

Study Limitations

A retrospective cohort study using the herein-described hospital-based claims MDV database was considered to be the most appropriate approach for investigating patients with dyslipidemia and high CV risk in the real-world setting;

however, the study design has inherent limitations. First, the generalizability of the results to patients with dyslipidemia in Japan may be somewhat limited because the data were obtained from acute care hospitals. Thus, further investigation of clinics and non-acute care hospitals is required. Second, the first statin prescription was identified in the hospital participating in this database during this study period, which may have resulted in the inclusion of patients who were prescribed statins before enrollment in this study. Third, this study was performed to evaluate the effectiveness of initial treatment with statins; the effects of neither further dose adjustments (i.e., intensifications) nor switching to other statins were evaluated. Thus, our results may not reflect the effects of statin treatment at any dosage.

Conclusions

Using a large hospital-based claims database, the present study estimated the LDL-C GA rates in patients with dyslipidemia treated with statin monotherapy. In total, 77.5% and 69.9% of patients in the primary prevention with high CV risk group and secondary prevention group, respectively, achieved the LDL-C goals defined in the JAS guidelines in 2012. Patients who do not achieve the LDL-C goals by initial statin monotherapy require more aggressive treatment approaches towards achievement of the LDL-C targets. Further efforts are required to ensure persistent and adherent LLT, which could be the key to success for continuous and life-long management of LDL-C for the purpose of decreasing potential CV risks.

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Disclosure

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Supplementary Files

Supplementary File 1

Table S1. LDL-C GA rates according to the JAS guidelines 2017 (LDL-C goal of <70 mg/dL) in the secondary prevention group by type of statin

Table S2. Number of patients on statins stratified by CV prevention group according to adherence rate

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