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Second-line treatments for dyslipidemia in patients at risk of cardiovascular disease

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Abstract. Previous studies have shown that approximately 50% patients at risk of cardiovascular disease do not achieve lipid management goals. Thus, improvements dyslipidemia management are needed. We investigated the clinical choice and efficacy of second-line treatments for dyslipidemia in the Japanese clinical setting. Using a retrospective cohort design, we collected lipid profile data from patients who had been treated with hypolipidemic agents at a stable dosage for at least 12 weeks. These patients had then been administered a second-line treatment for dyslipidemia because they had not achieved the low-density lipoprotein cholesterol (LDL-C) management goals. We included data from 641 patients in our analysis. The top three choices for second-line treatment were adding ezetimibe, switching to strong statins (statin switching), and doubling the original statin dosage (statin doubling). Adding ezetimibe, statin switching, and statin doubling decreased LDL-C levels by 28.2 ± 14.5%, 23.2 ± 24.4%, and 23.5 ± 17.2%, respectively. Among these three strategies, adding ezetimibe decreased LDL-C levels to the maximum extent. In patients with dysglycemia, baseline-adjusted change in hemoglobin A1c (HbA1c) levels decreased slightly in the adding-ezetimibe, statin-switching, and statin-doubling groups, but the differences were not statistically significant among the groups (−0.10 ± 0.62%, −0.22 ± 0.54%, and −0.12 ± 0.52%, $p = 0.19$). In conclusion, the most common second-line treatment options for dyslipidemia were adding ezetimibe, statin switching, or statin doubling. Adding ezetimibe resulted in the highest reduction in LDL-C levels. These strategies did not increase HbA1c levels when administered with conventional diabetes treatment.

Key words: Dyslipidemia, Second-line treatment, Statins, Ezetimibe

EPIDEMIOLOGICAL DATA show a continuous, graded relationship between serum cholesterol levels and the risk of cardiovascular disease (CVD) [1, 2]. Although the incidence of CVD in Japan is much lower than that in Western countries [3], the frequency of CVD among the Japanese is increasing with the increasingly high levels of low-density lipoprotein cholesterol (LDL-C) [4], high levels of triglycerides (TG) [5], and low levels of high-density lipoprotein cholesterol (HDL-C) [6]. Statins are the most commonly prescribed class of LDL-C-lowering medications. They constitute the mainstream treatment for dyslipidemia in both primary and secondary prevention of CVD [7, 8, 9].

However, some studies show that patients at risk of CVD do not achieve lipid management goals after primary treatment [10, 11]. Second-line treatments for dyslipidemia are required for such patients. Many second-line treatment strategies such as adding ezetimibe, switching to strong statins, and doubling the baseline statin dosage are currently exist. However, the current trend regarding the choice and efficacy of second-line treatments for dyslipidemia is not clear.

The aim of this study was to investigate the choice and efficacy of pharmacological second-line treatments

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for dyslipidemia in the Japanese clinical setting using data from a retrospective cohort study.

Materials and Methods

This multicenter retrospective cohort study analyzed the medical records of Japanese patients with dyslipidemia treated by endocrinologists at seven teaching hospitals between January 2008 and April 2013. We included (a) patients with dyslipidemia who changed the hypolipidemic agents to achieve the LDL-C management goals according to the recommendation of Japan Atherosclerosis Society (JAS) guidelines [12], (b) patients with at least one CVD risk factor (age, cigarette smoking, glucose intolerance, family history of CVD, hypertension, or low HDL-C levels (HDL-C <40 mg/dL)), (c) patients whose baseline treatment was continued for >12 weeks without dosage change, and (d) patients undergoing second-line dyslipidemia treatment, unchanged for 24 weeks. We excluded patients with the following conditions: (a) familial hypercholesterolemia, (b) hepatobiliary disease including hepatitis B and C infection, (c) thyroid disease, (d) nephrosis, and (e) Cushing syndrome or steroid treatment.

The lipid management goals were also determined according to the guidelines of JAS [12]. The LDL-C goal was defined as <140 mg/dL for primary prevention with moderate risk (primary moderate), <120 mg/dL for primary prevention with high risk (primary high), and <100 mg/dL for secondary prevention. The HDL-C and TG goals were defined as ≥40 mg/dL and <150 mg/dL, respectively, regardless of CVD risk factors. The non-HDL-C goal was defined as <170 mg/dL for the primary-moderate group, <150 mg/dL for the primary-high group, and <130 mg/dL for the secondary-prevention group.

We collected the following data: (a) demographic characteristics (age, gender, height, and body weight), (b) CVD risk factors (age, cigarette smoking, glucose intolerance, and family history of CVD), (c) prevalence of hypertension and low HDL-C levels, (d) presence of fatty liver, (e) details of baseline treatment and second-line treatment.

We collected lipid profile data such as total cholesterol (TC), HDL-C, TG, LDL-C, and hemoglobin A1c (HbA1c, %) levels at baseline and after 24 weeks of second-line treatment. We calculated serum LDL-C levels according to the Friedewald formula [13] in case of fasting blood sampling; otherwise we used data from homogeneous assays for direct determination of LDL-C levels. We collected HbA1c data as Japan Diabetes Society (JDS) values, and then converted them to National Glycohemoglobin Standardization Program (NGSP) values using the following conversion formula: HbA1c (NGSP, %) = 1.02 × HbA1c (JDS, %) + 0.25% [14]. Patients were considered to have peripheral arterial disease if the ankle–brachial index was <0.9. Fatty liver was diagnosed by examining the results of abdominal ultrasound or computed tomography. The primary endpoint was the effect of second-line treatments on the percentage change in LDL-C levels from baseline in patients with risk of CVD. The secondary endpoint was the effect of second-line treatments on the percentage change from baseline in TC, HDL-C, non-HDL-C, and HbA1c levels.

In this study, no patient-identifying information was collected. The institutional review board waived IRB approval because this study was a retrospective chart review study.

In statistical analysis, continuous values following a normal distribution are expressed as means ± standard deviations, and analysis of variance, *post hoc* Tukey's honestly significant difference test, or Dunnett test were used for their analysis. Continuous values with asymmetric distribution are expressed as medians and interquartile ranges, and Kruskal–Wallis test was used for their analysis. Paired *t*-test was used to evaluate the effects of each second-line treatment on lipid profiles and HbA1c levels. HbA1c levels were adjusted for baseline characteristics by a multiple linear regression model. Categorical values are expressed as frequencies and percentages, and Pearson's chi-square test was used for their analysis. The last-observation-carried-forward method was used to impute missing values. A two-sided p value of <0.05 was considered statistically significant. We used JMP 10 software (SAS Institute Inc., Cary, NC, USA) for all statistical analyses.

Results

We initially detected 854 patients whose hypolipidemic agents were changed irrespective of their status with regard to the achievement of their lipid management goal. Among them, 645 patients met our inclusion criteria. Four patients were later excluded, leaving 641 patients, whose records were used in our analysis.

Baseline treatment of dyslipidemia and clinical characteristics are shown in Table 1. The top three base-

Table 1 Clinical characteristics according to baseline treatment of dyslipidemia

	Total	Strong-statin monotherapy	Standard-statin monotherapy	Ezetimibe monotherapy	*p* value[1]
Number (%)	641 (100)	356 (56)	137 (21)	34 (5)	
Age (years)	63.2 ± 12.4	62.4 ± 12.4	65.4 ± 12.4	64.1 ± 10.6	0.05
Male, n (%)	396 (62)	229 (64)	75 (55)	15 (44)	0.02
Body mass index (kg/m^2)	25.3 ± 3.7	25.5 ± 3.7	25.0 ± 4.0	26.0 ± 3.4	0.32
History of CVD, n (%)	200 (31)	128 (36)	36 (26)	6 (18)	0.02
History of ischemic stroke, n (%)	65 (10)	34 (10)	17 (12)	2 (6)	0.45
Family history of CVD, n (%)	76 (12)	54 (15)	11 (8)	2 (6)	0.04
Low HDL-C, n (%)	103 (16)	64 (1)	13 (10)	3 (9)	0.04
Smoking, n (%)	275 (43)	176 (49)	45 (33)	9 (27)	<0.001
Alcohol, n (%)	164 (26)	104 (29)	31 (23)	4 (12)	0.04
Diabetes, n (%)	501 (78)	273 (77)	108 (79)	29 (85)	0.49
Hypertension, n (%)	392 (61)	230 (65)	80 (58)	22 (65)	0.43
PAD, n (%)	34 (5)	19 (5)	6 (4)	2 (6)	0.89
Fatty liver, n (%)	214 (33)	118 (33)	36 (2)	17 (50)	0.03
TC (mg/dL)	232.0 ± 37.8	227.2 ± 35.9	233.0 ± 37.5	242.1 ± 41.0	0.04
TG (mg/dL)	154 (115.8, 227.0)	154 (111.0, 221.5)	134 (112.0, 195.0)	189 (157.3, 239.0)	0.004
LDL-C (mg/dL)	148.0 ± 29.1	143.6 ± 28.0	148.9 ± 27.9	160.4 ± 34.2	0.002
HDL-C (mg/dL)	53.7 ± 16.5	54.0 ± 16.7	55.9 ± 16.3	53.6 ± 14.6	0.50
Non-HDL-C (mg/dL)	178.3 ± 36.2	173.2 ± 33.6	177.1 ± 36.9	188.5 ± 40.2	0.04
HbA1c (%)	7.39 ± 1.30 (n = 565)	7.39 ± 1.29 (n = 320)	7.68 ± 1.51 (n = 114)	7.11 ± 1.12 (n = 33)	0.04

Data are expressed as number (%), mean ± standard deviation or median (interquartile range). [1], Differences between strong-statin monotherapy, standard-statin monotherapy, and ezetimibe monotherapy groups were compared with analysis of variance, Kruskal–Wallis test or Pearson's chi-square test. CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; PAD, peripheral arterial disease; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c.

line treatments chosen were strong-statin monotherapy (56%), standard-statin monotherapy (21%), and ezetimibe monotherapy (5%) (Fig. 1). In the strong-statin monotherapy group, patients were treated with atorvastatin (n = 129, 20%, 11.2 ± 7.1 mg/day), pitavastatin (n = 115, 18%, 1.4 ± 0.6 mg/day), and rosuvastatin (n = 112, 18%, 3.6 ± 2.1 mg/day). In the standard-statin group, patients were treated with pravastatin (n = 122, 19%, 9.4 ± 4.0 mg/day), fluvastatin (n = 8, 1%, 26.9 ± 15.3 mg/day), and simvastatin (n = 7, 1%, 7.2 ± 2.6 mg/day). Baseline statins were used in a relatively low dose compared with the maximum dosage of each drug. In the ezetimibe monotherapy group, all patients took 10 mg of ezetimibe (n = 34, 5%, 10 mg/day). Baseline LDL-C levels were lower in patients with increased CVD risk than in those with moderate risk (Table 2). In primary-high and secondary-prevention groups, second-line treatments were undertaken if LDL-C levels exceeded each management goal by approximately 30 mg/dL.

Choices of second-line treatments for dyslipidemia and their effects of are shown in Fig. 2 and Table 3.

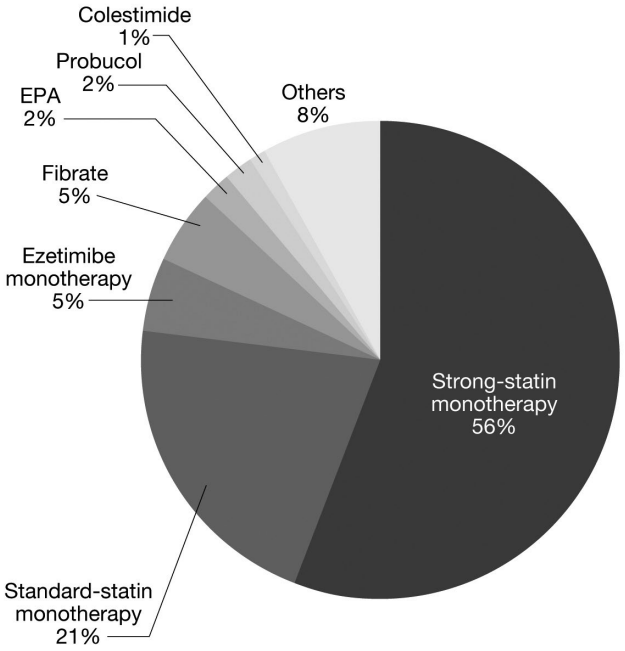

Fig. 1 Baseline treatment of dyslipidemia
EPA, eicosapentaenoic acid

Table 2 Timing of initiation of second-line therapy for dyslipidemia

CVD risk	n	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)	Non-HDL-C (mg/dL)
Primary moderate	45	172.0 ± 24.6	59.5 ± 14.4	150 (102.5, 239.0)	202.2 ± 34.0
Primary high	396	153.6 ± 27.4‡	54.7 ± 16.9	155.5 (115.3, 232.0)	184.0 ± 36.4‡
Secondary prevention	200	131.7 ± 25.0‡	50.2 ± 15.7‡	155 (116.0, 208.0)	161.8 ± 29.1‡
p value[1]		<0.001	<0.001	0.85	<0.001

Data are expressed as numbers, mean ± standard deviation or median (interquartile range). [1], Differences between CVD risks were compared with analysis of variance or Kruskal–Wallis test. CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol. ‡, $p < 0.05$ with *post-hoc* Dunnett test *vs*. primary-moderate CVD risk group.

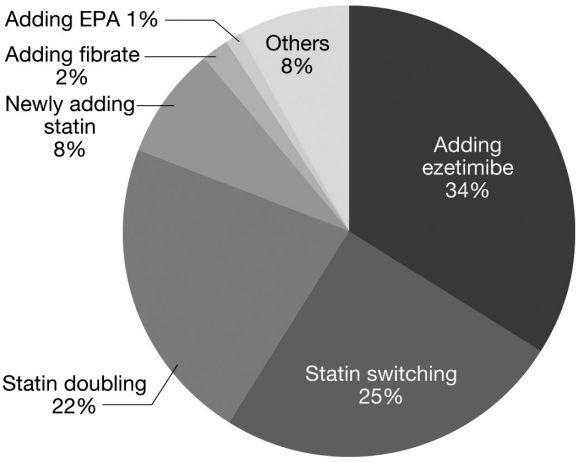

Fig. 2 The choice of second-line therapies for dyslipidemia
EPA, eicosapentaenoic acid

Table 3 Characteristics of the top three choices and effects of second-line therapy.

	Adding ezetimibe	Statin switching	Statin doubling	Others	*p* value[1]
Number (%)	218 (34)	158 (25)	143 (22)	122 (19)	
Age (years)	62.2 ± 12.4	62.9 ± 13.5	63.4 ± 11.2	65.1 ± 12.1	0.68
Male, n (%)	138 (63)	98 (62)	94 (66)	66 (54)	0.80
Body mass index (kg/m^2)	25.6 ± 3.9	25.7 ± 4.1	24.8 ± 3.4	24.9 ± 3.3	0.13
History of CVD, n (%)	81 (37)	55 (35)	35 (25)	29 (24)	0.04
History of ischemic stroke, n (%)	21 (10)	13 (8)	20 (14)	11 (10)	0.23
Family history of CVD, n (%)	38 (17)	16 (10)	16 (11)	6 (5)	0.08
Low HDL-C, n (%)	37 (17)	19 (12)	26 (18)	21 (17)	0.28
Cigarette smoking, n (%)	101 (46)	60 (38)	76 (54)	38 (31)	0.03
Alcohol, n (%)	48 (22)	41 (26)	48 (34)	27 (22)	0.05
Diabetes, n (%)	161 (74)	125 (79)	121 (85)	94 (77)	0.05
Hypertension, n (%)	135 (62)	92 (58)	88 (62)	77 (63)	0.75
PAD, n (%)	13 (6)	6 (4)	2 (1)	13 (11)	0.10
Fatty liver, n (%)	66 (30)	57 (36)	47 (33)	44 (36)	0.50
Baseline TC (mg/dL)	230.5 ± 37.3	229.7 ± 42.3	230.4 ± 29.5	239.6 ± 40.7	0.98
Baseline LDL-C (mg/dL)	148.9 ± 28.2	144.8 ± 31.2	144.6 ± 24.0	154.8 ± 32.0	0.24
Baseline HDL-C (mg/dL)	53.3 ± 17.5	56.0 ± 16.8	53.0 ± 14.9	52.2 ± 16.2	0.19
Baseline TG (mg/dL)	152 (111.0, 239.8)	134 (104.5, 182.5)	170 (122.5, 241.0)	170.5 (126.3, 258.0)	0.003
Baseline non-HDL-C (mg/dL)	177.2 ± 35.2	173.7 ± 40.3	177.4 ± 30.1	187.4 ± 37.5	0.56
Baseline HbA1c (%)	7.37 ± 1.40 (n = 193)	7.38 ± 1.22 (n = 138)	7.56 ± 1.20 (n = 126)	7.25 ± 1.33 (n = 108)	0.40
Change in TC (%)	−19.0 ± 12.6**	−15.5 ± 15.0**‡	−16.2 ± 15.2**	−16.7 ± 14.0**	0.04
Change in LDL-C (%)	−28.2 ± 14.5**	−23.2 ± 24.4**‡	−23.5 ± 17.2**‡	−22.3 ± 20.0**	0.02
Change in HDL-C (%)	0.2 ± 18.4	−2.2 ± 18.8	−1.9 ± 15.5	0.4 ± 18.6	0.35
Change in non-HDL-C (%)	−24.2 ± 16.7**	−19.5 ± 19.7**‡	−20.4 ± 19.2**	−20.9 ± 17.0**	0.03
Change in HbA1c (%)	−0.24 ± 1.18*	−0.03 ± 1.18	−0.21 ± 1.03*	0.01 ± 0.93	0.22
Adjusted change in HbA1c (%)	−0.10 ± 0.62*	−0.22 ± 0.54*	−0.12 ± 0.52*	−0.02 ± 0.52	0.19

Data are expressed as number (%), mean ± standard deviation, or median interquartile range. [1], Differences between adding-ezetimibe, statin-switching, and statin-doubling groups were compared with analysis of variance, Kruskal–Wallis test or Pearson's chi-square test. *, $p < 0.05$ in paired *t*-test *vs*. each baseline. Change in HbA1c was adjusted for age, gender, baseline treatment for dyslipidemia and baseline HbA1c. **, $p < 0.001$ in paired *t*-test *vs*. each baseline; ‡, $p < 0.05$ in *post-hoc* Dunnett test vs. the adding-ezetimibe group; TC, total cholesterol; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c

The top three second-line treatments were: adding ezetimibe (34%), switching from one statin to other strong statins (statin switching, 25%), and doubling the statin dosage (statin doubling, 22%). Among these three second-line treatments, baseline characteristics were similar, apart from the history of CVD, cigarette smoking, and TG levels.

As shown in Table 3 and Fig. 3a, with regard to the intervention effect, all the top three treatment groups showed significantly decreased LDL-C levels from the baseline and the effect was greater in the adding-ezetimibe group (−28.2 ± 14.5%, $p < 0.001$) than in the statin-switching group (−23.2 ± 24.4%, $p < 0.001$) and the statin-doubling group (−23.5 ± 17.2%, $p < 0.001$). Adding ezetimibe, statin switching, and statin doubling significantly decreased TC levels by 19.0 ± 12.6% ($p < 0.001$), 15.5 ± 15.0% ($p < 0.001$), and 16.2 ± 15.2% ($p < 0.001$), respectively, from the baseline. The adding-ezetimibe group showed a greater decrease in TC levels than the statin-switching group ($p = 0.03$). HDL-C levels were not significantly changed from the baseline in these three groups. Adding ezetimibe, statin switching, and statin doubling also significantly decreased non-HDL-C levels by 24.2 ± 16.7% ($p < 0.001$), 19.5 ± 19.7% ($p < 0.001$), and 20.4 ± 19.2% ($p < 0.001$), respectively, from the baseline (Fig. 3b). The adding-ezetimibe group showed a greater decrease in non-HDL-C levels than the statin-switching group ($p = 0.03$).

In patients with dysglycemia, after the changes in HbA1c levels were adjusted (adjusted for age, gender, BMI, baseline treatment for dyslipidemia, and baseline HbA1c levels), compared with those at baseline, these levels decreased slightly, but significantly, in the adding-ezetimibe (−0.10 ± 0.62%, 95% confidence interval (CI) −0.19 to 0.00, $p = 0.04$), statin-switching (−0.22 ± 0.54%, 95% CI −0.31 to −0.12, $p < 0.001$) and statin-doubling (−0.12 ± 0.52%, 95% CI −0.21 to −0.02, $p = 0.02$) groups, but the differences were not statistically significant among the other groups ($p = 0.19$).

In the statin-switching group, the top three switching patterns were caused by changing from pravastatin to rosuvastatin (34%), atorvastatin to rosuvastatin (23%), and pravastatin to pitavastatin (16%). Most effective switching pattern was demonstrated after the change from pravastatin to rosuvastatin, resulting in a reduction in LDL-C levels by 29.1 ± 15.5% from the baseline ($p < 0.001$, Table 4).

Statin-doubling group included the treatment with rosuvastatin (34%), pitavastatin (31%), atorvastatin (27%), and pravastatin (8%). The results of simvastatin doubling are not shown; there was only one case of such treatment.

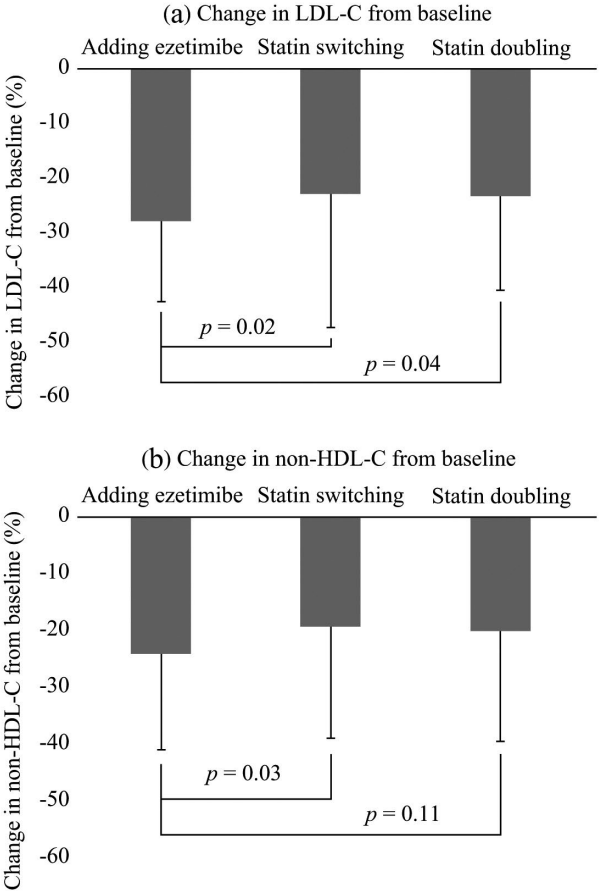

Fig. 3 The effect of top three choices of second-line therapy for dyslipidemia.
Data are expressed as change in LDL-C or non-HDL-C ± standard deviation from baseline, LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; *p* values were determined by analysis of variance and *post-hoc* Dunnett test.

All the statin-doubling groups showed significant decrease in TC, LDL-C, and non-HDL-C levels from their corresponding baselines, but the differences were not statistically different among these groups (Table 5).

The rates of achievement of lipid management goals by second-line treatments for dyslipidemia are shown in Table 6. Although 66.7% patients with primary moderate CVD risk achieved the LDL-C management goal, this ratio decreased to 58.5% for patients undergoing second-line therapy. Only 36.7% of patients under secondary-prevention therapy achieved all the lipid management goals (including LDL-C, TG, HDL-C, and

Table 4 Effect of top three choices of statin switching

Baseline treatment Switched to	Pravastatin Rosuvastatin	Atorvastatin Rosuvastatin	Pravastatin Pitavastatin	*p* value[1]
n (% of statin switching)	54 (34)	36 (23)	25 (16)	
Baseline dose (mg/day)	10.0 ± 3.9	10.3 ± 4.0	9.0 ± 3.2	
Switched dose (mg/day)	2.7 ± 0.7	4.0 ± 1.9	1.4 ± 0.5	
Change in TC (%)	−18.9 ± 11.9**	−8.6 ± 17.6*‡	−16.5 ± 11.2**	0.003
Change in LDL-C (%)	−29.1 ± 15.5**	−14.2 ± 24.9*‡	−23.4 ± 18.2**	0.003
Change in HDL-C (%)	−1.2 ± 18.8	−1.3 ± 17.1	0.5 ± 21.7	0.92
Change in non-HDL-C (%)	−25.3 ± 16.0**	−11.6 ± 22.4*‡	−20.2 ± 14.9**	0.003
Change in HbA1c (%)	−0.18 ± 0.99	−0.10 ± 0.86	−0.37 ± 1.11	0.58

TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; [1], Differences between three statin switching groups were compared with analysis of variance; *, $p < 0.05$ in paired *t*-test *vs*. each baseline; **, $p < 0.001$ in paired *t*-test *vs*. each baseline; ‡, $p < 0.05$ in *post-hoc* Dunnett test *vs*. pravastatin to rosuvastatin-switching group

Table 5 Effect of statin doubling for dyslipidemia

	Rosuvastatin (n = 49)	Pitavastatin (n = 44)	Atorvastatin (n = 38)	Pravastatin (n = 11)	*p* value[1]
N (% of statin doubling)	49 (34)	44 (31)	38 (27)	11 (8)	
Baseline dose (mg/day)	2.45 ± 0.25	1.09 ± 0.29	6.51 ± 2.43	7.27 ± 2.61	
Change in TC (%)	−14.6 ± 15.8**	−18.7 ± 12.3**	−16.9 ± 18.9**	−12.6 ± 6.7**	0.50
Change in LDL-C (%)	−22.3 ± 20.4**	−24.0 ± 16.7**	−26.6 ± 15.3**	−18.5 ± 5.7**	0.49
Change in HDL-C (%)	1.0 ± 11.4	−3.1 ± 18.5	−2.8 ± 15.7	−7.3 ± 17.2	0.34
Change in non-HDL-C (%)	−19.4 ± 19.6**	−22.6 ± 16.0**	−21.4 ± 24.2**	−14.1 ± 6.3**	0.58
Change in HbA1c (%)	−0.07 ± 0.76 (n = 40)	−0.09 ± 1.05 (n = 44)	−0.56 ± 1.27* (n = 35)	−0.15 ± 0.38 (n = 7)	0.14

TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; [1], Differences between four statin doubling groups were compared with analysis of variance; *, $p < 0.05$ in paired *t*-test *vs*. each baseline; **, $p < 0.001$ in paired *t*-test *vs*. each baseline.
The results for simvastatin doubling are not shown because there was only one case.

Table 6 Achievement rate of lipid management goal with second-line therapy for dyslipidemia

	CVD Risk	Total	Adding ezetimibe	Statin switching	Statin doubling	*p* value
Achievement in LDL-C (%)	Primary moderate	66.7	76.9	57.1	100	0.10
	Primary high	66.4	69.4	70.8	71.3	0.95
	Secondary	58.5	63.0	60.0	57.1	0.83
Achievement in overall profile (%)	Primary moderate	42.2	46.2	35.7	71.4	0.30
	Primary high	29.6	35.8	31.5	30.7	0.68
	Secondary	36.7	38.3	38.2	40.0	0.98

CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol
P values were determined by Pearson chi-square test between the adding-ezetimibe, statin-switching, and statin-doubling groups.

non-HDL-C goals).

Discussion

Our study showed that even when a second-line treatment for dyslipidemia was administered, 33.3%–41.5% patients at risk of CVD did not achieve the LDL-C management goals. If we take into account the overall lipid profile management, 63.3% patients under secondary-prevention therapy did not achieve their lipid management goals.

The choice of the best treatment strategy for patients who do not achieve the optimal lipid levels during the primary therapy is a common problem. The top three strategies chosen by endocrinologists in our study were adding ezetimibe, statin switching, and statin doubling. Adding ezetimibe resulted in the highest LDL-C reduction rate among these three treatments. Some studies previously reported that adding ezetimibe to the original treatment was more effective in decreasing LDL-C levels than increasing statin doses [15, 16].

It has been also reported that monotherapy with high doses of statins decreases limited LDL-C levels because continuous use of statins increases the absorption of cholesterol from the intestine [17, 18]. In our analysis, the reduction in LDL-C levels after adding ezetimibe to standard-statin treatment (n = 33) or strong-statin treatment (n = 142) was not statistically significant (−30.0 ± 12.9% *vs*. −30.2 ± 14.3%, $p = 0.95$). Statin doubling decreased LDL-C levels by 23.5% from the baseline.

Some previous studies in Western countries have reported that statin doubling decreases LDL-C levels by only 6%; this effect is called a "rule of six" [17, 19]. However, in our study, the decrease in LDL-C levels achieved by statin doubling was >6%. Some other studies in Asian population also show similar high rates for LDL-C level reduction from 11.4% to 17.9% [15, 20, 21]. These interstudy variations in drug response of LDL-C levels might have been caused by difference in baseline statin dosage. Strong inhibition of cholesterol synthesis by higher doses of statins can increase the intestinal cholesterol absorption leading to better response to ezetimibe. On the contrary, the increase of the intestinal cholesterol absorption in patients with low-dose statins may be relatively mild. Thus these patients may show better response to statin doubling treatment, as was observed in this research.

With regard to the effect on glucose metabolism, some studies have shown that statin use might cause insulin resistance and deterioration in glucose metabolism [22, 23]. Meta-analysis of some randomized controlled studies [24], including the JUPITER trial [25], has reported that statin use can cause diabetes onset. Our study showed that the intensification of lipid management after modification of statin treatment did not worsen glucose levels. Even though our study was a retrospective cohort study and diabetes treatment was not controlled for, we found that HbA1c levels were not elevated even after adjustment for baseline characteristics. The data which show deterioration in glucose levels after modifications in lipid management strategies, including statin switching and statin doubling, can be covered by the conventional treatment strategies in patients with diabetes.

There are some limitations to this study. First, our study was conducted using a retrospective cohort design, and selection bias may influence the results. However, we decided on a retrospective cohort design because we intended to assess actual choices of second-line treatments for dyslipidemia and their effects. Second, most of the patients were treated with low-dose statins at baseline; it had been assumed that most of them might have diabetes and management was undertaken after considering the adverse effect of statins on diabetes. Third, because lipid panels were obtained after fasting for only a third of the patients, the effect of the treatment on TG levels could not be accurately assessed. Forth, in two third of patients, their LDL-C levels were measured by the direct measurement method, which is not yet reliable because it has not been standardized. [26, 27] Recent studies reported non–HDL-C shows accuracy for cardiovascular risk score classification compared to both directly measured and calculated LDL-C [28, 29, 30]. However, in our study, the adding-ezetimibe group also showed a greater decrease in non-HDL-C levels than other two groups. Finally, because all patients were treated by endocrinologists and most of the patients had dysglycemia, the choice of second-line therapy might have been biased towards the drugs may not cause deterioration in glucose levels, such as pitavastatin and ezetimibe [31, 32].

In conclusion, adding ezetimibe as the second-line treatment achieved a higher reduction in LDL-C levels than statin switching or statin doubling. These treatment modifications did not worsen HbA1c levels in patients undergoing diabetes treatment. The differences between the rates of achievement of lipid management goals after these treatments were not statistically sig-

nificant. Although some of the results were promising, >60% patients did not achieve the overall goal of lipid management. These data suggest that patients with CVD risks might need a varied, precisely controlled intensification of treatment for dyslipidemia.

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