Medication Adherence/Persistence and Demographics of Japanese Dyslipidemia Patients on Statin-Ezetimibe as a Separate Pill Combination Lipid-Lowering Therapy — An Observational Pharmacy Claims Database Study —

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Background: This study aimed to identify potential predictors of medication adherence and persistence with statin-ezetimibe combinational lipid-lowering therapy (LLT) as a separate pill combination in a real-world setting in Japan.

Methods and Results: Patients newly switched to statin-ezetimibe combinational LLT from statin monotherapy were identified within a Japanese national pharmacy claims database during January 2015 to April 2018. Adherence and persistence were measured by the proportion of days covered (PDC), time to treatment discontinuation and persistence rate at 1 year. A stepwise multivariate logistic regression model and Cox proportional hazards regression model were used to explore potential predictors associated with adherence and persistence, respectively. Among 6,921 patients, 71.9% were adherent (PDC $\geq 80\%$), and 83.6% were persistent at 1 year after initiation. Patients aged ≤ 54 years and ≥ 75 years were prone to be more non-adherent. Secondary prevention was associated with better adherence and longer persistence. Concomitant use of medications for depression/anxiety was associated with shorter persistence, whereas use of antihypertensive drugs was associated with better adherence and persistence.

Conclusions: Age, concomitant use of certain classes of medications (or the existence of these diseases) and secondary prevention were associated with adherence and persistence of statin-ezetimibe combinational LLT. Given that dyslipidemia is a chronic disease requiring life-long control, active interventions are required for patients with poor adherence and persistence.

Key Words: Adherence; Dyslipidemia; Ezetimibe; Risk factors; Statins

Statin monotherapy is the recommended first-line treatment for controlling low-density lipoprotein cholesterol (LDL-C), followed by combination therapy of a statin with other lipid-lowering medicines such as ezetimibe or colestimide. This is well specified in the Japan Atherosclerosis Society (JAS) guidelines, as well as the USA and European guidelines.^{1–3} Dyslipidemia is a known risk factor for cardiovascular disease (CVD). Reduction of plasma LDL-C is crucial for preventing CVD events and clinical trials suggest a 1.0 mmol/L reduction in LDL-C is associated with reductions of 10% in all-cause death, 24% in major coronary events and 15% in stroke events.^{4,5}

Adherence and persistence to statin therapy are reported to be lower in real-world clinical settings^{6–9} compared with well-controlled patients in the clinical trial setting where participants are actively managed for treatment compliance. Low adherence to medication can lead to poor control of LDL-C,^{9–12} resulting in a poor prognosis for CVD.¹³ Consequently, the importance of adhering to lipid-lower-

ing therapy (LLT) for the management of CVD is emphasized in the treatment guidelines. In order to provide the most optimal patient support and maximize the efficacy of treatment, it is important to identify the characteristics of patient groups with poor adherence or persistence, or the potential predictors of poor adherence and persistence of patients who need strict management of LDL-C.

Factors that could affect medication adherence and discontinuation of statin monotherapy have been discussed in previous studies.^{14–17} Comorbidities have been shown to both positively and negatively affect adherence. For example, patients with dementia or respiratory disorders are at higher risk of being non-adherent with statin monotherapy, whereas patients with diabetes mellitus or hypertension showed a relatively low risk of medication discontinuation.^{14,17} A pooled meta-analysis of 45 studies suggested that patients on secondary prevention for CVD had better adherence than patients on primary prevention.¹⁴ Patients on secondary prevention may have a strong awareness of the impor-

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tance of LDL-C control, given that they have experienced CVD events already, and it may affect patients' drug-taking behavior with statin therapy. Although the risk factors for discontinuation and non-adherence of statin monotherapy have been studied previously, it remains unclear which patients in Japan on statin-ezetimibe combinational LLT for better management of LDL-C are prone to poor adherence and persistence.

To our knowledge, this is the first study to explore the factors associated with the adherence and persistence of statin-ezetimibe LLT as a separate pill combination (SPC) regimen in a real-world setting. Utilizing one of the largest pharmacy claims database in Japan, this study aimed to identify potential predictors of medication adherence and persistence with the combination of statin-ezetimibe LLT in patients with dyslipidemia.

Methods

Study Design and Subjects

This was a retrospective study using Japanese national pharmacy dispensing claims data from January 2015 to April 2018 (**Figure 1**). Eligible patients were aged ≥ 20 years and had been switched from statin monotherapy to the combination of statin with ezetimibe between July 2015 to April 2017. All statins on the Japanese market (pravastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin and rosuvastatin) were considered. The index date was defined as the date when statin and ezetimibe were initially and concomitantly dispensed during July 2015 to April 2017 to the individual patient. Patients were included if they had another dispensing claim of statin-ezetimibe during the follow-up period after the index date, and had dispensing claims of statins as the only lipid-lowering agent during the look-back period. Patients were excluded if they could not be followed up for 1 year post-index and the 6-month pre-index period, and had any add-on lipid-lowering agents other than a statin or ezetimibe during the follow-up period.

Data Source

Prescription claims data were extracted from the IQVIA National Prescription Audit database. This database covers roughly 15.1% of all the national prescription records in 2016: 120 million prescriptions and 24.8 million patients.

The dispensing records were obtained from approximately 7,500 out-of-hospital pharmacies, which includes prescription information (e.g., generic names of therapeutic drugs, dosage forms, the date of dispensing, the number of days of supply) and patient characteristics (e.g., age, sex). The age distribution of the population in the database was similar to patients' demographics at the national level, based on surveys from the Ministry of Health, Labour and Welfare.¹⁸ All individual records were anonymized for secondary data analysis, and individuals could not be identified or linked to other data sources.

Outcomes: Adherence and Persistence

The primary outcome of this study was to evaluate the medication adherence of the dyslipidemic patients satisfying the study's criteria. The proportion of days covered (PDC) method was used to define adherence. PDC was calculated as the total number of dispensed days during a specified observation period divided by the number of observation days.¹⁹ Because the existence of multiple concomitant medications was under consideration of adherence measurements in this study,^{20,21} the number of days patients had both classes of medications (i.e., statin and ezetimibe) available during the 1-year post-index period was divided by 360 days for calculation of PDC. Patients with PDC $< 80\%$ were categorized as non-adherent, and those with PDC $\geq 80\%$ were adherent. The threshold of 80% is commonly used for evaluating adherence to medications in previous studies.¹⁹

The secondary outcome was to evaluate persistence with combination therapy (statin-ezetimibe). Persistence was measured as (1) time to discontinuation, and (2) estimated persistence rate at 1 year. Time to discontinuation for an individual patient was defined as the number of days from the index date to the date when the patient discontinued the statin-ezetimibe combination regimen. Considering the gap between prescription date and supply, we regarded discontinuation as occurring when the first gap ≥ 90 days without concomitant use of statin and ezetimibe appeared. The discontinuation date was determined as the date when the prescription of the previous combination regimen of statin-ezetimibe ended. Persistence was considered as censored and the time to discontinuation was from the index date to the end of follow-up in the time-to-event analysis if

the ≥ 90 -day gap could not be identified before the end of follow-up. The ≥ 90 -day grace period has been used in many previous studies with regard to discontinuation of lipid-lowering drugs.^{22,23} The estimated persistence rate at 1 year was the estimated proportion of patients with continued use of statin-ezetimibe at 1-year post-index.

Potential Predictors

The following variables were considered as potential predictors for adherence and persistence: age, sex, secondary prevention of CVD events, therapeutic area of interest, the number of concurrent therapeutic areas, the number of concurrent medications and the number of pills administered concurrently. Patients' concurrent therapeutic areas were estimated from the medication information and the drug's Anatomical Therapeutic Chemical (ATC) code prescribed during the look-back period. The therapeutic areas of interest to us were hypertension (ATC code: C02, C03, C07, C08, C09), diabetes mellitus (A10), chronic obstructive pulmonary disease/asthma (R03), gout (M04), depression/anxiety (N05B, N06A, N06C) and dementia (N06D, N07AB), which were either major comorbidities in patients with LLT or diseases associated with medication adherence. If patients had medications for coronary artery disease (ATC code: B01, C01) before the index date, they were considered as secondary prevention of CVD events. The number of concurrent medications was determined by the medications provided and available at the index date, and the number of pills received concurrently was counted accordingly.

Statistical Analysis

Mean and standard deviation are reported as continuous variables, and frequency (N) and percentage (%) are reported as categorical variables. The proportions of patients being adherent or non-adherent, and estimated persistence rate at 1-year post-index were summarized by characteristics. A stepwise multivariate logistic regression model was used to explore potential predictors associated with being adherent. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) are presented. For persistence, we used the Kaplan-Meier method to plot the time to discontinuation and performed a log-rank test to examine the difference between covariates, and calculate the estimated persistence rate at 1 year. A stepwise Cox proportional hazards regression model was used to explore potential predictors associated with time to discontinuation. Adjusted hazard ratios (HRs) and 95% CIs are presented. As the stepwise procedure, the covariates remaining in the model were determined statistically with a threshold for inclusion set at $P < 0.05$. The variable selection process was automatically performed by the statistical program. A significance level was set at $\alpha = 0.05$ and all tests were two-sided. All the statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patients' Characteristics

A total of 24,661 patients received statin-ezetimibe as the SPC regimen during the period between January 2015 and April 2017. Of them, a total of 6,921 patients met the eligibility criteria and were identified as the study population who were newly initiated to a statin-ezetimibe regimen after being switched from statin monotherapy (**Supplementary Figure 1**). The mean age of the patients was 64.3 years, and

Table 1. Baseline Patients' Characteristics

Characteristic	Overall (n=6,921)
Age (years)	
Mean $\pm$ SD	64.3 $\pm$ 12.1
Age group, n (%)	
<45	468 (6.8)
45–54	1,027 (14.8)
55–64	1,679 (24.3)
65–74	2,288 (33.1)
≥ 75	1,459 (21.1)
Sex, male, n (%)	3,626 (52.4)
Secondary prevention, yes, n (%)	3,219 (46.5)
Therapeutic area of interest, n (%)	
Diabetes	2,043 (29.5)
Hypertension	4,567 (66.0)
Respiratory disease	521 (7.5)
Gout	1,026 (14.8)
Dementia	72 (1.0)
Depression/anxiety	709 (10.2)
No. of concurrent therapeutic areas	
Mean $\pm$ SD	1.8 $\pm$ 1.2
Group, n (%)	
0	1,196 (17.3)
1	1,700 (24.6)
2	2,140 (30.9)
3	1,435 (20.7)
≥ 4	450 (6.5)
No. of concurrent medications	
Mean $\pm$ SD	3.0 $\pm$ 2.6
Group, n (%)	
0	1,352 (19.5)
1	1,028 (14.9)
2	969 (14.0)
3	896 (12.9)
4	839 (12.1)
5	648 (9.4)
6–7	778 (11.2)
≥ 8	411 (5.9)
No. of pills received concurrently	
Mean $\pm$ SD	4.1 $\pm$ 4.0
Group, n (%)	
0	1,394 (20.1)
1	902 (13.0)
2	814 (11.8)
3	642 (9.3)
4	640 (9.2)
5	491 (7.1)
6–7	789 (11.4)
8–10	723 (10.4)
≥ 11	526 (7.6)

SD, standard deviation.

over half were aged ≥ 65 years. Patients receiving secondary prevention accounted for 46.5% of the study population. Regarding comorbidities, nearly two-thirds of patients suffered from hypertension (66.0%), followed by diabetes (29.5%) and gout (14.8%). The average number of concur-

Table 2. Adherence by Patients' Characteristics		
Characteristic	Adherent (PDC $\geq$80%), n (%)	P value*
Age group, n (%)		<0.0001
<45	300 (64.1)	
45–54	683 (66.5)	
55–64	1,229 (73.2)	
65–74	1,715 (75.0)	
$\geq$ 75	1,048 (71.8)	
Sex, n (%)		<0.0001
Male	2,685 (74.0)	
Female	2,290 (69.5)	
Secondary prevention, n (%)		<0.0001
Yes	2,535 (78.8)	
No	2,440 (65.9)	
Therapeutic area of interest, n (%)		
Diabetes	1,486 (72.7)	0.3067
Hypertension	3,438 (75.3)	<0.0001
Respiratory disease	359 (68.9)	0.116
Gout	784 (76.4)	0.0005
Dementia	47 (65.3)	0.2102
Depression/anxiety	491 (69.3)	0.1001
No. of concurrent therapeutic areas, n (%)		<0.0001
0	750 (62.7)	
1	1,166 (68.6)	
2	1,609 (75.2)	
3	1,099 (76.6)	
$\geq$ 4	351 (78.0)	
No. of concurrent medications, n (%)		<0.0001
0	848 (62.7)	
1	686 (66.7)	
2	698 (72.0)	
3	674 (75.2)	
4	647 (77.1)	
5	510 (78.7)	
6–7	603 (77.5)	
$\geq$ 8	309 (75.2)	
No. of pills received concurrently, n (%)		<0.0001
0	872 (62.6)	
1	605 (67.1)	
2	584 (71.7)	
3	489 (76.2)	
4	474 (74.1)	
5	381 (77.6)	
6–7	609 (77.2)	
8–10	572 (79.1)	
$\geq$ 11	389 (74.0)	

*P value calculated by Chi-square test. PDC, proportion of days covered.

rent medication and pills prescribed concomitantly at the index date were 3.0 and 4.1, respectively, covering a mean of 1.8 therapeutic areas (**Table 1**).

Adherence by Characteristics

Adherence stratified by patients' characteristics is shown in **Table 2**. It was found that 71.9% of the patients were adherent (i.e., PDC $\geq$ 80%), and 28.1% were non-adherent (i.e., PDC <80%). The proportion of patients who were

adherent was lower for females than for males. The proportion of patients being adherent was lower in the relatively younger group (age <45 years) and older group (age $\geq$ 75 years), and was the highest in the mid-age group (age 65–74 years). In addition, a significantly higher proportion of patients receiving statin-ezetimibe therapy for secondary prevention were adherent compared with those receiving it for primary prevention (78.8% vs. 65.9%; $P<0.05$). In terms of comorbidities, a higher proportion of adherent patients

was observed among those with medications for gout (76.4%), hypertension (75.3%), or diabetes (72.7%). On the other hand, the proportion of patients being adherent was lower among those prescribed treatment for dementia (65.3%), depression/anxiety (69.3%) or respiratory diseases (68.9%). Patients without any other concomitant medications indicated for other therapeutic areas showed the lowest rate of being adherent. Patients tended to be more adherent with an increased number of concurrent therapeutic areas. In the group of patients prescribed concomitant medications in ≥ 4 different estimated therapeutic areas, 78.0% were adherent, and 62.7% were adherent among patients without any concurrent therapeutic areas. Furthermore, the lowest proportion of being adherent (62.7%) occurred for patients without any concurrent medications. The proportion of patients being adherent increased consecutively up to 78.7% among patients with 5 concomitant medications. However, when the number of concomitant medications was >5 , the proportion of patients being adherent decreased. The trend for increasing adherence was similarly observed as the number of pills being prescribed concomitantly increased; however, the proportion of patients being adherent decreased in the group of patients prescribed >10 pills concurrently.

Factors Associated With Adherence

We investigated factors associated with adherence/non-adherence by multivariate logistic regression analysis (**Figure 2**). Compared with the age group 65–74 years, patients aged ≤ 54 years or ≥ 75 years were less adherent to the statin-ezetimibe therapy after adjusting other potential predictors. On the other hand, the adjusted OR (95% CI) for being adherent was 1.72 (1.52–1.94) for secondary prevention patients, using patients on primary prevention as the reference group. In addition, patients with medications for hypertension or gout were associated with better medication adherence, with OR (95% CI) of 1.27 (1.13–1.43) and 1.18 (1.01–1.39), respectively. Factors including sex, the number of concurrent medications, the number of pills prescribed concomitantly, and the number of concurrent therapeutic areas were excluded by stepwise selection procedure in the

logistic regression model.

Persistence by Characteristics

The proportion of patients being persistent on statin-ezetimibe therapy was evaluated at 1 year after the initiation of this combination prescription (**Table 3**). Similarly, the time to treatment discontinuation was evaluated over that time (**Figure 3**). Patients aged <45 years and those aged ≥ 75 years discontinued treatment earlier than those aged 65–74 years. Early discontinuation (≈ 60 days after the index date) was particularly observed in patients aged 20–44 years and patients with primary prevention. Moreover, patients prescribed with medications presumably indicated for dementia or depression/anxiety were prone to discontinue treatment earlier, while patients prescribed with medications for gout and hypertension were more likely to be persistent with treatment (**Figure 3**). The persistence rate was higher in patients with ≥ 4 concurrent therapeutic areas than in patients without concurrent therapeutic areas. The estimated persistence rate in the overall population at 1 year after initiation of combination therapy was 83.6%. Patients receiving statin-ezetimibe therapy for secondary prevention and also prescribed medications for gout, hypertension or diabetes showed higher persistence after 1 year of treatment.

Factors Associated With Treatment Persistence

Treatment discontinuation was further documented by the Cox proportional hazards model with adjusted HR (**Figure 4**). Patients aged ≥ 75 years had a significantly higher risk of treatment discontinuation compared with those aged 65–74 years (HR: 1.28, 95% CI: 1.09–1.51). Patients with secondary prevention had a significantly lower risk (HR: 0.70, 95% CI: 0.61–0.80) of discontinuation than patients with primary prevention. Regarding the effect of comorbidities, patients treated with medications for hypertension were more likely to be persistent with treatment (HR: 0.76, 95% CI: 0.67–0.87). In contrast, patients treated with medications for depression/anxiety were associated with a higher risk of discontinuation (HR: 1.27, 95% CI: 1.06–1.51). The covariates of “sex”, “the number of concurrent medications used” and “the number of pills received concurrently” were

Table 3. Persistence Rate at 1 Year by Patients' Characteristics			
Characteristic	Persistence rate at 1 year (%)	95% CI	P value*
Overall	83.6	82.7, 84.5	
Age group			0.0005
<45	81.4	77.6, 84.7	
45–54	81.2	78.7, 83.5	
55–64	86.1	84.3, 87.6	
65–74	84.5	83.0, 85.9	
≥75	81.7	79.6, 83.6	
Sex			0.0027
Male	84.9	83.7, 86.0	
Female	82.2	80.9, 83.5	
Secondary prevention			<0.0001
Yes	87.1	85.9, 88.2	
No	80.6	79.3, 81.8	
Therapeutic area of interest, n (%)			
Diabetes	84.7	83.0, 86.2	0.1184
Hypertension	85.8	84.7, 86.8	<0.0001
Respiratory disease	81.2	77.6, 84.3	0.1082
Gout	87.5	85.3, 89.4	0.0003
Dementia	80.6	69.4, 88.0	0.5146
Depression/anxiety	79.8	76.7, 82.6	0.0032
No. of concurrent therapeutic areas			<0.0001
0	78.2	75.7, 80.4	
1	82.4	80.5, 84.1	
2	85.1	83.5, 86.5	
3	85.6	83.7, 87.4	
≥4	89.1	85.9, 91.7	
No. of concurrent medications			<0.0001
0	78.2	75.9, 80.3	
1	79.7	77.1, 82.0	
2	85.2	82.8, 87.3	
3	85.7	83.2, 87.8	
4	84.9	82.3, 87.1	
5	88.3	85.5, 90.5	
6–7	87.9	85.4, 90.0	
≥8	84.7	80.8, 87.8	
No. of pills received concurrently			<0.0001
0	78.2	75.9, 80.3	
1	79.7	76.9, 82.2	
2	84.4	81.7, 86.7	
3	86.6	83.7, 89.0	
4	84.8	81.8, 87.4	
5	86.6	83.2, 89.3	
6–7	86.9	84.4, 89.1	
8–10	88.0	85.4, 90.1	
≥11	84.4	81.0, 87.2	

*P value calculated by log-rank test. CI, confidence interval.

automatically excluded by the stepwise selection procedure in the model.

Discussion

Study patients of interest were those prescribed statin-ezetimibe LLT in Japan, because of requiring more strict management of LDL-C control. We found that approxi-

mately 71.9% of patients were adherent (PDC ≥80%), and the overall persistence rate at 1 year was 83.6%. These results suggested that management in dyslipidemia is still suboptimal and represents potential unmet clinical need for further improvement. Patients aged ≤54 years or ≥75 years were more prone to be non-adherent than patients aged 55–74 years, which was consistent with a systematic literature review showing that relatively younger and older

Figure 3. Kaplan-Meier analysis of time to discontinuation of statin-ezetimibe therapy. (A) Stratified by age groups; (B) stratified by secondary prevention (Yes/No); (C) stratified by therapeutic area of interest; (D) stratified by number of concurrent therapeutic areas.

Figure 4. Hazard ratios of factors associated with discontinuation.

patients had poor adherence.¹⁷ It has been reported that younger patients have poor adherence because of lifestyle factors such as being busy at work and prone to forgetting to take medicine.²⁴ Another previous study showed that younger patients on statin therapy had relatively poor persistence with medications.²⁵ Our findings confirmed

those trends shown in previously reported literature on the Japanese population. We found that patients on secondary prevention were associated with better adherence and longer persistence than patients on primary prevention, who were associated with poor adherence and persistence. Our results are consistent

with the pooled results from 45 articles in a meta-analysis study, which suggested 33% lower likelihood of non-adherence and 40% lower risk of discontinuation for patients on secondary prevention compared with patients on primary prevention.¹⁴ Another literature review suggested that the adherence is better in patients with a history of CVD events because of their appreciation of both the severity of potential complication and the perceived benefits.²⁶ A study showed better adherence was associated with an approximately 3-fold higher probability of achieving target LDL-C level recommended in the treatment guidelines in 6 months (OR=2.74, 95% CI: 2.27–3.31).²⁷ Thus, control of LDL-C is a major component in the secondary prevention strategy, which is aimed at patients with a history of CVD events. Consistent with this finding, our study suggested that patients on secondary prevention, who require stricter management of LDL-C, might be associated with adherence and persistence of statin-ezetimibe LLT because of their increased awareness of the importance of risk management. The IMPROVE-IT trial reported a benefit of statin-ezetimibe vs. statin alone in CVD risk reduction aligned with LDL-C reduction, in a median study period of 6 years.²⁸ It suggests that persistence with medication in the long-term requires drug administration guidance and pharmacist intervention to maximize the benefit of the combination treatment in the control of CVD events. Not limited to patients on secondary prevention, actively managing treatment and optimal prescription with less treatment burden are also important for those on primary prevention.

Our study showed that LLT with concomitant medications for the treatment of depression/anxiety was associated with shorter persistence, whereas patients with medications for hypertension or gout were associated with better adherence and longer persistence. The finding of depression increasing the risk of discontinuation was consistent with the previous meta-analysis study.¹⁴ Anxiety and depression are most commonly reported as obstacles hindering the adoption of a healthier lifestyle as a result of emotional issues.²⁹ A previous study suggested that patients with a healthy lifestyle are more adherent because they are more likely to seek for healthier behaviors, such as refilling prescriptions and visiting their physicians routinely.³⁰

A previous survey in Japan revealed that patients on hypertensive medicine had a higher awareness of the necessity of taking medication appropriately as compared with those on antidyslipidemic medicine (85.5% vs. 37.2%, $P<0.001$).²⁴ In clinical practice in Japan, routine and frequent measurement of blood pressure at home is highly recommended by the treatment guidelines,³¹ which may enhance disease awareness in patients being treated for hypertension. The finding of this study showing better adherence and persistence in patients with elevated blood cholesterol levels on antihypertensive medications may have resulted from the enhanced awareness of drug-taking behavior. At present, limited studies have revealed a direct association between adherence and LLT and gout therapy. Our results demonstrated that patients on LLT with concomitant medications for gout were more likely to be adherent to medications, which could result from increased awareness of treatment importance because of the severe gout pain experienced by patients.

Although a high number of concomitant pills was reported to be associated with poor adherence in previous studies, that factor was excluded from the current model by the stepwise selection procedure. Multiple reasons could explain

this. First, the increasing number of concomitant pills highly reflects the number of comorbidities, which may lead to improved health literacy and awareness of diseases by individual patients. Second, 66% of our study patients were concomitantly using antihypertensive medication, which was previously reported as being associated with better adherence. Also, our additional analysis showed that pill number was associated with age (**Supplementary Figure 2**), where older age patients (i.e., 55–74 years old) were found to have better adherence.

Long-term persistence and adherence to LLT are essential for maximizing the clinical effectiveness for patients with dyslipidemia. Our findings found potential predictors resulting in poor adherence and persistence with statin-ezetimibe LLT. However, the follow-up period in our study was only 1 year and given that dyslipidemia is a chronic disease that requires life-time control, it is important to actively control dyslipidemia for decades for the prevention of CVD events. In particular, continuing medication management is crucial for those patients with relatively poorer adherence. For individuals requiring multiple LLTs with poor adherence and persistence, active interventions may improve adherence; for example, (1) long-term patient education program aimed at improving awareness of the negative effects of dyslipidemia and the significance of treatment; (2) reminder systems for medication adherence; (3) choosing a simple treatment regimen to reducing the patient's pill burden (e.g., medications with fixed-dose combination and/or less frequent dosing); and (4) explanation given to patients with a higher risk of poor adherence.

Study Strengths and Limitations

There are a number of strengths to our study. We used an administrative pharmacy claims database that collect dispensing records electronically and systematically, which could minimize patient recall bias compared with other data collection methods such as face-to-face interview or questionnaire. Unlike other hospital-based claims databases mostly from acute care hospitals in Japan, the database we used in our study covers out-of-hospital pharmacies and many prescription records, which may provide a comprehensive picture of drug utilization patterns, especially for non-acute conditions such as dyslipidemia.

Several limitations in our study should be considered when interpreting the study results. First, the actual intake of medication is neither trackable nor recorded in the database; thus, we cannot know if a patient takes the dispensed medications. Second, as there was a lack of diagnostic history and medical procedure records, dispensed medications were used as a proxy for estimating certain therapeutic area/comorbidities of patients, which can result in some misclassification bias. Third, because of the nature of database, we could not capture dispensing records taking place in uncontracted pharmacies.

Conclusions

To the best of our knowledge, this is the first study to focus on adherence of statin-ezetimibe combinational LLT in a real-world setting. Patients characterized as younger or older (<45, 45–54, ≥75 years old) and on primary prevention were associated with poor adherence. Patients characterized as older (≥75 years) and on primary prevention were associated with shorter persistence. Concomitant use of medications for hypertension and gout was associated

with better adherence and persistence, and concomitant use of medications for depression/anxiety was associated with shorter persistence. Active interventions are required for patients with poor adherence and persistence.

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Disclosure Statement

T.U. and S.T. own stock/stock options of Merck & Co., Inc., Kenilworth, NJ, USA. A.H. and Y.P. are currently employed by AstraZeneca K.K. All other authors declare no conflicts of interest.

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Supplementary Files

Please find supplementary file(s);
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