Real-World Data to Identify Hypercholesterolemia Patients on Suboptimal Statin Therapy

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Aim: Statins are generally well-tolerated but some patients develop adverse events and down-titrate or discontinue statins. It is important to understand the frequency of dyslipidemia patients with the inability to continue statins. The aim of the present study was to identify the frequency of high-risk dyslipidemia patients who are unable to take or not taking statins for any reason using Japanese hospital claims database.

Methods: 2,527,405 dyslipidemia patients with atherosclerotic cardiovascular disease were investigated between April 2008 and September 2017. Definition 1 included statin discontinuation or down-titration with non-statin lipid modifying therapy (LMT) prescription, rhabdomyolysis or muscle-related symptoms with statin down-titration or discontinuation, or prescription for ≥3 statin types. Definition 2 included all components of Definition 1 in addition to statin down-titration or discontinuation for any reason. Patients never given statins but who started non-statin LMT were considered as Definition 3. The achievement rate of the target LDL-C level was investigated.

Results: Among 54,296 patients with statin prescription, 2.32% and 48.38% patients were identified as Definition 1 and 2, respectively. Of eligible patients, 13.16% patients were identified as Definition 3. The achievement rate of target LDL-C level was lower in patients meeting each definition than not satisfying each definition.

Conclusions: There is a proportion of high-risk dyslipidemia patients unable to take or not taking statins for any reason, and it is associated with lower achievement rates of target LDL-C levels. Suboptimal management of LDL-C is directly associated with residual cardiovascular risk and implementation of alternative therapeutic options in addition to existing LMT is warranted.

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Key words: Hypercholesterolemia, Claim data, Statin, Non-HDL-cholesterol, LDL-cholesterol

Introduction

Lowering low-density lipoprotein cholesterol (LDL-C) level is one of the most widely available approaches to prevent atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease (CAD), which is a major cause of mortality in Japan and worldwide¹, ²). The Japan Atherosclerosis Society (JAS) guidelines recommend lowering LDL-C to <100 mg/dL in patients with a history of CAD and to <70 mg/dL (or by 50% or more) in high-risk patients with heterozygous familial hypercholesterolemia or acute coronary syndrome.
for secondary prevention of CAD.

The JAS guidelines as well as those of other major international associations including the American College of Cardiology/American Heart Association (ACC/AHA), the European Society of Cardiology/European Atherosclerosis Society, the National Lipid Association, and the International Atherosclerosis Society recommend statins as the first-line treatment for dyslipidemia patients with elevated LDL-C levels. Asian patients often show an increased response to drug therapy compared to Western populations, leading to lowered doses of therapeutic drugs such as statins. The approved maximum dose of statin is lower (e.g., atorvastatin 40 mg/day and rosuvastatin 20 mg/day) as well as clinically used dose. Statins are generally well tolerated, and serious adverse events are infrequent; however, some patients experience statin-associated muscle symptoms (SAMS) such as myositis and rhabdomyolysis and hepatic disorder that result in dose reductions or discontinuation of statin treatment. The inability to continue an effective dosage or the discontinuation of a statin treatment may limit clinically important effects, such as CAD risk reductions.

Statin intolerance is a term that is widely used to describe clinical phenomenon such as the inability to continue an effective dosage or the discontinuation of statin treatment due to adverse events, but there are no globally accepted criteria for statin intolerance. Previous studies have attempted to estimate the proportion of dyslipidemia patients unable to continue an effective dosage or who need to discontinue statin treatment using various criteria; results range from 1% to 30%. With the complexity of a dose-dependent relationship of adverse effects and more sensitive response in the Asian population to medications, the precise number of the inability to continue an effective dosage or the discontinuation of statin treatment due to adverse events is unknown.

In an era of new alternative lipid-lowering therapies supported by emerging evidence, it is important to understand the frequency of dyslipidemia patients with an inability to continue an effective dosage of statins by quantifying patients with high cardiovascular risk who may be candidates for non-statin lipid-modifying therapy (LMT) such as PCSK9 inhibitors, cholesterol absorption inhibitors, and fibrates in Japan.

**Aim**

The aim of the present study was to identify the frequency of dyslipidemia patients with a history of ASCVD such as CAD with an inability to continue an effective dosage or who need to discontinue statin treatment for any reason in Japanese clinical practice using a Japanese electrical medical record (EMR) database. Because lipid management in these patients might be poor, we also investigated the frequency of patients who achieved target values such as LDL-C recommended by the JAS guidelines.

**Methods**

**Database**

This retrospective observational study was conducted using the EBM Provider, which contains hospital claims database stored in electronic hospital information systems constructed by Medical Data Vision Co., Ltd. (MDV; Tokyo, Japan). The EBM Provider covers approximately 20.8 million patients from 323 hospitals across Japan (as of December 2017) with bed numbers ranging from 20 to over 1000. This database also includes approximately 19% of all acute phase hospitals in Japan, including university hospitals, which use the Diagnostic Procedure Combination (DPC) payment system/Per-Diem Payment System.

The EBM Provider includes anonymized patient-level information on sex, age, previous medical history (diagnosed diseases), medical procedure, and prescribed drug. Laboratory test values were also provided by 35 hospitals. Information about the diagnosis and drugs is extractable based on the International Classification of Disease (ICD)-10 codes and the Anatomical Therapeutic Chemical (ATC) code, respectively.

**Patient Selection**

All patients diagnosed with ASCVD (ICD-10 code: I20, I21, I22, I23, I24, I25, I63, I65, I66, I67, I69, I70, I71, I72, I73, I74) between April 2008 and September 2017 (defined as the study period) were identified from the EBM Provider database. Patients who met all of the following criteria were included in the present study: 1) diagnosis of dyslipidemia (standardized Japanese disease codes: 2724036; high LDL cholesterolemia, 2720004; hypercholesterolemia, 8840108; essential hypercholesterolemia, 8833881; mixed hyperlipidemia, 2724007; hyperlipidemia, 8833722; hyperlipoproteinemia, 8844446; dyslipidemia, 2724012; essential hyperlipidemia, 2729002; disorder of lipid metabolism, 8845052; type1 diabetic hypercholesterolemia, 8845081; type2 diabetic hypercholesterolemia, 8838067; diabetic hypercholesterolemia) during the study period; 2) initiation of any statin (ATC code: C10A1, C11A1) agents during the study period and initiation of non-statin LMT (ATC code: C10, C11) if statin agents were not prescribed during the study period (as an index date); 3) at least 365 days of medical data available before and after the index date; 4) age at the index date over 20 years; 5) no prescription of LMT during the
look-back period of 365 days before the index date; and 6) diagnosis of ASCVD before the index date. Patients with age at the index date younger than 20 years old and index date before April 2009 or after September 2016 were excluded from the study.

Definition of dyslipidemia patients who were unable to take or were not on statin treatment for any reason was modified to fit a Japanese setting with reference to the definitions used in previous studies. In the present study, three definitions of dyslipidemia patients who were not able to take or not taking statin treatment for any reason were considered. Patients included in the present study who met any of following criteria between 365 days from index date were considered to meet the criteria for Definition 1.

- Statin discontinuation (not prescribed within 90 days after the addition statin prescription days on last visit to the last visit date) with prescription of non-statin LMT.
- Statin down-titration with prescription of non-statin LMT.
- Rhabdomyolysis with statin down-titration or discontinuation.
- Muscle-related symptoms with statin down-titration or discontinuation.
- Prescription for ≥3 types of statins.

A dyslipidemia patient who was unable to take or was not taking statin treatment for any reason was considered to be down-titrated or discontinued without prescribing non-statin LMT. Definition 2 included the following criteria in addition to all components of Definition 1.

- Down-titration of statin for any reason
- Discontinuation of statin for any reason

Patients who had never been prescribed statin but had started non-statin LMT during the study period were considered to satisfy the criteria for Definition 3. Details of each definition component are described in Table 1.

Study Measures

The number and proportion of patients who met the criteria for each definition of dyslipidemia patients unable to take or not taking statin treatment due to any reason were identified. Patient characteristics (sex, age, previous disease history, medication use, and Charlson Comorbidity Index) for Definitions 1, 2, and 3 during the 365 days before the index date were described and compared with those of patients with statin prescription who did not meet the criteria for Definitions 1 and 2 (defined as comparator of each definition).

The number and proportion of patients who achieved the target laboratory test values were identified to confirm lipid controls for each definition and each comparator. The earliest LDL-C and non-high-density lipoprotein (HDL-C) level recorded 365 days after the index date were used. The target value of each laboratory test parameter was referred the value of a patient with a history of CAD recommended by the JAS guidelines (LDL-C: <100 mg/dL, <70 mg/dL, non-HDL-C: <130 mg/dL, <100 mg/dL). In addition, subgroup analysis of patients with a history of CAD and diabetes mellitus (DM) was also conducted.

Statistical Analysis

For patient characteristics, categorical variables were presented as number of patients and percentages and continuous variables were presented as mean and standard deviation (SD). The chi-squared test was used for categorical variables and the Student t-test was used for continuous variables to evaluate group differences. The achievement of a target laboratory test value was presented as the number of patients and percentages. Since not all patients had laboratory data stored in the EBM Provider, the denominator of the achievement proportion was the number of patients with clinical laboratory values during the follow-up period. A chi-square test was used to test differences between the groups.

All analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, North Carolina). When the p-value on the 2-sided test was <0.05, the difference was regarded as statistically significant.

Results

A total of 2,527,405 patients diagnosed with ASCVD during the study period were identified from the EBM Provider. Among the 62,522 eligible patients who matched all inclusion criteria, 54,296 patients were started on statins and were included in the analysis based on Definitions 1 and 2. Among patients with statin prescription, 1260 patients (2.32%) were identified according to Definition 1; 26,271 patients (48.38%) were identified as satisfying Definition 2 criteria. Among all eligible patients, 8226 patients (13.16%) were treated only with non-statin LMT (Definition 3). “Statin discontinuation with prescription of non-statin LMT” (48.65%) and “Muscle-related symptoms with statin down-titration or discontinuation” (38.73%) were the most common reasons for satisfying Definition 1 criteria. “Discontinuation of statin for any reason” (92.91%) was the most common reason for satisfying Definition 2 criteria (Fig. 1).

Patient characteristics for each definition and comparators are shown in Tables 2 to 4.

For the patients satisfying Definition 1 criteria and the comparators of Definition 1, the number was 1260
The proportion of patients with diabetes, CAD, stroke, and heart failure satisfying Definition 3 criteria was lower than that of the comparators of Definition 3. The frequency of patients satisfying each definition criteria and the comparators who achieved the target value recommended by the JAS guidelines for LDL-C and non-HDL-C are shown in Figs. 2 to 4.

Table 1. Components and details of each definition group

| Definition 1 | Details |
|--------------|---------|
| Statin down-titration with prescription of non-statin LMT. | All of the following four criteria: |
| Statin discontinuation with prescription of non-statin LMT. | • Prescribed non-statin LMT between 365 days from index date (defined as assessment period). |
| Rhabdomyolysis with statin down-titration or discontinuation. | • Had no statin prescription for the same or higher intensity (Supplementary Table 1) than the initial statin prescription on the same day or after the first LMT prescription and during the remainder of the assessment period. |
| Muscle-related symptoms with statin down-titration or discontinuation. | • Had a statin prescription at a lower intensity than the initial statin prescription any time before or within 7 days after the first non-statin LMT prescription. |
| Prescription for ≥ 3 types of statins. | • Had ≥ 1 statin prescription at a lower intensity than the initial statin prescription including the statin prescription closest to and before the first non-statin LMT prescription and any subsequent statin prescription through the end of the assessment period. |
| LMT: lipid-modifying therapy |

and 53,036, with a mean age of 69.9 and 71.2 years ($p < 0.001$), and the proportion of males was 55.71% and 59.62% ($p = 0.005$), respectively. The proportion of patients with CAD in the comparators of Definition 1 was higher than that of those satisfying Definition 1 criteria.

For the patients satisfying Definition 2 criteria and the comparators of Definition 2, the number was 26,271 and 28,025, the mean ages were 72.8 and 69.5 years ($p < 0.001$), and the proportion of males was 57.71% and 61.23% ($p < 0.001$), respectively. The individual proportions of patients with diabetes, stroke, and chronic kidney disease satisfying Definition 2 criteria were higher than those in the comparators of Definition 2.

For the patients satisfying Definition 3 criteria and the comparators of Definition 3, the number was 8226 and 54,296, the mean age was 69.9 and 71.1 years ($p < 0.001$), and the proportion of males was 56.54% and 59.53% ($p < 0.001$), respectively. The proportion of patients with diabetes, CAD, stroke, and heart failure satisfying Definition 3 criteria was lower than that of the comparators of Definition 3.

The frequency of patients satisfying each definition criteria and the comparators who achieved the target value recommended by the JAS guidelines for LDL-C and non-HDL-C are shown in Figs. 2 to 4.

For Definition 1, the achievement rates of LDL-C $< 100$ mg/dL and LDL-C $< 70$ mg/dL were significantly lower than in the comparators (LDL-C $< 100$ mg/dL: 36.03% vs. 62.99%; $p < 0.001$, LDL-C $< 70$ mg/dL: 10.29% vs. 19.14%; $p = 0.009$). The achievement rates of non-HDL-C $< 130$ mg/dL and non-HDL-C $< 100$ mg/dL were also significantly lower than in the comparators (non-HDL-C $< 130$ mg/dL: 45.59% vs. 72.27%; $p < 0.001$, non-HDL-C $< 100$ mg/dL: 15.44% vs. 35.08%; $p < 0.001$).

For Definition 2, the achievement rates of LDL-C...
Among the 62,522 eligible patients who met all the inclusion criteria, 54,296 patients were started on statins and were included in the analysis for Definition 1 and 2. Among patients with statin prescription, 1260 patients (2.32%) met Definition 1 criteria, 53,036 patients (54,296 – 1260) were identified as the comparators of Definition 1, while 26,271 patients (48.38%) met Definition 2 criteria and 28,025 patients (54,296 – 26,271) comprised the comparators of Definition 2. Among all eligible patients, 8226 patients (13.16%) were identified to meet Definition 3 criteria and 54,296 patients (62,522 – 8,226) were identified as the comparators of Definition 3 (the same as for patients starting any statin agent). ASCVD: atherosclerotic cardiovascular disease. LMT: lipid-modifying therapy.

Fig. 1. Patient flow diagram

Among the 62,522 eligible patients who met all the inclusion criteria, 54,296 patients were started on statins and were included in the analysis for Definition 1 and 2. Among patients with statin prescription, 1260 patients (2.32%) met Definition 1 criteria, 53,036 patients (54,296 – 1260) were identified as the comparators of Definition 1, while 26,271 patients (48.38%) met Definition 2 criteria and 28,025 patients (54,296 – 26,271) comprised the comparators of Definition 2. Among all eligible patients, 8226 patients (13.16%) were identified to meet Definition 3 criteria and 54,296 patients (62,522 – 8,226) were identified as the comparators of Definition 3 (the same as for patients starting any statin agent). ASCVD: atherosclerotic cardiovascular disease. LMT: lipid-modifying therapy.
### Table 2. Patient characteristics: Definition 1

|                      | Total patients | Definition 1 | Comparator of definition 1 | p-Value |  
|----------------------|----------------|--------------|-----------------------------|---------|  
| N, %                 | 54,296 (100.00%) | 1,260 (2.32%) | 53,036 (97.68%)             | –       |  
| Sex                  |                |              |                             |         |  
| Male (n, %)          | 32,321 (59.53%) | 702 (55.71%)  | 31,619 (59.62%)             | 0.005   |  
| Female (n, %)        | 21,975 (40.47%) | 558 (44.29%)  | 21,417 (40.38%)             |         |  
| Age                  |                |              |                             |         |  
| Mean (SD)            | 71.1 (10.668)  | 69.9 (11.154) | 71.2 (10.655)               | <0.001  |  
| Previous disease history |            |              |                             |         |  
| Diabetes (n, %)      | 11,927 (21.97%) | 270 (21.43%)  | 11,657 (21.98%)             | 0.641   |  
| Coronary artery disease (n, %) | 28,028 (51.62%) | 602 (47.78%)  | 27,426 (51.71%)             | 0.006   |  
| Stroke (n, %)        | 4,204 (7.74%)  | 97 (7.70%)    | 4,107 (7.74%)               | 0.952   |  
| Heart failure (n, %) | 17,114 (31.52%) | 382 (30.32%)  | 16,732 (31.55%)             | 0.353   |  
| Peripheral artery disease (n, %) | 12,280 (22.62%) | 310 (24.60%)  | 11,970 (22.57%)             | 0.088   |  
| Hypothyroidism (n, %) | 2,119 (3.90%)  | 56 (4.44%)    | 2,063 (3.89%)               | 0.315   |  
| Chronic kidney disease (n, %) | 4,394 (8.09%)  | 111 (8.81%)   | 4,283 (8.08%)               | 0.345   |  
| Mild liver disease (n, %) | 6,910 (12.73%) | 190 (15.08%)  | 6,720 (12.67%)              | 0.011   |  
| Moderate/severe liver disease (n, %) | 211 (0.39%)  | 5 (0.40%)     | 206 (0.39%)                 | 0.962   |  
| Antihypertensive medication use (n, %) | 33,067 (60.90%) | 768 (60.95%)  | 32,299 (60.90%)             | 0.970   |  
| Cyclosporine use (n, %) | 111 (0.20%)   | 4 (0.32%)     | 107 (0.20%)                 | 0.369   |  
| Charlson comorbidity index |                |              |                             |         |  
| Mean score (SD)      | 2.8 (2.137)    | 2.9 (2.130)   | 2.8 (2.137)                 | 0.100   |  

SD: standard deviation

### Table 3. Patient characteristics: Definition 2

|                      | Total patients | Definition 2 | Comparator of definition 2 | p-Value |  
|----------------------|----------------|--------------|-----------------------------|---------|  
| N, %                 | 54,296 (100.00%) | 26,271 (48.38%) | 28,025 (51.62%)             | –       |  
| Sex                  |                |              |                             |         |  
| Male (n, %)          | 32,321 (59.53%) | 15,161 (57.71%) | 17,160 (61.23%)             | <0.001  |  
| Female (n, %)        | 21,975 (40.47%) | 11,110 (42.29%) | 10,865 (38.77%)             |         |  
| Age                  |                |              |                             |         |  
| Mean (SD)            | 71.1 (10.668)  | 72.8 (10.361) | 69.5 (10.709)               | <0.001  |  
| Previous disease history |            |              |                             |         |  
| Diabetes (n, %)      | 11,927 (21.97%) | 6,497 (24.73%) | 5,430 (19.38%)              | <0.001  |  
| Coronary artery disease (n, %) | 28,028 (51.62%) | 13,665 (52.02%) | 14,363 (51.25%)             | 0.075   |  
| Stroke (n, %)        | 4,204 (7.74%)  | 2,372 (9.03%)  | 1,832 (6.54%)               | <0.001  |  
| Heart failure (n, %) | 17,114 (31.52%) | 7,958 (30.29%) | 9,156 (32.67%)              | <0.001  |  
| Peripheral artery disease (n, %) | 12,280 (22.62%) | 5,726 (21.80%) | 6,554 (23.39%)              | <0.001  |  
| Hypothyroidism (n, %) | 2,119 (3.90%)  | 960 (3.65%)   | 1,159 (4.14%)               | 0.004   |  
| Chronic kidney disease (n, %) | 4,394 (8.09%)  | 2,467 (9.39%)  | 1,927 (6.88%)               | <0.001  |  
| Mild liver disease (n, %) | 6,910 (12.73%) | 2,763 (10.52%) | 4,147 (14.80%)              | <0.001  |  
| Moderate/severe liver disease (n, %) | 211 (0.39%)  | 112 (0.43%)   | 99 (0.35%)                  | 0.171   |  
| Antihypertensive medication use (n, %) | 33,067 (60.90%) | 14,227 (54.15%) | 18,840 (67.23%)             | <0.001  |  
| Cyclosporine use (n, %) | 111 (0.20%)   | 36 (0.14%)    | 75 (0.27%)                  | <0.001  |  
| Charlson comorbidity index |                |              |                             |         |  
| Mean score (SD)      | 2.8 (2.137)    | 2.8 (2.171)   | 2.8 (2.105)                 | 0.470   |  

SD: standard deviation
Discussion

This retrospective observational study was conducted using the EBM Provider database, which contains hospital claims data stored in electronic hospital information systems. This provider was used to identify the frequency of dyslipidemia patients who had a history of ASCVD and who were unable to take or were not taking statin treatment for any reason. The number of patients who met the criteria for Definitions 1, 2, and 3 was 1260 (2.32%), 26,271 (48.38%), and 8226 (13.16%), respectively. For Definition 1, 48.65% of patients had “statin discontinuation with prescription of non-statin LMT” significantly more frequently than “statin down-titration with prescription of non-statin LMT” (5.56%). Asian patients often show an increased response to drug therapy compared with Western populations, leading to lower approved and clinically used doses of therapeutic drugs such as statins, and with a lower approved maximum dose of statin (e.g., atorvastatin 40 mg/day and rosuvastatin 20 mg/day) as the clinically used dose.

With regard to the Definition 3 group, the achievement rates of LDL-C <70 mg/dL and non-HDL-C <100 mg/dL were significantly lower than in the comparators (53.78% vs. 66.53%; p<0.001). The achievement rates of LDL-C <70 mg/dL were significantly different (17.57% vs. 19.58%; p=0.079). The achievement rates of non-HDL-C <130 mg/dL and non-HDL-C <100 mg/dL were significantly lower than in the comparators (non-HDL-C <130 mg/dL: 63.72% vs. 75.50%; p<0.001, non-HDL-C <100 mg/dL: 30.56% vs. 36.58%; p<0.001).

With the definition of CAD and DM who achieved the target value recommended by the JAS guidelines for LDL-C and non-HDL-C are shown in Supplementary Figs. 1 to 10.

The achievement rates of patients with a history of disease were significantly higher than that of patients with no history of the diseases evaluated.

The frequencies of patients with a history of CAD and DM who achieved the target value recommended by the JAS guidelines for LDL-C and non-HDL-C are shown in Supplementary Figs. 1 to 10.

The achievement rates of patients with a history of disease were significantly higher than that of patients with no history of the diseases evaluated.
meeting Definition 2 criteria, and was observed in 24,408/54,296 (44.95%) of the patients who were started on any statins during the study period. As the EBM Provider collects information from each hospital separately, if patients who became stable of lipid control in the hospital move to other institutes such as clinic, the record of these patients will be terminated. This is a database limitation that patients moved to other institutes could not be follow-up. This would likely increase the discontinuation rate and thus lead to overestimation of the rate of medication discontinuation, especially for Definition 2. Similar to our analysis, Vinogradova et al. reported a statin discontinuation rate of 41% in a study of patients on statins for secondary prevention\textsuperscript{18}. In a previous study in Japan using another claims database called Japan Medical Data Center (JMDC) database, Nagar et al., investigated treatment pattern and possible statin intolerance in 32.9% of ASCVD patients discontinuing statins\textsuperscript{19}. Different from the MDV database used in the current analysis, the JMDC database comprises retrospective claims data from the Japanese union-managed health insurance system (Health Insurance Association) and follows patients who move to other institutes, which may explain the reason for the lower discontinuation rate observed. However, even the JMDC database showed that over 30% of patients discontinued statins and supported the observation that “discontinuation of statins for any reason” was common.

Definition 1 is a more stringent definition, which takes into consideration one of the most common adverse events, SAMS, as well as other signs of inability to take statins such as initiation of non-statin LMT following statin discontinuation/down-titration. In the present study, in the population satisfying Definition 1 criteria, SAMS was identified in 38.73% of patients as a likely cause of statin discontinuation or down-titration. Although it was not possible to include elevation of CK in an algorithm, there was no case of statin discontinuation directly due to rhabdomyolysis in this database analysis. Chang et al. searched the EBM provider for cases of muscle toxicity, defined as occurrence of rhabdomyolysis or myositis, and estimated the incidence rate of muscle toxicity leading to statin discontinuation to be 0.17/1000 person-year\textsuperscript{11}. The results indicate that statin discontinuation due to
studies. One of the reasons for this higher prevalence was considered to be a difference in the definition, that is, “Muscle-related symptoms with statin down-titration or discontinuation” was used as a component of Definition 1 in the present study, while in a previous study “antihyperlipidemic adverse event” was used. Since there is no code corresponding to “antihyperlipidemic adverse event” among the ICD-10 codes in Japan, “muscle-related symptoms” was used in the present study. In previous studies by Colantonio et al. and Serban et al., 11.7% and 11.4% patients met the definition of “Rhabdomyolysis with statin down-titration or discontinuation,” respectively, while 7% and 1.2% patients met the definition of “antihyperlipidemic adverse event with statin down-titration or discontinuation,” respectively. Had the definition “antihyperlipidemic adverse event” been used instead of “muscle-related symptoms” as in the present study, it is likely that the proportion of patients meeting the definition would also increase in previous studies.

In the present study, the definition of dyslipidemia patients who are unable to take or not taking statin treatment due to any reason was modified to adapt to the Japanese setting with regard to the definitions used in previous studies15, 16). A previous study that compared the background of patients with high statin adherence and those with statin discontinuation or down-titration for any reason using Medicare claims data by Colantonio et al., indicated that 1.0% of patients (1320/134,863) corresponded to Definition 1, and 33.6% of patients (45,266/134,863) corresponded to Definition 2 in this analysis. In addition, a previous study comparing the incidence of CAD and recurrence of myocardial infarction (MI) in patients with a prior history of MI with high adherence to statin and statin discontinuation or down-titration for any reason using Medicare claim data by Serban et al., indicated that 1.65% of patients (1741/105,329) corresponded to Definition 1 in this analysis.

The proportion of patients with Definition 1 in the present study was slightly higher than in previous studies. One of the reasons for this higher prevalence was considered to be a difference in the definition, that is, “Muscle-related symptoms with statin down-titration or discontinuation” was used as a component of Definition 1 in the present study, while in a previous study “antihyperlipidemic adverse event” was used. Since there is no code corresponding to “antihyperlipidemic adverse event” among the ICD-10 codes in Japan, “muscle-related symptoms” was used in the present study. In previous studies by Colantonio et al. and Serban et al., 11.7% and 11.4% patients met the definition of “Rhabdomyolysis with statin down-titration or discontinuation,” respectively, while 7% and 1.2% patients met the definition of “antihyperlipidemic adverse event with statin down-titration or discontinuation,” respectively. Had the definition “antihyperlipidemic adverse event” been used instead of “muscle-related symptoms” as in the present study, it is likely that the proportion of patients meeting the definition would also increase in previous studies.

In the study by Serban et al., the proportion of patients satisfying the condition “prescription for ≥3 types of statins” was higher than in the present study.
When comparing patients with or without a history of CAD and DM, the achievement rates of LDL-C and non-HDL-C target levels in patients with a history of each disease were higher than that of patients with no history of either disease. A likely explanation can be the lower target LDL-C levels recommended by the JAS guidelines\(^3\), and the positive life-style changes made as a consequence of the diagnosis of CAD and DM. However, the trend of LDL-C and non-HDL-C target level achievement remained consistent with higher rates of achievement in patients who did not satisfy the definition criteria.

Although non-statin LMT (i.e., a cholesterol absorption inhibitor and fibrates) could be prescribed for patients who are unable to take or are not taking statin treatment for any reason, the present study suggested that fewer patients on non-statin LMT achieved the target lipid levels recommended by the JAS guidelines\(^3\), and the positive life-style changes made as a consequence of the diagnosis of CAD and DM. However, the trend of LDL-C and non-HDL-C target level achievement remained consistent with higher rates of achievement in patients who did not satisfy the definition criteria.

When comparing patients with or without a history of CAD and DM, the achievement rates of LDL-C and non-HDL-C target levels in patients with a history of each disease were higher than that of patients with no history of either disease. A likely explanation can be the lower target LDL-C levels recommended by the JAS guidelines\(^3\), and the positive life-style changes made as a consequence of the diagnosis of CAD and DM. However, the trend of LDL-C and non-HDL-C target level achievement remained consistent with higher rates of achievement in patients who did not satisfy the definition criteria.
by Serban et al. However, these results have not been reported herein to avoid misinterpretation of the clinical characteristics due to the limitations of the database.

Limitations

There were several limitations in the present study. First, as mentioned above, the EBM Provider collects information from each hospital separately. If patients are transferred to other institutions for any reason, their records will be terminated in the database. This can lead to increase and overestimation of the rate of medication discontinuation.

Second, the clinical laboratory test values included in the EBM Provider were specified by only 35 of the 323 medical institutions for which data were provided. Therefore, it could not be considered to reflect the data of the entire patient cohort included in the EBM Provider. This limitation influences both the generalizability and internal validity of the present study.

Third, since the definition of dyslipidemia patients who are unable to take or not taking statin treatment for any reason was not clearly defined in the established guidelines, the definitions used in the present study were based on hypothesis. Therefore, patients who had any other reason to discontinue treatment, which was not directly considered in the definitions, were not included. Previous studies have used various methods to define patients with dyslipidemia who were unable to take or were not on statin treatment. A previous study using the US Administrative Database by Schluman et al. categorized patients on the basis of changes in the statin prescription patterns (e.g., number of statin prescription, discontinuation), AE, and clinical laboratory test value (creatinine kinase)\(^2\). In a study using the IMS LifeLink PharMetrics Plus commercial claims, Quek et al. defined statin treatment intolerance and/or ineffectiveness in high CVD risk patients with type 2 diabetes on the basis of only changes in statin prescriptions\(^2\). In the present study, the definitions used by Serban et al. and Colantonio et al. were adopted to integrate the information on potential adverse effects and rhabdomyolysis in addition to the prescription data. However, there was no code corresponding to “antihyperlipidemic adverse event” among the ICD-10 codes in Japan, and “muscle-related symptoms” was used for Definitions 1 and 2 in the present study. The ICD codes for “muscle-related symptoms” were carefully selected and were analyzed in relationship to statin prescription; however, this process does not exclude all the unrelated diagnoses.

Although there were several limitations, as described above, the EBM Provider managed by the MDV comprised approximately 19% of all acute phase hospitals using the DPC system and was not biased towards a specific area in Japan. Thus, generalizability of the results for in-hospital treatment may be considered to be high.

Conclusion

The present study showed the risk of being unable to continue lipid-lowering therapy with statins exists to a certain degree in dyslipidemia patients and is associated with lower rates of target LDL-C and non-HDL-C level achievement, leaving patients untreated or undertreated. Suboptimal management of LDL-C and non-HDL-C is directly associated with residual cardiovascular event risk and implementation of alternative therapeutic options in addition to cholesterol absorption inhibitor, fibrates, and PCSK9 inhibitors is warranted.

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Conflict of Interest Statement

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Supplementary Table 1. Categorization of high-, moderate-, and low-intensity statins

| Statin type | High-intensity (mg/day) | Moderate-intensity (mg/day) | Low-intensity (mg/day) |
|-------------|-------------------------|----------------------------|-----------------------|
| Atorvastatin | 30-40                   | 10-20                      | 5                     |
| Rosuvastatin | 15-20                   | 5-10                       | 2.5                   |
| Simvastatin  | 20                      |                            | 5-10                  |
| Pravastatin  | –                       | –                          | 10-20                 |
| Fluvastatin  | –                       | 60                         | 20-40                 |
| Pitavastatin | –                       | 2-4                        | 1                     |

*The intensity for each statin type in accordance with the American College of Cardiology/American Heart Association Cholesterol Guidelines and was modified according to Japanese prescription dosages.
## Supplementary Table 2. The list of muscle related symptom

| ICD-10 code | standardized Japanese disease code | Disease name | ICD-10 code | standardized Japanese disease code | Disease name |
|-------------|-----------------------------------|--------------|-------------|-----------------------------------|--------------|
| M609        | 7280003                           | Myositis     | M791        | 7231008                           | Nuchal muscle pain |
| M609        | 7280005                           | Femoral region myositis | M791      | 7291049                           | Trapezius muscle pain |
| M609        | 7291060                           | Psoiri       | M791        | 8831297                           | Triceps surae muscle pain |
| M609        | 7291058                           | Thigh myositis | M791      | 7291012                           | Thoracoabdominal muscle pain |
| M609        | 7289022                           | Biceps brachii myositis | M791      | 8839751                           | Abdominal wall muscle pain |
| M609        | 8837265                           | Greater pectoral myositis | M791      | 7231006                           | Nucha muscle pain |
| M609        | 7291040                           | Brachial myositis | M791      | 7291011                           | Sternoclidelostoid muscle pain |
| M609        | 7291095                           | Cervical myositis | M791      | 8835524                           | Triceps brachii muscle pain |
| M609        | 7291059                           | Rectus femoris myositis | M791      | 7291063                           | Cephalic muscle pain |
| M609        | 7289021                           | Triceps brachii myositis | M791      | 8835552                           | Biceps brachii muscle pain |
| M609        | 7291078                           | Rectus abdominis myositis | M796      | 7295003                           | Melosalgia |
| M609        | 7291088                           | Gluteal myositis | M796        | 8837336                           | Meralgia |
| M609        | 7291009                           | Acute myositis | M796        | 8831316                           | Lower leg pain |
| M609        | 7104008                           | Localized myositis | M796        | 8836736                           | Podalgia |
| M609        | 7291010                           | Sternoclidelostoid | M796        | 8835547                           | Brachialgia |
| M609        | 7291028                           | Nuchal myositis | M796        | 7295022                           | Hand pain |
| M609        | 7291064                           | Spine myositis | M796        | 7295020                           | Finger pain |
| M609        | 8842239                           | Masseter myositis | M796      | 8835434                           | Arm pain |
| M609        | 7291080                           | Abdominal myositis | M796      | 8836617                           | Forearm pain |
| M626        | 7298036                           | Muscle fatigue | M796        | 8831096                           | Heel pain |
| M628        | 8831347                           | Shoulder discomfort | M796     | 8840187                           | Hallucis pain |
| M628        | 8841635                           | Rhabdomyolysis | M796        | 8834411                           | Toe pain |
| M791        | 7291015                           | Muscle pain    | M796        | 7295058                           | Thumb pain |
| M791        | 7291003                           | Muscle pain of the lower extremity | M796   | 7295073                           | Forefoot pain |
| M791        | 8833247                           | Shoulder muscle pain | M796      | 7295033                           | Acrotarsium pain |
| M791        | 7291068                           | Muscular backache | M796      | 7295032                           | Planatar pain |
| M791        | 8840783                           | Psoas myalgia  | M796        | 7295015                           | Thigh pain |
| M791        | 7291092                           | Neck-shoulder muscle pain | M796     | 7295045                           | Digitus medius pain |
| M791        | 7231018                           | Cervical muscle pain | M796      | 7295074                           | Metatarsal pain |
| M791        | 7289005                           | Chest muscle pain | M796        | 7295077                           | Indicus pain |
| M791        | 8835426                           | Upper limb muscle pain | M796      | 7295007                           | Annularis pain |
| M791        | 7291039                           | Upper arm muscle pain | M796      | 7295024                           | Minimus Pain |
| M791        | 7291021                           | Scapular region muscle pain | M796   | 7295016                           | Melalgia |
| M791        | 7291055                           | Multiple muscle pain | M796      | 7295021                           | Opisthenar pain |
| M791        | 8837285                           | Thigh muscle pain | M796        | 7295061                           | Sural pain |
| M791        | 7291032                           | Lumbar muscle pain syndrome | M796     | 7295075                           | Metapodium pain |
| M791        | 8839366                           | Gastrocnemius pain | M796      | 7299023                           | Poditis |
| M791        | 7248003                           | Thoracodorsal muscle pain | M796   | 7295041                           | Inner thigh pain |
| M791        | 7291062                           | Gluteal region muscle pain | M796      | 7295056                           | Thenar region pain |
| M791        | 7291047                           | Forearm muscle pain | M796        | 7295017                           | Distal extremity pain |
| M791        | 7291085                           | Intercostal muscle pain | M796      | 7295017                           | Distal extremity pain |
Supplementary Fig. 1. The frequency of patients who achieved the target value: history of coronary artery disease (patients with statin prescription)

For patients with and without history of CAD (patients with statin prescription), 2895 (2895/28,028: 10.33%) and 2404 (2,404/26,268: 9.15%) had available LDL-C data, while 2938 (2938/28,028: 10.48%) and 2243 patients (2243/26,268: 8.54%) had non-HDL-C data available, respectively. The achievement rates of LDL-C < 100 mg/dL and LDL-C < 70 mg/dL in patients with history of CAD were significantly higher than those in patients with no history (LDL-C < 100 mg/dL: 67.15% vs. 56.45%; \(p < 0.001\), LDL-C < 70 mg/dL: 22.94% vs. 14.06%; \(p < 0.001\)). The achievement rates of non-HDL-C < 130 mg/dL and non-HDL-C < 100 mg/dL in patients with a history of CAD were also significantly higher than those in patients with no history (non-HDL-C < 130 mg/dL: 75.90% vs. 65.89%; \(p < 0.001\), non-HDL-C < 100 mg/dL: 38.46% vs. 29.47%; \(p < 0.001\)). CAD: coronary artery disease, LDL-C: low-density lipoprotein, non-HDL-C: non-high-density lipoprotein.
Supplementary Fig. 2. The frequency of patients who achieved the target value: Definition 1 (history of coronary artery disease)

For patients who satisfied Definition 1 criteria with and without history of CAD and the comparators of Definition 1 with and without history of CAD, 69 (69/602: 11.46%), 67 (67/658: 10.18%), 2826 (2826/27,426: 10.30%), and 2337 (2337/25,610: 9.13%) had available LDL-C data, while 69 (69/602: 11.46%), 67 (67/658: 10.18%), 2869 (2869/27,426: 10.46%), and 2176 patients (2176/25,610: 8.50%) had non-HDL-C data available, respectively. For the patients who satisfied the Definition 1 criteria, the achievement rates of LDL-C < 100 mg/dL and LDL-C < 70 mg/dL in those with a history of CAD were higher than that in those with no history (LDL-C < 100 mg/dL: 43.48% vs. 28.36%; p = 0.066, LDL-C < 70 mg/dL: 14.49% vs. 5.97%; p = 0.102). The achievement rates of non-HDL-C < 130 mg/dL and non-HDL-C < 100 mg/dL were also higher than those with no history (non-HDL-C < 130 mg/dL: 53.62% vs. 37.31%; p = 0.056, non-HDL-C < 100 mg/dL: 18.84% vs. 11.94%; p = 0.266). For the comparators of Definition 1, the achievement rates of LDL-C < 100 mg/dL and LDL-C < 70 mg/dL of those with a history of CAD were significantly higher than those in patients with no history (LDL-C < 100 mg/dL: 67.73% vs. 57.25%; p < 0.001, LDL-C < 70 mg/dL: 23.14% vs. 14.29%; p < 0.001). The achievement rates of non-HDL-C < 130 mg/dL and non-HDL-C < 100 mg/dL were also significantly higher than those in patients with no history of CAD (non-HDL-C < 130 mg/dL: 76.44% vs. 66.77%; p < 0.001, non-HDL-C < 100 mg/dL: 38.93% vs. 30.01%; p < 0.001). CAD: coronary artery disease, LDL-C: low-density lipoprotein, non-HDL-C: non-high-density lipoprotein.
Supplementary Fig. 3. The frequency of patients who achieved the target value: Definition 2 (history of coronary artery disease).

For patients who satisfied the criteria for Definition 2 with and without history of CAD, and the comparators of Definition 2 with and without history of CAD, 1016 (1016/13,665: 7.44%), 743 (743/12,606: 5.89%), 1879 (1879/14,363: 10.30%), and 1661 (1661/13,662: 12.16%) had available LDL-C data, and 1017 (1017/13,665: 7.44%), 711 (711/12,606: 5.64%), 1921 (1,921/14,363: 13.37%), and 1532 (1,532/13,662: 11.21%) had non-HDL-C data available, respectively. For patients who met the criteria for Definition 2, the achievement rates of LDL-C <100 mg/dL and LDL-C <70 mg/dL in those with a history of CAD were significantly higher than those in patients with no history (LDL-C <100 mg/dL: 60.73% vs. 44.28%; \( p < 0.001 \), LDL-C <70 mg/dL: 21.16% vs. 12.65%; \( p < 0.001 \)). The achievement rates of non-HDL-C <130 mg/dL and non-HDL-C <100 mg/dL were also significantly higher than in those with no history (non-HDL-C <130 mg/dL: 69.71% vs. 55.13%; \( p < 0.001 \), non-HDL-C <100 mg/dL: 34.81% vs. 24.47%; \( p < 0.001 \)). For the comparators of Definition 2, the achievement rates of LDL-C <100 mg/dL and LDL-C <70 mg/dL in those with a history of CAD were significantly higher than those in patients with no history (LDL-C <100 mg/dL: 70.62% vs. 61.89%; \( p < 0.001 \), LDL-C <70 mg/dL: 23.90% vs. 14.69%; \( p < 0.001 \)). The achievement rates of non-HDL-C <130 mg/dL and non-HDL-C <100 mg/dL were also significantly higher than those in patients with no history (non-HDL-C <130 mg/dL: 79.18% vs. 70.89%; \( p < 0.001 \), non-HDL-C <100 mg/dL: 40.40% vs. 31.79%; \( p < 0.001 \)). CAD: coronary artery disease, LDL-C: low-density lipoprotein, non-HDL-C: non-high-density lipoprotein.
Supplementary Fig. 4. The frequency of patients who achieved the target value: history of coronary artery disease (all eligible patients)

For patients with and without a history of CAD (all eligible patients), 3259 (3259/30,973: 10.52%) and 2909 (2909/31,549: 9.22%) had available LDL-C data, while 3301 (3301/30,973: 10.66%) and 2670 (2670/31,549: 8.46%) had non-HDL-C data available, respectively. The achievement rates of LDL-C < 100 mg/dL and LDL-C < 70 mg/dL in patients with a history of CAD were significantly higher than those in patients with no history (LDL-C < 100 mg/dL: 64.16% vs. 52.53%; p < 0.001, LDL-C < 70 mg/dL: 21.20% vs. 12.65%; p < 0.001). The achievement rates of non-HDL-C < 130 mg/dL and non-HDL-C < 100 mg/dL in patients with a history of CAD were also significantly higher than those in patients with no history (non-HDL-C < 130 mg/dL: 73.13% vs. 61.80%; p < 0.001, non-HDL-C < 100 mg/dL: 35.90% vs. 26.70%; p < 0.001). CAD: coronary artery disease, LDL-C: low-density lipoprotein, non-HDL-C: non-high-density lipoprotein.
Supplementary Fig. 5. The frequency of patients who achieved the target value: Definition 3 (history of coronary artery disease)

For patients who met the criteria for Definition 3 with and without a history of CAD, and the comparators of Definition 3 with and without a history of CAD, 364 (364/2945: 12.36%), 505 (505/5281: 9.56%), 2895 (2895/28,028: 10.33%) and 2404 (2404/26,268: 9.15%) had available LDL-C data, while 363 (363/2945: 12.33%), 427 (427/5281 8.09%), 2938 (2938/28,028: 10.48%), and 2243 (2243/26,268: 8.54%) had available non-HDL-C data, respectively. For patients satisfying the Definition 3 criteria, the achievement rate of LDL-C <100 mg/dL was significantly higher than those with no history (40.38% vs. 33.86%; p=0.049) and that of LDL-C <70 mg/dL was also higher than in those with no history (7.42% vs. 5.94%; p=0.386). The achievement rate of non-HDL-C <130 mg/dL was significantly higher than that in those with no history (50.69% vs. 40.28%; p=0.003) and that of non-HDL-C <100 mg/dL was higher than in those with no history (15.15% vs. 12.18%; p=0.224). For the comparators of Definition 3, the achievement rates of LDL-C <100 mg/dL and LDL-C <70 mg/dL in those with a history of CAD was significantly higher than those with no history (LDL-C <100 mg/dL: 67.15% vs. 56.45%; p<0.001, LDL-C <70 mg/dL: 22.94% vs. 14.06%; p<0.001). The achievement rates of non-HDL-C <130 mg/dL and non-HDL-C <100 mg/dL were also significantly higher than in those with no history (non-HDL-C <130 mg/dL: 75.90% vs. 65.89%; p<0.001, non-HDL-C <100 mg/dL: 38.46% vs. 29.47%; p<0.001). CAD: coronary artery disease, LDL-C: low-density lipoprotein, non-HDL-C: non-high-density lipoprotein.
Supplementary Fig. 6. The frequency of patients who achieved the target value: history of diabetes mellitus (patients with statin prescription)

For patients with and without history of DM (patients with statin prescription), 1172 (1172/11,927: 9.83%) and 4127 patients (4127/42,369: 9.74%) had available LDL-C data, while 1483 (1483/11,927: 12.43%), and 3698 (3698/42,369: 8.73%) had available non-HDL-C data, respectively. The achievement rates of LDL-C $<100$ mg/dL and LDL-C $<70$ mg/dL in the patients with a history of DM were significantly higher than in those with no history (LDL-C $<100$ mg/dL: 71.08% vs. 59.80%; $p<0.001$, LDL-C $<70$ mg/dL: 27.47% vs. 16.48%; $p<0.001$). The achievement rates of non-HDL-C $<130$ mg/dL and non-HDL-C $<100$ mg/dL in those with a history of DM were also significantly higher than in those with no history (non-HDL-C $<130$ mg/dL: 77.41% vs. 69.23%; $p<0.001$, non-HDL-C $<100$ mg/dL: 39.99% vs. 32.40%; $p<0.001$). DM: diabetes mellitus, LDL-C: low-density lipoprotein, non-HDL-C: non-high-density lipoprotein.
Supplementary Fig. 7. The frequency of patients who achieved the target value: Definition 1 (history of diabetes mellitus)

For patients who satisfied the criteria of Definition 1 with and without a history of DM, and the comparators of Definition 2 with and without a history of DM, 23 (23/270: 8.52%), 113 (113/990: 11.41%), 1149 (1149/11,657: 9.86%), and 4014 (4014/41,379: 9.70%) had available LDL-C data, while 38 (38/270: 14.07%), 98 (98/990: 9.90%), 1445 (1445/11,657: 12.40%), and 3600 (3600/41,379: 8.70%) had available non-HDL-C data, respectively. For patients who met the criteria for Definition 1, the achievement rates of LDL-C <100 mg/dL and LDL-C <70 mg/dL in those with a history of DM were significantly higher than in those with no history (LDL-C <100 mg/dL: 60.87% vs. 30.97%; \( p = 0.006 \), LDL-C <70 mg/dL: 26.09% vs. 7.08%; \( p = 0.006 \)). The achievement rate of non-HDL-C <130 mg/dL was higher than in those with no history of DM (57.89% vs. 40.82%; \( p = 0.073 \)) and that of non-HDL-C <100 mg/dL was significantly higher than in those with no history (28.95% vs. 10.20%; \( p = 0.007 \)). For the comparators of Definition 1, the achievement rates of LDL-C <100 mg/dL and LDL-C <70 mg/dL in those with a history of CAD were significantly higher than in those with no history (LDL-C <100 mg/dL: 71.28% vs. 60.61%; \( p < 0.001 \), LDL-C <70 mg/dL: 27.50% vs. 16.74%; \( p < 0.001 \)). The achievement rates of non-HDL-C <130 mg/dL and non-HDL-C <100 mg/dL were also significantly higher than in those with no history of DM (non-HDL-C <130 mg/dL: 77.92% vs. 70.00%; \( p < 0.001 \), non-HDL-C <100 mg/dL: 40.28% vs. 33.00%; \( p < 0.001 \)). DM: diabetes mellitus, LDL-C: low-density lipoprotein, non-HDL-C: non-high-density lipoprotein.
Supplementary Fig. 8. The frequency of patients who achieved the target value: Definition 2 (history of diabetes mellitus)

For patients satisfying the criteria for Definition 2 with and without a history of DM, and the comparators of Definition 2 with and without a history of DM, 494 (494/6497: 7.60%), 1265 (1265/19,774: 6.40%), 678 (678/5430: 12.49%), and 2862 (2862/22,595: 12.67%) had available LDL-C data, while 519 (519/6497: 7.99%), 1209 (1209/19,774: 6.11%), 964 (964/5430: 17.75%), and 2489 (2489/22,595: 11.02%) had available non-HDL-C data, respectively. For patients who satisfied the criteria for Definition 2, the achievement rates of LDL-C \(\leq 100\) mg/dL and LDL-C \(\leq 70\) mg/dL in those with a history of DM were significantly higher than in those with no history (LDL-C \(\leq 100\) mg/dL: 65.38% vs. 49.25%; \(p<0.001\), LDL-C \(\leq 70\) mg/dL: 24.09% vs. 15.02%; \(p<0.001\)). The achievement rates of non-HDL-C \(\leq 130\) mg/dL and non-HDL-C \(\leq 100\) mg/dL were also significantly higher than in those with no history (non-HDL-C \(\leq 130\) mg/dL: 71.10% vs. 60.55%; \(p<0.001\), non-HDL-C \(\leq 100\) mg/dL: 36.03% vs. 28.21%; \(p<0.001\)). For the comparators of Definition 2, the achievement rates of LDL-C \(\leq 100\) mg/dL and LDL-C \(\leq 70\) mg/dL in those with a history of DM were significantly higher than in those with no history of DM (LDL-C \(\leq 100\) mg/dL: 75.22% vs. 64.47%; \(p<0.001\), LDL-C \(\leq 70\) mg/dL: 29.94% vs. 17.12%; \(p<0.001\)). The achievement rates of non-HDL-C \(\leq 130\) mg/dL and non-HDL-C \(\leq 100\) mg/dL were also significantly higher than in those with no history of DM (non-HDL-C \(\leq 130\) mg/dL: 80.81% vs. 73.44%; \(p<0.001\), non-HDL-C \(\leq 100\) mg/dL: 42.12% vs. 34.43%; \(p<0.001\)). DM: diabetes mellitus, LDL-C: low-density lipoprotein, non-HDL-C: non-high-density lipoprotein.
Supplementary Fig. 9. The frequency of patients who achieved the target value: history of diabetes mellitus (all eligible patients)

For patients with and without a history of DM (all eligible patients), 1288 (1288/13,318: 9.67%) and 4880 (4880/49,204: 9.92%) had available LDL-C data, while 1639 (1639/13,318: 12.31%) and 4332 (4332/49,204: 8.80%) had non-HDL-C data available, respectively. The achievement rates of LDL-C < 100 mg/dL and LDL-C < 70 mg/dL in patients with a history of DM were significantly higher than in those with no history (LDL-C < 100 mg/dL: 69.25% vs. 55.88%; p < 0.001, LDL-C < 70 mg/dL: 25.93% vs. 14.86%; p < 0.001). The achievement rates of non-HDL-C < 130 mg/dL and non-HDL-C < 100 mg/dL in those with a history of DM were also significantly higher than in those with no history (non-HDL-C < 130 mg/dL: 75.29% vs. 65.33%; p < 0.001, non-HDL-C < 100 mg/dL: 37.83% vs. 29.50%; p < 0.001). DM: diabetes mellitus, LDL-C: low-density lipoprotein, non-HDL-C: non-high-density lipoprotein.
Supplementary Fig. 10. The frequency of patients who achieved the target value: Definition 3 group (history of diabetes mellitus)

For patients who satisfied Definition 3 criteria with and without a history of DM, and the comparators of Definition 3 with and without a history of DM, 116 (116/1391: 8.34%), 753 (753/6835: 11.02%), 1,172 (1172/11,927: 9.83%), and 4127 (4127/42,369: 9.74%) had available LDL-C data, while 156 (156/1391: 11.21%), 634 (634/6835: 9.28%), 1,483 (1483/11,927: 12.43%), and 3,698 (3,698/42,369: 8.73%) had available non-HDL-C data, respectively. For patients who satisfied Definition 3 criteria, the achievement rate of LDL-C ≤ 100 mg/dL in those with a history of DM was significantly higher than in those with no history (50.86% vs. 34.40%; p < 0.001) and that of LDL-C ≤ 70 mg/dL was also higher than in those with no history (10.34% vs. 5.98%; p = 0.077). The achievement rate of non-HDL-C ≤ 130 mg/dL was significantly higher than in those with no history (55.15% vs. 42.59%; p = 0.005) and that of non-HDL-C ≤ 100 mg/dL was higher than in those with no history (17.31% vs. 12.62%; p = 0.125). For the comparators of Definition 3, the achievement rates of LDL-C ≤ 100 mg/dL and LDL-C ≤ 70 mg/dL in those with a history of DM were significantly higher than in those with no history (LDL-C ≤ 100 mg/dL: 71.08% vs. 59.80%; p < 0.001, LDL-C ≤ 70 mg/dL: 27.47% vs. 16.48%; p < 0.001). The achievement rates of non-HDL-C ≤ 130 mg/dL and non-HDL-C ≤ 100 mg/dL were also significantly higher than in those with no history (non-HDL-C ≤ 130 mg/dL: 77.41% vs. 69.23%; p < 0.001, non-HDL-C ≤ 100 g/dL: 39.99% vs. 32.40%; p < 0.001). DM: diabetes mellitus, LDL-C: low-density lipoprotein, non-HDL-C: non-high-density lipoprotein.