Low-density lipoprotein cholesterol levels and lipid-modifying therapy prescription patterns in the real world: An analysis of more than 33,000 high cardiovascular risk patients in Japan

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ABSTRACT

Background and aims: Low-density lipoprotein cholesterol (LDL-C) is a key modifiable risk factor in the development of cardiovascular (CV) disease. In 2012, the Japan Atherosclerosis Society (JAS) issued guidelines recommending statins as first-line pharmacotherapy for lowering LDL-C in patients at high risk for CV events. This study assessed achievement of recommended LDL-C goals and lipid-modifying therapy (LMT) use in a high CV risk population in Japan.

Methods: Patients from the Medical Data Vision (MDV) database, an electronic hospital-based claims database in Japan, who met the following inclusion criteria were included in this study: LDL-C measurement in 2013; ≥21 years of age; ≥2 years representation in the database; and a high CV risk condition (recent acute coronary syndrome (ACS), other coronary heart disease (CHD), ischemic stroke, peripheral arterial disease (PAD) or diabetes). LDL-C goal attainment was assessed based on LDL-C targets in the JAS guidelines.

Results: A total of 33,325 high CV risk patients met the inclusion criteria. Overall, 68% of the cohort achieved guideline recommended LDL-C targets, with only 42% receiving current treatment with statins. Attainment of LDL-C goals was 68% for ACS, 55% for CHD, and 80% each for ischemic stroke, PAD, and diabetes patients. Concomitant use of non-statin LMTs was low.

Conclusions: In a high CV risk population in a routine care setting in Japan, guideline recommended LDL-C goal attainment and utilization of statins and other LMT was low. In addition, physicians appeared to be more likely to consider the initiation of statins in patients with higher baseline LDL-C levels.

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1. Introduction
Cardiovascular (CV) disease is the second leading cause of mortality in Japan, accounting for 29% of total deaths in 2012 [1]. Globally, and within Southeast Asia and Japan specifically, abnormal lipids have been identified as having a high population attributable risk [2]. Elevated levels of low-density lipoprotein cholesterol (LDL-C), a key modifiable risk factor, is associated with an increased risk of atherosclerotic CV events including myocardial infarction (MI), unstable angina (UA), coronary revascularization, ischemic stroke, and CV death [3–7]. A number of large randomized clinical trials (RCTs) with statin-based and non-statin based therapies have demonstrated that a reduction in LDL-C levels results in a reduced risk of CV events [8–11]. A meta-analysis of 26 RCTs with statins demonstrated that each 1 mmol/L decrease in LDL-C...
resulted in a 22% reduction in the relative risk of major CV events, with the relationship being consistent for populations with varying levels of baseline risk, including primary and secondary prevention populations, and at varying levels of baseline LDL-C [3]. Further, a large RCT conducted in Japan reported that the risk of coronary heart disease (CHD) was 33% lower in patients treated with statin plus diet therapy compared with patients on diet alone [12].

Guidelines relevant to the treatment of elevated LDL-C recommend treatment approaches based on patients’ CV risk profile. While major guidelines such as the American College of Cardiology/American Heart Association (ACC/AHA), European Society of Cardiology/European Atherosclerosis Society (ESC/EAS), National Lipid Association (NLA), and the International Atherosclerosis Society (IAS) differ slightly with respect to goal attainment, all recommend statins as the first-line drug treatment for elevated LDL-C [4,5,13,14]. In Japan, the 2012 Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic CV diseases in Japan recommend achievement of LDL-C <100 mg/dL in patients with established CHD and LDL-C <120 mg/dL in patients with any of the following conditions: history of ischemic stroke, peripheral arterial disease (PAD), diabetes mellitus (DM), and coronary artery disease (CAD) [4]. Among the following high CV risk coronary artery disease (CAD), the JAS guidelines recommend lifestyle modification such as smoking cessation, healthy diet and regular exercise before drug therapy is considered; however, for those with CAD, guidelines suggest drug therapy to be simultaneously considered with lifestyle modifications. Similar to other major guidelines across the world, JAS guidelines recommend statins as first-line pharmacotherapy for lowering LDL-C, with consideration of non-statin lipid-modifying therapies (LMT) such as bile acid sequestrants and/or ezetimibe either as add-on to statins or as monotherapy where statins may not be appropriate.

The objective of the current study was to conduct a point in time analysis to summarize LDL-C levels of patients and to examine patients’ LDL-C goal attainment versus the recommended target levels by the JAS guidelines using a real-world population at high CV risk in Japan. The secondary objective was to assess the utilization of statins and other LMT in this population. This study aimed to provide insights into the utilization patterns of statins and non-statin LMT and LDL-C goal attainment among specific sub-categories of patients considered at high risk for CV events.

2. Materials and methods

2.1. Database and cohort selection

This retrospective, cross-sectional, observational study utilized the Medical Data Vision (MDV) database, which contains electronic hospital-based health insurance claims and Diagnosis Procedure Combination (DPC) data. The database represents inpatient and outpatient medical care from a panel of 136 hospitals distributed in different regions across Japan. All hospitals in the database were for outpatient medical care from a panel of 136 hospitals distributed in different regions across Japan. All hospitals in the database were for acute care, with an average bed number of 350. The database contains anonymized patient-level information on demographics, clinical diagnoses, procedures, prescriptions, and costs. Laboratory test results are also available for a subset of patients.

Patients meeting the following inclusion criteria were selected: at least 1 recorded LDL-C value (measured by direct assay) in 2013 with the last LDL-C measurement in 2013 defined as the index date, ≥20 years of age, and evidence for ≥ 1 of the following high CV risk conditions: recent acute coronary syndrome (ACS); acute MI or UA with concurrent hospitalization within 12 months prior to the index date), other CHD (any history of CHD except defined as “Recent ACS”), ischemic stroke, PAD (any history of peripheral vascular disease, abdominal aortic aneurism, or carotid artery disease) or DM (type 1 or type 2). All high CV-risk conditions were identified using International Classification of Disease, Tenth Revision (ICD-10) codes as well as Japanese procedure codes within the MDV database (Supplementary Table 1). All codes were carefully examined by experts to ensure selected codes represented disease states in which treatment with statin could be realized. In order to capture complete medical history for classification into CV risk conditions and to determine historical LMT use, we also required ≥2 years of continuous representation in the database prior to the index date.

Patients were hierarchically classified into the highest mutually exclusive categories in the following order: 1) recent ACS; 2) other CHD; 3) ischemic stroke; 4) PAD; and 5) DM. For example, if an individual had a diagnosis for both ischemic stroke and diabetes, she/he would be categorized into the ischemic stroke category. Patients were also examined by prevalent conditions where each patient was placed in every disease profile for which they qualified. For example, a patient with stable CHD and symptomatic PAD was placed in both other CHD and PAD categories.

2.2. Achieved baseline LDL-C levels

Patients’ current LDL-C level was defined as the LDL-C value on the index date. In order to ascertain goal attainment, we defined goal as <100 mg/dL for patients with recent ACS and other CHD, and <130 mg/dL for patients with ischemic stroke, PAD, or diabetes. Although the JAS guidelines recommend an LDL-C target of <120 mg/dL for the latter group, we retained a more conservative threshold which is 10 mg/dL higher in order to facilitate comparison with studies outside Japan and maintain uniformity in LDL-C categorization for other analyses presented in this study. We also summarized LDL-C for all high-CV risk patients using standard LDL-C thresholds, <70 mg/dL, 100 mg/dL, and 130 mg/dL.

Among patients on LMT, we estimated the baseline LDL-C level which was intended to represent LDL-C levels prior to initiation of LMT. This baseline LDL-C was estimated as current LDL-C level/ (1 – expected percent LDL-C lowering by the current LMT). A justification of this approach is supported by the limited influence of patient factors, including baseline LDL-C levels, on expected percent LDL-C lowering efficacy of statin and non-statin LMTs [15]. Asian patients frequently have an increased response to medications compared to patients from Western countries due to genetic differences in drug metabolism [16]. There is very little data available assessing the effect of statins in Asian populations, and is mainly composed of phase II trials with small sample sizes, non-placebo controlled studies, non-randomized studies and open-label studies [17–30]. Thus, the LDL-C lowering percentages of each LMT were based on the data obtained from previously published meta-analyses of large RCTs. The detailed information is presented in Supplementary Table 2. A sensitivity analysis was also conducted to assess the robustness of the mean LDL-C reduction used in baseline LDL-C calculations. The co-efficient of variation for LDL-C reduction response while on treatment in randomized clinical trials is approximately 36% [31,32]. Thus, the LDL-C lowering value for each LMT utilized in the baseline LDL-C estimation calculation was reduced by 36%.

2.3. Determination of treatment with LMT

Patients were assigned into mutually exclusive categories based on medication status at index: 1) currently treated by LMT — if medication supply via a recorded LMT prescription was present on or within 30 days prior to the index date; 2) previously treated by LMT — not currently treated but evidence of a prior recorded LMT during the 2 year pre-index period; 3) no history of treatment with
LMT — defined as no recorded LMT during the 2 year pre-index period. We further categorized LMT use into the following three mutually exclusive categories: high-intensity statin therapy with or without other non-statin LMT, low- to moderate-intensity statin with or without other non-statin LMT, and non-statin LMT. High-intensity statin included atorvastatin >20 mg, rosuvastatin >10 mg, pitavastatin >4 mg. All the other statins and doses were classified as low- to moderate-intensity. Non-statin LMTs included ezetimibe, niacin (nicotinic acid), and bile acid sequestrants (cholestyramine and colestipol).

2.4. Statistical analyses

Demographic and clinical characteristics as well as LMT utilization and achieved LDL-C levels were summarized descriptively via proportions and mean ± standard deviation (SD) as appropriate. Student’s t-test and chi-square tests were used to compare the demographic and clinical characteristics of: 1) patients currently on any statin therapy vs. no statin and 2) patients currently treated with high-intensity statins vs. low- to moderate-intensity statins. No adjustments for multiple testing were performed. All analyses were conducted with SAS software version 9.2.

3. Results

3.1. Baseline characteristics

A total of 33,325 patients met the inclusion criteria (Supplementary Fig. 1). The mean age (SD) was 70 (12) years and about one fifth of the sample was greater than 80 years old. Approximately 61% were male, 77% were hypertensive, and roughly 3% had a severely elevated LDL-C of >190 mg/dL. Assignment by hierarchical category resulted in the following subgroups: 3% recent ACS (n = 1145); 48% other CHD (n = 16,045); 2% ischemic stroke (n = 731); 9% PAD (n = 3161); and 37% diabetes (n = 12,243). Categorization by prevalent conditions led to the following proportions in these categories, respectively: 3%, 51%, 3%, 18%, and 59%.

3.2. Achievement of LDL-C levels

Overall, approximately 68% of the study cohort achieved LDL-C goals as recommended by the JAS guidelines with a mean (SD) LDL-C of 101.3 (30.2) mg/dL. Among the ACS and CHD populations, 56% met their LDL-C goal <100 mg/dL, although in individual subgroups 68% and 55% of ACS and CHD patients achieved their goals, respectively. Among those with ischemic stroke, PAD, and diabetes, 80% (for each) met their LDL-C goal of <130 mg/dL. When analyzing the population by LDL-C target attainment, 14%, 50%, and 84% of the population achieved <70 mg/dL, <100 mg/dL, and <130 mg/dL, respectively.

By hierarchical risk categorization, the mean LDL-C mg/dL was 88.8 (29.9) mg/dL for recent ACS, 98.0 (29.1) mg/dL for other CHD, 105.2 (30.3) mg/dL for ischemic stroke, 104.6 (31.7) mg/dL for PAD, and 105.7 (30.4) mg/dL for diabetes. The percentage of those achieving an LDL-C of <100 mg/dL was 68%, 55%, 44%, 45%, and 43%, while those achieving <130 mg/dL was 92%, 87%, 80%, 80%, and 80%, for recent ACS, other CHD, ischemic stroke, PAD, and diabetes, respectively (Fig. 1).

3.3. Utilization of LMT

Overall, 45% of the study cohort was treated with LMT as of index date with 42% of the study cohort receiving a statin. Treatment with statins was 57%, 48%, 32%, 33%, and 35% by hierarchical categorization of recent ACS, other CHD, ischemic stroke, PAD, and diabetes, respectively.
diabetes, respectively. Of those treated with LMT, only 1% received a high-intensity statin with this proportion being 3%, 2%, 0%, 1%, and 0% by hierarchical categorization of recent ACS, other CHD, ischemic stroke, PAD, and diabetes, respectively (Fig. 2A). Of those not currently treated with LMT (55% of the cohort), previous treatment was examined and it was found that only 6% of the study cohort had evidence of prior treatment with LMT during the 2 years prior to the index date. This proportion was 13%, 7%, 6%, 5%, and 5% by hierarchical categorization of recent ACS, other CHD, ischemic stroke, PAD, and diabetes, respectively (Fig. 2B). Approximately 49% of the study cohort did not have evidence of treatment with LMT in the 2 years before the index date.

For patients currently treated with LMT, the use of combination therapy was low with the majority of patients using statins as monotherapy. Overall, 74% patients treated with high-intensity statin were on monotherapy and 24% were concomitantly prescribed ezetimibe. A majority of the patients (94%) on low- to moderate-intensity statin were on monotherapy with only 5% also receiving ezetimibe.

Fig. 3 shows the distribution of LMT utilization by LDL-C levels. The utilization of LMT was higher in the patients achieving LDL-C of <100 mg/dL compared to those with LDL-C ≥100 mg/dL. For example, 52% of the patients were receiving LMT who achieved LDL-C of <70 mg/dL compared to only 35% of those with LDL-C ≥100 mg/dL.

An unadjusted comparison indicated that patients on statin treatment (as compared with no statin treatment) were more likely to be female, have a severely elevated LDL-C level of ≥190 mg/dL, coronary high-risk conditions (recent ACS and other CHD), hypertension, and congestive heart failure (CHF). Patients treated with statins were also more likely to be receiving treatment with other CV medications. Patients treated with high-intensity statins (as compared with low- to moderate-intensity statins) were more likely to be younger, male, have severely elevated LDL-C levels of ≥190 mg/dL, coronary high-risk conditions (recent ACS and other CHD), hypertension, CHF, and no concomitant diabetes. Patients treated with high-intensity statins were also more likely to be receiving treatment with other CV medications (Supplementary Table 3).

3.4. LMT utilization by estimated baseline LDL-C

The utilization of LMT was further examined against the estimated baseline LDL-C levels, defined as expected LDL-C level in...
absence of LMT treatment (estimation approach described in methods). Within each hierarchical risk subgroup, patients with higher baseline LDL-C were more likely to be treated with LMT, especially with a statin. Within all subgroups, the proportion of patients on statin therapy increased progressively with increasing baseline LDL-C levels. In the recent ACS group, only 25% of the patients with baseline LDL-C <70 mg/dL were treated with a statin. However, in patients whose baseline LDL-C was ≥160 mg/dL, 74% were treated with a statin (Fig. 4A). The same pattern was observed in the hierarchical subgroups representing other CHD, ischemic stroke, PAD, and diabetes (Fig. 4B–E). The likelihood of receiving statin therapy also increased progressively according to the presumed severity of CV risk. For example, within each baseline LDL-C category, the proportion of patients receiving statin therapy was consistently higher in those with recent ACS and other CHD as compared to those with ischemic stroke, PAD, or diabetes (Fig. 4). In the sensitivity analysis, the same trend, that those with higher baseline LDL-C levels were more likely to be treated with LMT, was seen (results not shown).

4. Discussion

In this study, we assessed the LDL-C attainment and LMT utilization patterns in a high CV risk population in Japan and examined the findings against recommendations from the JAS 2012 guidelines, although we utilized a more conservative approach by using an LDL-C value of 130 mg/dL in lieu of 120 mg/dL. Only 56% of the high-risk subgroups with recent ACS and other CHD met the JAS guidelines LDL-C goal of <100 mg/dL, where the recommendation is to consider LMT together with lifestyle modification. When the less aggressive LDL-C goals were examined for the subgroups with ischemic stroke, PAD, and diabetes, 80% met the JAS guidelines of achieving and LDL-C <130 mg/dL where the recommendation is to consider LMT after lifestyle modification.

The findings from our study are consistent with previous studies examining LDL-C achievement in high-risk populations in Japan as well as other Asian countries. A multicenter, retrospective study of Japanese adults taking dyslipidemia medications in 2009 reported that 45% of CAD patients (population with recent ACS or CHD)
achieved LDL-C of <100 mg/dL and 63% with ischemic stroke, PAD, or diabetes achieved LDL-C <120 mg/dL. [33]. Another cross-sectional survey on patients with dyslipidemia on statin therapy in Japan reported that 25% of CAD patients in achieved an LDL-C of <100 mg/dL while 57% of high-risk non-CAD achieved LDL-C of <120 mg/dL. [34]. Moreover, similar LDL-C attainment trends were reported in other Asian countries. A Pan-Asian cross-sectional survey was conducted in eight Asian countries for hypercholesterolemia patients treated with lipid-lowering pharmacological treatment [35]. Overall LDL-C goal attainment was reported in 49.1% of patients with specific LDL-C goal attainment in 34.9%, 55.3%, and 75.4% of patients with very high-risk (LDL-C goal of <70 mg/dL), high risk (LDL-C goal of >100 mg/dL), and moderate risk (LDL-C goal of <130 mg/dL) of CV events, respectively. Our study indicated a somewhat higher LDL-C goal attainment with 56% of the CAD patients achieving LDL-C of <100 mg/dL. The variation in findings can be due to differences in study population and design of previous studies, which specified elevated LDL-C or treatment with LMT as part of inclusion criterion. For patients currently on LMT in our study, 58% achieved an LDL-C level less than 100 mg/dL, which was consistent with the previous studies for subjects on LMT. Despite these differences, our conclusions were consistent in that the LDL-C targets set by JAS were not fully achieved.

Our study also found that only 45% of the study population was currently receiving treatment with any LMT, with 42% of the study population receiving treatment with statins. In addition, high-intensity statins were found to be underutilized. Although the study population was not fully comparable, these proportions are similar to, but slightly lower than those from the International Reduction of Atherothrombosis for Continued Health (REACH) study where 51% of the high-risk patients were on LMT and 45% were on statins [36]. The slight discrepancy is potentially due to the different inclusion criteria in the REACH study with a requirement for at least 45 years of age with established CAD, cerebrovascular disease, or PAD, or with at least three atherosclerosis risk factors. Statin underutilization has also been reported in studies based in other countries. A study based on data from the 2010 Medial Expenditure Panel Survey in the US reported that only 58% of patients with CHD and 52% of patients with diabetes were treated with a statin [37]. One possible reason for low LMT use in Japan is that guidelines recommend that the lipid management goals should generally be achieved via lifestyle modification for all patients, with drug therapies to “be considered” even for patients with a history of CHD [6]. Another possible reason for somewhat lower rates of LMT and statin use in our definition of “current treatment,” with patients being considered to be treated only if medication supply via recorded prescription was present on or within 30 days prior to the index date. The total proportion of patients who received prior (in the last 2 years) or current LMT was 51% and 47%, respectively.

Our investigation of the utilization patterns of statins by patients’ baseline LDL-C levels suggests that in Japan the likelihood of patients receiving treatment by statins increases with increasing baseline LDL-C levels. Thus, even among the subgroup with baseline LDL-C levels exceeding guideline recommendations (e.g. a CHD subgroup with baseline LDL-C >100 mg/dL), those with baseline LDL-C levels farther from the recommended threshold (e.g. those with LDL-C from 130 to 160 mg/dL or >160 mg/dL) were more likely to receive statin therapy. Although JAS guidelines do not require consideration of the initiation of a statin based on distance from LDL-C goal, our data suggest that in real-world practice physicians are likely to consider distance from goal in treatment decisions. Taking into account that pharmacotherapy is only a consideration, it is possible that physicians would manage with lifestyle modification only for patients within a reasonable distance from their LDL-C goal.

In terms of the effectiveness of statins in facilitating LDL-C goal achievement, it is difficult to derive robust conclusions from the study in light of its observational nature. However, more patients who achieved LDL-C <100 mg/dL were treated with statins, as compared to those with LDL-C ≥100 mg/dL, which suggests the key role of statins in facilitating LDL-C goal achievement and ultimately reductions in CV risk.

Our study has several notable limitations. Ischemic stroke represented a relatively small proportion of patients in our study. A possible explanation is the requirement of a LDL-C measurement, which may result in an underestimation of this population if LDL-C is not measured frequently in ischemic stroke patients in Japan. Thirdly, rural populations were underrepresented, which may further limit the generalizability of findings. However, the database included hospitals with outpatient and inpatient services, which reflected the system in Japan. In addition, 55% of the patients in the current study visited outpatient clinics only, indicating good coverage of both inpatients and outpatients. Although there may be differences between inpatient and outpatients due to acute cases of hospitalization potentially affecting LDL-C levels, our primary focus was on their prior treatments and their current LDL-C level utilizing the prior 2 years. Regarding LDL-C measurement, the data were obtained from the record of direct assay and were limited for patients with multiple assays only. Additionally, due to the lack of robust data demonstrating a differential LDL-C lowering of statins in a Japanese population, the baseline LDL-C was estimated using data from large meta-analyses of clinical trials which may not reflect real-world treatment effects. If Japanese patients have a heightened response to statins compared with Western patients, the baseline LDL-C estimates may be underestimated. Furthermore, LDL-C data was derived from hospitals, where LDL-C is measured after adequate fasting; however, the current dataset does not guarantee that all patients conducted adequate fasting prior to lab tests. Lastly, the database cannot capture potential health services, including prescriptions, that were obtained at institutions outside of the panel represented in the database. We explored whether this limitation might be relevant and if it could impact the estimates of measures such as LMT or statin utilization by examining the overall distributions of prescription-related encounters in the study cohort during past 3 years for any medication, and concluded that most patients received prescriptions within the institutions represented in the database.

The present study concluded that in a high-risk cohort in Japan only 68% achieved guideline-recommended LDL-C goals and only 42% were treated with a statin, suggesting that statins are underutilized in Japanese high-risk populations. This represents an opportunity to increase statin utilization in order to further decrease residual risk.

**Conflict of interest**

T. Teramoto, H. Arai, and S. Yamashita receive modest consultant fees from Sanofi and Regeneron. I. Khan, K. Gorcyca, K. Uno, and I. Miyoshi are employees of Sanofi. R. Sanchez is an employee of Regeneron. S. Yoshida, K. Mawatari, and T. Masaki are employees of IMS.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2016.07.001.

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