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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

Tamio Teramoto [a, *], Kiyoko Uno [b], Izuru Miyoshi [b], Irfan Khan [c], Katherine Gorcyca [c], Robert J. Sanchez [d], Shigeto Yoshida [e], Kazuhiro Mawatari [e], Tomoya Masaki [e], Hidenori Arai [f], Shizuya Yamashita [g]

[a] Teikyo Academic Research Center, 2-11-1, Kaga, Itabashi-ku, Tokyo 173-8605, Japan
[b] Sanofi, Tokyo, Japan
[c] Sanofi, Bridgewater, NJ, USA
[d] Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA
[e] IMS Japan K.K., Tokyo, Japan
[f] Department of Human Health Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan
[g] Rinku General Medical Center, Osaka, 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; ≥20 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.

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

* Corresponding author.
E-mail address: ttera@med.teikyo-u.ac.jp (T. Teramoto).

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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 a Japanese population 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 chronic kidney disease (CKD) [6]. Among high-risk patients without 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 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