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Cardiovascular risk in patients achieving low-density lipoprotein cholesterol and particle targets

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ABSTRACT

Objectives: Previous research suggests that LDL particle number (LDL-P) may be a better tool than LDL cholesterol (LDL-C) to guide LDL-lowering therapy. Using real-world data, this study has two objectives: [1] to determine the incidence of CHD across LDL-P thresholds; and [2] to compare CHD/stroke events among patients achieving comparably low LDL-P or LDL-C levels.

Methods: A claims analysis was conducted among high-risk patients identified from the HealthCore Integrated Research Database^{SM}. The impact of LDL levels on risk was compared across cohorts who achieved LDL-P <1000 nmol/L or LDL-C <100 mg/dL. Cohorts were matched to balance demographic and comorbidity differences.

Results: Among 15,569 patients with LDL-P measurements, the risk of a CHD event increased by 4% for each 100 nmol/L increase in LDL-P level (HR 1.04; 95% CI 1.02–1.05, $p < .0001$). The comparative analysis included 2,094 matched patients with ≥12 months of follow-up, 1,242 with ≥24 months and 705 with ≥36 months. At all time periods, patients undergoing LDL-P measurement were more likely to receive intensive lipid-lowering therapy and had a lower risk of CHD/stroke than those in the LDL-C cohort (HR: 0.76; 95% CI: 0.61–0.96; at 12 months).

Conclusions: In this real-world sample of commercially insured patients, higher LDL-P levels were associated with increased CHD risk. Moreover, high-risk patients who achieved LDL-P <1000 nmol/L received more aggressive lipid-lowering therapy than patients achieving LDL-C <100 mg/dL, and these differences in lipids and therapeutic management were associated with a reduction in CHD/stroke events over 12, 24 and 36 months follow-up.

1. Introduction

The causal link between increased quantity of LDL and the development of CHD is well established [1–4]. Elevated LDL quantity accelerates the development of atherosclerotic disease and the longer the exposure to elevated LDL, the greater the risk of such cardiovascular events as myocardial infarction, ischemic stroke, and coronary mortality. Lowering LDL quantity is a key strategy for reducing CHD risk recommended by treatment guidelines which were developed on the basis of strong evidence from primary and secondary prevention trials with statins [1–5].

LDL-C has served as the principal biomarker for LDL quantity for many years. An alternative measure of LDL quantity is LDL particle number (LDL-P), determined directly by nuclear magnetic resonance spectroscopy or estimated from apolipoprotein B concentrations [6,7]. LDL-C is a measure of the cholesterol content of LDL particles which can vary significantly between individuals and in response to drug and lifestyle interventions; therefore, LDL-C levels do not always accurately reflect a patient's LDL-related risk [8–10]. This is especially true for patients with T2DM, metabolic syndrome, or hypertriglyceridemia who often have LDL particles that are

Abbreviations list: CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; LDL-P, low-density lipoprotein particle number; MESA, multiethnic study of atherosclerosis; PH, proportional hazards; T2DM, type 2 diabetes mellitus.

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cholesterol-depleted, small in size and large in number [9,10]. Data from multiple epidemiological studies have demonstrated that LDL-P better predicts cardiovascular events than LDL-C concentrations, particularly in patients whose LDL-P and LDL-C levels are discordant [11–13].

Recognizing that measurements of LDL-P may provide a better indicator of CHD risk, several expert panels and guidelines advocate the use of LDL-P as a target of therapy in the management of appropriate at-risk patients [14–17]. Most recently, the American Association of Clinical Endocrinologist's (AACE) Comprehensive Diabetes Management Algorithm 2013 Consensus Statement specified a LDL-P target of <1000 nmol/L for patients with T2DM at high risk of CVD [14]. Additional real-world evidence is needed to demonstrate that clinical management aided by access to LDL-P information leads to improvement in cardiovascular outcomes.

To this end, we used a national sample of commercially insured high-risk patients to evaluate two objectives: First, to determine the frequency of CHD events across different LDL-P thresholds; and second, to compare baseline characteristics and CHD/stroke outcomes in high-risk patients achieving comparably low levels of LDL-C and LDL-P. To our knowledge this is the first large-scale, real-world study investigating the potential benefit of LDL-P as an aid to patient management to prevent CHD/stroke events.

2. Methods

2.1. Data source and patient identification

Administrative claims were obtained from the HealthCore Integrated Research Database^{SM} (HIRD^{SM}). The HIRD contains eligibility, medical, and pharmacy claims for approximately 36 million members of Blue Cross and Blue Shield health plans geographically dispersed across the United States. Laboratory results (including LDL-P measurements) which had been provided to physicians and patients in the course of their normal medical care were also obtained from the HIRD and augmented with additional LDL-P and lipid panel data from LipoScience, Inc. Researchers only had access to a limited data set and procedures were in compliance with the 1996 Health Insurance Portability and Accountability Act. The study was approved by a central Institutional Review Board.

The analysis included adults (≥18 years of age) who had at least one electronic LDL-P result (CPT 83704 or LOINC 54434-6) between January 1, 2006 and September 30, 2012. Patients had to be enrolled in a commercial health plan or Medicare Advantage to be included in the study. Inclusion of LDL-P results provided by LipoScience, Inc. increased the total available sample size by approximately 13%, relative to the sample based solely on HIRD data.

2.2. Study design

The study design was comprised of two parts: Part 1 (CHD Incidence), an observational cohort study comparing CHD risk among patients with varying levels of LDL-P to inform optimal LDL-P targets, and Part 2 (LDL-P vs. LDL-C Comparison), an observational cohort study comparing CHD, stroke, and combined CHD/stroke risk between patients achieving pre-specified targets for LDL-C and LDL-P.

2.2.1. Part 1: assessment of CHD incidence by LDL-P

To assess the frequency of CHD events across LDL-P thresholds, all patients with at least 1 LDL-P result were included. The index date was defined as the date of the most recently available LDL-P result preceding a CHD event, or the end of the follow-up period for patients who did not have a CHD event. All patients were required to have at least 6 months of continuous medical and pharmacy health plan enrollment prior to the index date to establish baseline medication use and comorbidities. Patients were followed until either the end of continuous health plan eligibility, the end of the available data stream, or death (as recorded in the Social Security Administration's Death Master File), whichever occurred first. Patients were also required to have at least 1 LDL-C result pre-index. Lastly, the analysis focused on high-risk patients with prior CHD or CHD risk-equivalents. High-risk was determined based on the occurrence of at least 1 of the following events at any time prior to the index date: (1) established CHD, stroke, TIA, or peripheral arterial disease as identified by relevant *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes or a prescription fill for clopidogrel; (2) at least 2 medical claims for diabetes mellitus (ICD-9-CM code 250.xx) or at least 1 prescription fill for an antidiabetic medication.

2.2.2. Part 2: comparative effectiveness analysis of LDL-P vs. LDL-C on CHD/stroke risk

Given the consistent observation from a number of prospective epidemiologic cohorts that LDL-P better predicts cardiovascular outcomes than LDL-C even after rigorous adjustment for established cardiovascular risk factors [11–13], we evaluated whether high-risk patients who achieved LDL-P <1000 nmol/L experienced lower cardiovascular event rates compared to patients who achieve LDL-C <100 mg/dL (based on NCEP ATP III guidelines [1]). Patients who had at least 1 LDL-P level <1000 at any point in the study period were placed in the LDL-P target cohort; patients with at least 1 LDL-C result <100 but no LDL-P measurements were placed in the LDL-C target cohort. The index date for both cohorts was set as the earliest observed test date where the target laboratory value was achieved. All patients were again required to have at least 6 months of continuous medical and pharmacy health plan enrollment prior to the index date. Patients in the LDL-P target cohort were also required to have at least 1 LDL-C result of any value on or during the 6 months pre-index date. High-risk patients were identified using the same method as used in Part 1 for the CHD incidence assessment. Within the LDL-P and LDL-C target cohorts, patients were grouped into 12-month, 24-month and 36-month cohorts based on the length of their available follow-up period (at least 12, 24, or 36 months); patients with longer follow-up were allowed to be in multiple cohorts (for example, a patient with 25 months of follow-up was included in the 12 and 24 month cohorts). Within each cohort outcomes were assessed over the available follow-up time (for example, CHD events were assessed over 12 months in the LDL-P and LDL-C cohorts with at least 12 months of follow-up data).

2.3. Outcome measures

Both parts of this study captured patient characteristics such as demographics, comorbidities (including the Quan–Charlson Comorbidity Index (QCI) score [18]), medication utilization, and laboratory values (e.g. lipid panels, LDL-P, and HDL-P) during the baseline period, defined as the 6 months before the index date.

Part 1 (CHD Incidence) focused on CHD events as the primary outcome measure based on NCEP ATP III guidelines [1]. To encompass a broader spectrum of potentially affected outcomes, Part 2 (LDL-P vs. LDL-C Comparison) looked at CHD and stroke risk, as well as a combined CHD/stroke endpoint. CHD (which included myocardial infarction (MI), angina, and revascularization) and stroke were identified by ICD-9-CM diagnoses and procedural codes and Common Procedural Terminology (CPT) codes on medical claims. To ensure that only acute events were captured, the analysis focused on CHD and stroke events identified from medical claims in an inpatient or emergency room setting.

In Part 1 (CHD Incidence), outcomes were assessed during the entire follow-up period; in Part 2 (LDL-P vs. LDL-C Comparison), all