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

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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

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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 Endocrinologists (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 DatabaseSM (HIRDSM). 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 anti-diabetic 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 achieved 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
outcomes were assessed over a fixed time period (12, 24, or 36 months), except for laboratory values where a ±90-day window was used at the end of each follow-up period.

2.4. Statistical analysis

All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). Statistical significance was defined as a p-value <0.05.

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

Baseline characteristics were described for all high-risk patients with and without post-index CHD events. Descriptive analyses included means (standard deviation [SD]) and relative frequencies for continuous and categorical variables, respectively. Continuous outcomes were compared using independent t-tests or Wilcoxon rank sum tests (based on the distribution of each outcome). Categorical outcomes were compared using χ² tests. Cox proportional hazards models were used to compare CHD event incidence across LDL-P thresholds (<700 nmol/L, <1000 nmol/L, <1300 nmol/L, <1600 nmol/L, and <2000 nmol/L) after adjusting for baseline demographics, comorbidities, and LDL-C level. A separate Cox PH model using LDL-P as a continuous covariate was also created.

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

Baseline patient characteristics were compared between the LDL-C and LDL-P cohorts separately at 12-month, 24-month and 36-month follow-up periods, using the same statistical methods as in Part 1. Stringent 1:1 propensity score matching was used to balance the baseline demographic and comorbidity differences between each of the LDL-P and LDL-C cohorts defined by the length of the follow-up period [19–21]. Differences in treatment patterns and lipid values were left intact. Balance after matching was assessed using unpaired statistical tests as well as standardized differences. Thus, three separate matched LDL-P and LDL-C cohorts were identified.

CHD and stroke event risk was assessed as the percentage of patients experiencing at least 1 event as well as the mean number of events per patient. Unadjusted Cox PH models were used to compare CHD/stroke event incidence between LDL-C and LDL-P cohorts for each follow-up period. Kaplan–Meier curves for the combined CHD/stroke endpoint were created for each matched subsample.

3. Results

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

3.1.1. Patient characteristics

A total of 57,025 patients met the inclusion and exclusion criteria for the study; of these, 15,569 had prior CHD or CHD risk-equivalents and were included in the analysis (refer to Appendix Table 1 for additional patient selection information). Among high-risk patients, 1,291 (8.3%) had one or more CHD events during the follow-up period (Appendix Table 2). Patients with a post-index CHD event tended to be older (61 years vs. 56 years, p < 0.0001) men (65% vs. 55%, p < 0.0001), and more than 50% of patients had diabetes (77.5% vs. 57.1%, p < 0.0001).

At baseline, the mean LDL-P level was 1443 nmol/L for patients without a post-index CHD event, and 1426 nmol/L for those with a post-index CHD event (p = 0.237). Approximately 15% of the total study population had LDL-P levels below a threshold of 1000 nmol/L, while more than 50% of patients had LDL-C levels <100 mg/dL (Fig. 1). Differences in lipid values across the two cohorts were statistically significant but clinically similar.

3.1.2. CHD event risk

The risk of a CHD event increased approximately 4% for each 100 nmol/L increase in LDL-P level (hazard ratio 1.04; 95% confidence interval 1.02–1.05, p < 0.0001). Point estimates for CHD risk also increased monotonically across several pre-defined thresholds, with statistically significant increases observed for LDL-P levels exceeding 1300 nmol/L, 1600 nmol/L, and 2000 nmol/L (Fig. 2).

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

As described above, three separate pairs of matched cohorts were created to examine outcomes in patients with at least 12, 24, and 36 months of follow-up data. Patient characteristics and laboratory values at baseline are presented below in detail for the 12 month sample; outcomes are presented for all three cohort
comparisons. Additional information on the 24 and 36 month samples is available in the Appendix.

3.2.1. Patient characteristics
A total of 195,202 patients were included in the 12 month sample, 2,094 in the LDL-P target cohort and 193,108 in the LDL-C target cohort. The two groups differed significantly in several baseline characteristics including age, region of residence, and health plan enrollment; certain comorbidities including hyperlipidemia and diabetes; as well as laboratory values and medication utilization. After 1:1 propensity score matching, there were no significant differences between the groups in demographic characteristics or baseline comorbidities. Table 1 describes baseline characteristics after matching for patients with 12-months follow-up. For both cohorts, mean age was 56 years, 57% of patients were male, >60% residing in the southern US, with a high prevalence of hypertension, hyperlipidemia and diabetes. Between-group differences in laboratory values and medication utilization were expressly retained. In particular, a higher percentage of patients in the LDL-P cohort received higher potency statin therapy compared to patients in the LDL-C cohort. The baseline characteristics of matched cohorts with 24-months and 36-months follow-up are presented in Appendix Table 4.

3.2.2. Laboratory values
Patients in the LDL-C cohort had higher levels of LDL-C, total cholesterol, triglycerides, and non-HDL-C, and lower levels of HDL-C, compared with those in the LDL-P cohort both at baseline and at 12 months follow up (Appendix Table 5). Mean (SD) LDL-P on index date was 858 (106). Mean (SD) LDL-C at baseline was 73 (21) in the LDL-P cohort and 79 (15) in the LDL-C cohort. Most laboratory values were higher at 12 months follow-up than at baseline, and these changes over time were greater in the LDL-C cohort. Results for the 24 month and 36 month subsamples were similar (Appendix Table 6).

3.2.3. CHD/Stroke event risk
Compared with patients in the LDL-C cohort, fewer patients in the LDL-P cohort had a CHD event, stroke, or combined CHD/stroke events at 12 months, 24 months, and 36 months of follow up (Table 2). The relative risk reduction for the combined CHD/stroke endpoint was approximately 25% in the LDL-P target cohort, consistent across 12 months (HR: 0.76; 95% CI: 0.61–0.96), 24 months (HR: 0.78; 95% CI: 0.62–0.97), and 36 months (HR: 0.75; 95% CI: 0.58–0.97) of follow-up. Incidence rates increased over time, from a mean number of CHD/stroke events of 0.10 (LDL-P) vs. 0.11 (LDL-C) at 12 months to 0.28 vs. 0.34 at 36 months. KM survival curves at 36 months (Fig. 3) illustrate the increasing separation in CHD/stroke events between LDL-P and LDL-C cohorts.

4. Discussion
4.1. Summary of results
This is the first study demonstrating a real-world association between LDL-P levels and CHD/stroke risk. The longitudinal nature of this large database allowed for long-term assessments of up to three years. First, we found that increases in LDL-P are significantly associated with higher risk of CHD events, after accounting for LDL-C. Second, we observed that high-risk patients who achieved an LDL-P level <1000 nmol/L (20th population percentile based on MESA [13]) received more aggressive lipid lowering therapy and had fewer CHD/stroke events than patients who achieved an LDL-C level <100 mg/dL (also 20th population percentile in MESA). Compared to the LDL-C cohort, the proportion of patients with CHD/stroke events in the LDL-P cohort was reduced by 1.8, 2.9 and 4.4 percentage points at 12, 24 and 36 months follow-up, respectively. Similarly, the number of events per patient was reduced by 9%, 27% and 18% respectively within the same timeframes.

4.2. Interpretation and future research
These results are consistent with analyses of several epidemiological studies and clinical trials which have shown that cardiovascular events track with LDL-P [11–13]. In both the Framingham Offspring Study [11] and MESA [13], it was shown that when LDL-C and LDL-P were concordant (i.e., in agreement), each measure was equally associated with CHD risk whereas when LDL-C and LDL-P
were discordant (as occurs in patients with T2DM and metabolic syndrome), risk tracked with only LDL-P, not LDL-C. Statin trials have demonstrated that many subjects who achieve LDL-C goals remain at risk for CVD events [22–25]. This residual risk may be related to persistently elevated LDL-P levels resulting from greater lowering of LDL-C than LDL-P by statins [25]. These results suggest that using LDL-C levels alone to guide treatment decisions may mask the need to consider changes in lipid lowering therapy to achieve appropriate reductions in LDL-P. These changes may include increasing statin medication dosage, selecting a new agent, or using a combination therapy regimen to achieve highly reliable LDL measures that correlate with clinical outcomes.

The consistent reduction in risk observed in the LDL-P cohort raises several important questions. First, what was the provider’s motivation for ordering the LDL-P test in this population of high-risk patients? Patients achieving LDL-P levels <1000 nmol/L had similar LDL-C levels as patients in the LDL-C cohort (between 70 and 80 mg/dL, see Appendix Table 5) but received more aggressive lipid lowering therapy. While it seems reasonable to assume that LDL-P information was being utilized to guide treatment selection, no information regarding provider intent was available within the database. It may be that those providers who order an LDL-P profile are more aggressive in their lipid management practices and more likely to target atherogenic particles in addition to (or as well as) LDL-C. In addition, LDL-P monitoring may have provided physicians a better way to assess both the efficacy of mainly statin-based lipid lowering therapy as well as patients’ adherence to therapy. A reduction in LDL-P may provide a more sensitive measure of response to therapy when there is a lack of further reduction in mean LDL-C levels (Appendix Table 5).
A second important question is what portion of the risk reduction is attributable to reduced LDL-P levels or due to the effects of higher statin doses unrelated to LDL lowering? Although the majority of marketed lipid lowering pharmacotherapies are targeted toward decreasing LDL burden, these drugs do have variable effects on other lipid and nonlipid risk factors that could contribute to the observed reduction in CHD/stroke risk. It is also remarkable that among patients undergoing measurement of LDL-P, all other components of the lipid profile were significantly better over 12, 24, and 36 months compared to patients followed-up with LDL-C, thus likely impacting CVD event risk. Future research may also help to clarify whether very aggressive LDL-C lowering could mimic the reduction in CVD event risk observed in the LDL-P cohort; no appropriate LDL-C threshold for this approach has been defined to date.

Finally, does the improvement in clinical outcomes in patients treated more aggressively in the LDL-P cohort outweigh the costs of additional therapy? A recent study compared the cost-effectiveness of managing patients to LDL-P goals versus management to LDL-C goals [26]. An economic model was developed based on parameters from published literature, including clinical data from MESA. The results suggested that managing LDL-P, either alone or in combination with LDL-C, reduced costs and cardiovascular events and increased quality-adjusted life years in comparison with LDL-C-only management. Further research into cost-effectiveness, particularly in a real-world setting, is needed.

4.3. Limitations

There are some limitations in this type of analysis that are important to describe. The study sample was taken from one large US commercial health plan and results may not be generalizable to patients enrolled in different plans or outside the US. Because the study used a claims database, there was no information on race and other risk factors (e.g., family history of CHD, smoking status, BMI, diet, exercise, socioeconomic status) available in the dataset which could influence outcomes. However, most of these factors may plausibly be distributed equally across the LDL-P and LDL-C cohorts and thus would have little effect on outcome comparisons. Also, it is possible that the disease codes in the claims database used to

Table 2

Event risk for matched LDL-P and LDL-C target cohorts over 12, 24, and 36 month follow-up periods.

<table>
<thead>
<tr>
<th></th>
<th>12 months follow-up</th>
<th>24 months follow-up</th>
<th>36 months follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDL-P cohort</td>
<td>LDL-C cohort</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>p-value</td>
</tr>
<tr>
<td>12 months follow-up</td>
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<td></td>
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<td>2094</td>
<td>1242</td>
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<tr>
<td>LDL-C cohort</td>
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<td>157 (12.6)</td>
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</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.78 (0.61–0.98)</td>
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<td>0.035</td>
</tr>
<tr>
<td>p-value</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>≥1 event, n (%)</td>
<td>12 (0.86)</td>
<td>28 (1.34)</td>
<td>0.138</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.64 (0.36–1.16)</td>
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<td>0.141</td>
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<tr>
<td>Stroke risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events, mean ±SD</td>
<td>0.01 (0.12)</td>
<td>0.02 (0.15)</td>
<td>0.139</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.76 (0.61–0.96)</td>
<td>–</td>
<td>0.021</td>
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<tr>
<td>p-value</td>
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<td>–</td>
<td>–</td>
</tr>
<tr>
<td>≥1 event, n (%)</td>
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<td>170 (8.12)</td>
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<td>Events, mean ±SD</td>
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<tr>
<td>HR (95% CI)</td>
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<td>0.021</td>
</tr>
<tr>
<td>p-value</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tbody>
</table>

CHD = coronary heart disease; CI = confidence interval; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle number. p-values are from chi-square tests for categorical outcomes and t-tests for continuous outcomes. P-values for hazard ratios are from Cox PH models.

Fig. 3. CHD/stroke event risk over 36 months – Kaplan–Meier Curves for Combined CHD/Stroke Risk at 36 months of follow-up (Part 2: Comparative Effectiveness Analysis of LDL-P vs. LDL-C on CHD/stroke risk).
4.4. Conclusions

This study is the first to investigate the association between LDL-P and CHD/stroke events in a large-scale, real-world environment of commercially insured patients. Results suggest that (1) there is a direct association between increases in LDL-P and the risk of CHD events, after accounting for LDL-C levels, and (2) patients achieving an LDL-P level <1000 mg/dL received more aggressive lipid lowering therapy than patients achieving an LDL-C level <100 mg/dL and that these differences in lipids and therapeutic management were associated with significantly better control of all components of the standard lipid profile and a reduction in CHD/stroke events over 12, 24 and 36 months follow-up. This suggests that visibility to LDL-P levels may aid in patient management and result in more favorable clinical outcomes. Further research, including a prospective clinical trial, would be valuable to help confirm these results.

5. Conflict of interest statement

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Appendix A. Supplementary material

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References


