Cost Effectiveness of Achieving Targets of Low-Density Lipoprotein Particle Number Versus Low-Density Lipoprotein Cholesterol Level

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A recent analysis of a commercially insured US population found fewer cardiovascular disease (CVD) events in high-risk patients attaining low levels of low-density lipoprotein (LDL), as measured by LDL particle number (LDL-P) versus low LDL cholesterol (LDL-C). Here, we investigated the cost effectiveness of LDL-lowering therapy guided by LDL-P. Patients were selected from the HealthCore Integrated Research Database and followed for 12 to 36 months. Patients who achieved LDL-P <1,000 nmol/l were placed into the LDL-P cohort, whereas those without LDL-P tests, but who achieved LDL-C <100 mg/dl, were placed into the LDL-C cohort. CVD-related costs included all health plan paid amounts related to CVD events or lipid management. Cost effectiveness was assessed through incremental cost-effectiveness ratios, defined as difference in total costs across the cohorts divided by difference in CVD events, measured over follow-up. Each cohort included 2,094, 1,242, and 705 patients over 12-, 24-, and 36-month follow-up. Patients in the LDL-P cohort received more aggressive lipid-lowering therapy and had fewer CVD events during follow-up compared to patients in the LDL-C cohort. This led to greater pharmacy costs and lower medical costs over time. Incremental cost-effectiveness ratio estimates ranged from $23,131 per CVD event avoided at 12 months to $3,439 and −$4,555 at 24- and 36-month follow-up, suggesting a high likelihood that achieving LDL-P <1,000 nmol/l is cost effective. In conclusion, LDL-lowering therapy guided by LDL-P was demonstrated to be cost effective, with greater clinical and economic benefit seen over longer time horizons and with the increased use of generic statins. **(Am J Cardiol 2017;119:404−409)**

The potential benefit of attaining prespecified low-density lipoprotein (LDL) levels, as measured by nuclear magnetic resonance spectroscopy LDL particle number (LDL-P) versus LDL cholesterol (LDL-C) measured by a standard lipid panel, was previously reported using data from the HealthCore Integrated Research Database.[1] High-risk subjects achieving an LDL-P target <1,000 nmol/l received more intensive lipid-lowering therapy and experienced significant reductions in the risk of cardiovascular disease (CVD) events over 12-, 24-, and 36-month follow-up compared to subjects attaining an LDL-C target <100 mg/dl. To help put the previous clinical findings in economic context, we examined differences in health care costs between the 2 target groups and performed a cost-effectiveness analysis (CEA) to determine the economic implications of managing high-risk patients to LDL-P targets relative to LDL-C targets.

Methods

This study used the same data set on which the previous clinical analysis was conducted, and details of the method have been published previously.[1] Here, we summarize the key elements and describe the outcomes and statistical methods pertaining to the present economic analysis.

This was a retrospective, observational study using administrative claims and electronic laboratory results from the HealthCore Integrated Research Database, augmented with LDL-P and lipid panel data from LipoScience, Inc. (now LabCorp).[1] Patients had to be enrolled in a commercial health plan or Medicare Advantage to be included in the study. Adults (aged ≥18 years) who had ≥1 electronic LDL-P result from January 1, 2006, to September 30, 2012, were included in the LDL-P cohort. Patients without LDL-P measurements but who had LDL-C results were included in the LDL-C cohort. Index date was set as the earliest observed date with LDL-P <1,000 nmol/l or LDL-C <100 mg/dl. All patients were required to have at least 6 months of continuous medical and pharmacy health plan enrollment before the index date to establish baseline medication use and co-morbidities. The analysis focused on high-risk patients with previous CVD or CVD risk

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See page 409 for disclosure information.

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equivalents. Patients were subset into overlapping 12-, 24-, and 36-month cohorts based on the length of their available follow-up enrollment after the index date. Patients were observed until the end of each follow-up period or death (as recorded in the Social Security Administration's Death Master File), whichever occurred first.

Acute CVD and stroke events occurring in inpatient or emergency department settings were assessed among patient subgroups with 12-, 24-, and 36-month follow-up. CVD (which included myocardial infarction, unstable angina, and revascularization) and stroke were identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis and procedural codes and Common Procedural Terminology codes on medical claims.

The evaluation of health care costs included CVD-related health plan paid medical costs and pharmacy costs observed over 12-, 24-, and 36-month follow-up. CVD-related medical costs were derived from claims for medical encounters in which a diagnosis code for dyslipidemia was observed (for outpatient visits) or a diagnosis for CVD (acute CVD, stroke, transient ischemic attack, peripheral vascular disease) was observed (for inpatient and emergency department visits). CVD-related pharmacy costs were derived from outpatient pharmacy claims for observed lipid-altering medications. All costs were adjusted to 2012 dollars.

For the CEA, costs were summed across all patients in each cohort. Effectiveness was defined as the total number of CVD events avoided (number of events in the LDL-C cohort minus number of events in the LDL-P cohort), allowing for multiple events per patient. Cost effectiveness was assessed by calculating an incremental cost-effectiveness ratio (ICER; defined as the difference in total costs across the LDL-P and LDL-C cohorts, divided by the difference in effectiveness) and comparing it to a range of willingness-to-pay (WTP) thresholds, which represent the maximum amount of resources the decision-maker (such as a health plan) is willing to commit to avoid 1 event.[2] Such thresholds may vary across decision-makers and over time. Cost-effectiveness acceptability curves were created to present the likelihood of LDL-P targeting being cost effective for a wide range of WTP thresholds.[3] No discounting was used because of the short time horizon.

Statistical significance was defined as a p value <0.05. Baseline patient characteristics and CVD events over follow-up were compared between the LDL-C and LDL-P cohorts separately at 12, 24, and 36 months, using independent *t* tests or Wilcoxon rank-sum tests for continuous variables and the chi-square tests for categorical variables. Unadjusted Cox proportional hazards models were used to estimate relative CVD event risk reduction. Absolute risk reduction rates were calculated as the difference in cohort incidence rates. Number of patients needed to treat to LDL-P target to avoid 1 CVD event equaled the inverse of the absolute risk reduction rate.

Univariate analysis of per-patient costs suggested the presence of outliers in both cohorts. To address this issue, Winsorization was implemented at the fifth and ninety-fifth percentile, and the Winsorized costs were used for all remaining analyses.[4] Generalized linear models with a log link and gamma distribution were used to estimate differences in CVD-related per-patient costs across cohorts to account for cost skewness.[5]

Before the comparison of events and costs, and the CEA, stringent 1:1 propensity score matching was used to balance the baseline demographic and co-morbidity differences between each of the LDL-P and LDL-C cohorts.[6,7] Thus, 3 separate matches were conducted corresponding to subcohorts of LDL-C and LDL-P patients with 12-, 24-, and 36-month follow-up. Differences in treatment patterns and lipid values at baseline were left intact.

Sampling uncertainty in the ICER was estimated through scatter plots and cost-effectiveness acceptability curves based on 5,000 nonparametric bootstrap samples.[2] Percentile-based 95% confidence intervals for total cost and event differences, as well as for the ICER, were derived from the bootstrap. In addition, the ICER was reestimated under various alternative scenarios to further explore robustness:

(1) Inclusion of patient paid costs (vs health plan paid costs only);
(2) Using all-cause plan paid costs (vs CVD-related costs only); and
(3) Assuming a 75% or 90% cost reduction for atorvastatin and rosuvastatin due to availability of generic versions (vs branded costs as captured in the available data set; see the Supplementary Data for more details).

Results

Each matched cohort (LDL-C and LDL-P) included 2,094, 1,242, and 705 patients over 12-, 24-, and 36-month follow-up, respectively, as previously described.[1] Table 1 describes baseline characteristics and follow-up outcomes after matching. Mean age was 56 years, and ~42% of patients were women. Between-group differences in laboratory values and medication utilization were expressly retained and not controlled for during the matching process. In particular, greater utilization of lipid-lowering medications and maximum potency statins was observed among patients in the LDL-P cohort. The incidence of CVD events was lower among patients in each LDL-P subcohort than among patients in each LDL-C subcohort. The relative risk reduction for LDL-P patients was approximately 22% to 25% across all 3 timeframes. Number of patients needed to treat ranged from 23 to 55, with the lowest number corresponding to the highest absolute risk reduction rate observed among patients with 36 months of follow-up.

Compared to the LDL-C cohort, medical costs in the LDL-P cohort were typically lower, whereas pharmacy costs were greater (because of more medication use) during all three follow-up timeframes, irrespective of adjustment for outliers. Differences in medical costs increased over time such that, in the 24- and 36-month samples, greater pharmacy costs among LDL-P patients were offset resulting in similar total costs between cohorts (Supplementary Table 1).

The results of the primary CEA and the sensitivity analysis are presented in Table 2. At 12 months, total costs were $393,226 higher in the LDL-P cohort, where there were 17 fewer CVD events observed compared to the LDL-C cohort, resulting in an ICER of $23,131 per event avoided. The

Table 1
Patient baseline characteristics and follow-up CVD event risk

Variable	12 months			24 months			36 months		
	LDL-P Cohort (n=2,094)	LDL-C Cohort (n=2,094)	p-value	LDL-P Cohort (n=1,242)	LDL-C Cohort (n=1,242)	p-value	LDL-P Cohort (n=705)	LDL-C Cohort (n=705)	p-value
Age in years, mean (±SD)	57 (±11)	56 (±11)	0.055	57 (±11)	56 (±11)	0.054	57 (±11)	57 (±11)	0.872
Female	899 (43%)	881 (42%)	0.574	526 (42%)	539 (43%)	0.598	302 (43%)	320 (45%)	0.334
Diabetes mellitus	1,183 (57%)	1,198 (57%)	0.640	692 (56%)	715 (3%)	0.352	407 (58%)	408 (58%)	0.957
Cardiovascular disease	1,313 (63%)	1,279 (61%)	0.279	778 (63%)	776 (63%)	0.934	425 (60%)	396 (56%)	0.117
Comorbidity index, mean (±SD)	1.04 (±1.3)	1.12 (±1.2)	0.043	1.03 (±1.3)	1.10 (±1.3)	0.175	1.04 (±1.2)	1.07 (±1.2)	0.616
Lipid-lowering medications, patients with ≥1 fill	1,524 (73%)	1,464 (70%)	0.040	912 (73%)	838 (68%)	0.001	500 (71%)	485 (69%)	0.384
Statin high potency (40-50% LDL-C reduction)	794 (38%)	706 (34%)	0.005	460 (37%)	423 (34%)	0.001	252 (36%)	229 (33%)	0.196
Statin highest potency (>50% LDL-C reduction)	236 (11%)	125 (6%)	<.001	136 (11%)	63 (5%)	<.001	72 (10%)	24 (3%)	<.001
LDL-P, mean (±SD)	858 (±106)	-	-	862 (±105)	-	-	864 (±106)	-	-
LDL-C, mean (±SD)	73 (±21)	79 (±15)	<.001	73 (±21)	80 (±14)	<.001	73 (±22)	79 (±15)	<.001
HDL-C, mean (±SD)	54 (±15)	50 (±14)	<.001	53 (±14)	47 (±13)	0.001	52 (±14)	49 (±14)	0.001
Patients with ≥1 CVD event	130 (6.2%)	168 (8.0%)	0.022	135 (11%)	171 (14%)	0.028	103 (15%)	134 (19%)	0.027
Hazard Ratio (95% CI)	0.77 (0.61-0.96)		0.021	0.78 (0.62-0.98)		0.031	0.75 (0.58-0.97)		0.029
Absolute Risk Reduction/Number Needed to Treat	1.8% / 55		-	2.9% / 34		-	4.4% / 23		-

CI = confidence interval; CVD = cardiovascular disease; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; LDL-P = low density lipoprotein particle number; SD = standard deviation.

uncertainty surrounding this point estimate is visualized in a scatter plot (Figure 1, top-left panel), in which each dot represents an ICER estimate from 1 of the 5,000 bootstraps. The point estimate of the ICER and 72% of the replicates fell into the top-right quadrant, indicating greater effectiveness (fewer events) and greater costs for patients in the LDL-P cohort (vs those in the LDL-C cohort). Approximately 28% of replicates fell into the top-left quadrant, with lower effectiveness and greater costs in the LDL-P cohort.

To determine cost effectiveness, the ICER was compared to a wide range of WTP thresholds to avoid 1 CVD event by means of a cost-effectiveness acceptability curve. In Figure 1, the top-right panel presents such a curve for the 12-month sample. As WTP approaches $20,000, the likelihood that the achievement of LDL-P <1,000 nmol/l is a more cost-effective treatment strategy relative to a strategy of achieving LDL-C <100 mg/dl is 50%. This cost-effectiveness likelihood for LDL-P target achievement attains a maximum of close to 70% as WTP reaches $100,000.

At the 24- and 36-month time horizons, the event differences further increase compared to 12 months (i.e., there is a larger number of events observed in patients in each LDL-C subcohort relative to each corresponding LDL-P subcohort), whereas the cost differences narrow (i.e., the incremental total costs between corresponding LDL-P and LDL-C subcohorts are reduced), leading to ICER point estimates of $3,439 (24 months) and −$4,555 (36 months). Figure 1 illustrates the underlying changes, with the ICER cloud expanding and moving into the bottom-right quadrant, where LDL-P-guided treatment is both more effective and less costly than LDL-C–guided treatment. This also affects the cost-effectiveness acceptability curves, by shifting them upward such that the likelihood of LDL-P <1,000 nmol/l being a cost-effective treatment strategy versus achievement of LDL-C <100 mg/dl increases over the entire WTP range. For example, at 24 months, attaining LDL-P <1,000 nmol/l is estimated to be cost effective with a probability of 90% for a WTP of $20,000.

These results were robust under alternative assumptions as explored in the sensitivity analysis. As summarized in Table 2, the inclusion of patient paid costs increased the ICER to $31,152, whereas analysis using all-cause costs resulted in lower total costs in the LDL-P cohort and a negative ICER (with both lower costs and higher effectiveness in the LDL-P cohort). Finally, we examined a scenario in which atorvastatin and rosuvastatin pricing was reduced 75% or 90% to reflect more current generic statin prices. Because high-potency statins were used more often in the LDL-P cohort (Table 1), this price reduction yielded a diminished cost difference across the 2 cohorts. As illustrated by the broken line in Figure 1, when atorvastatin and rosuvastatin pricing is reduced by 75%, the ICER is lowered and the cost-effectiveness acceptability curve rotates upward, increasing the likelihood of cost effectiveness for a treatment strategy that targets LDL-P <1,000 nmol/L at lower WTP values. Most of the benefit is realized with a 75% reduction (vs 90%).

Discussion

We previously published data from the first real-world analysis of a large, commercially insured, high-risk patient population demonstrating that more intense lipid-lowering therapy guided by LDL-P resulted in fewer CVD events over 12-, 24-, and 36-month follow-up.[1] Here, we evaluated the cost effectiveness of such a treatment strategy relative to "standard care" of LDL-C management to a target of 100 mg/dl. The more intense therapy tended to be more costly to the health plan at 12-month, cost equivalent

Table 2
Costs, events, and incremental cost-effectiveness ratios

	Total Costs		Cost Difference, 95% CI			Total CVD events		Event Difference, 95% CI			ICER	ICER, 95% CI		% Dominated
	LDL-P	LDL-C	Δ	LL	UL	LDL-P	LDL-C	Δ	LL	UL		LL	UL	
Primary analysis														
12-month cohort	$2,777,600	$2,384,374	$393,226	$133,118	$653,334	204	221	17	-40	74	$23,131	$2,279	-$10,177	28%
24-month cohort	$3,888,975	$3,631,039	$257,936	-$275,284	$791,157	226	301	75	-2	152	$3,439	-$2,375	-$235,944	3%
36-month cohort	$3,418,705	$3,559,903	-$141,198	-$790,040	$507,645	190	221	31	-33	95	-$4,555	-	-	14%
Sensitivity analysis														
CVD-related plan paid plus patient paid costs (12 months)	$3,659,679	$3,130,102	$529,577	$204,552	$854,601	204	221	17	-40	74	$31,152	$3,547	-$13,625	28%
All-cause plan paid costs (12 months)	$16,789,428	$16,969,067	-$179,638	-$1,688,492	$1,329,215	204	221	17	-40	74	-$10,567	-	-	18%
Generic statin availability with 75% price reduction:														
12-month cohort	$2,214,317	$1,979,327	$234,990	$2,681	$467,298	204	221	17	-40	74	$13,823	-$15	-$6,687	28%
24-month cohort	$3,245,417	$3,212,848	$32,569	-$469,502	$534,641	226	301	75	-2	152	$434	-$4,650	-$162,226	3%
36-month cohort	$2,868,620	$3,212,486	-$343,866	-$953,263	$265,531	190	221	31	-33	95	-$11,092	-	-	8%

Δ = difference; CI = confidence interval; CVD = cardiovascular disease; ICER = incremental cost-effectiveness ratio (cost per 1 CV event avoided); LDL-C = low density lipoprotein cholesterol; LDL-P = low density lipoprotein particle number; LL = lower limit; SD = standard deviation; UL = upper limit.

at 24-month, and potentially cost saving at 36-month follow-up because of reductions in medical expenses from fewer CVD events.

Point estimates of the ICER ranged from $23,131 per event avoided at 12 months to $3,439 and −$4,555 at 24 and 36 months, respectively. Thus, LDL-P−guided treatment is likely to be highly cost effective at commonly used WTP thresholds, as shown in the cost-effectiveness acceptability curves. Previous studies of interventions to manage CVD have used a wide range of WTP thresholds for 1 CVD event avoided, ranging from $50,000 to $500,000.[8−10] Although use of a single threshold may appear more practical, it has been argued that thresholds should vary across payers, populations, and interventions.[11] Therefore, we present information about the likelihood of the cost effectiveness of LDL-P−guided treatment across a range of thresholds.

Because high-potency statins were used more often in the LDL-P cohort and such medications were largely sold as branded drugs during the study period from 2006 to 2012, a sensitivity analysis was conducted to explore the influence of generic statin pricing. Reducing the costs of atorvastatin and rosuvastatin by 75% lowered the ICER at every point in follow-up and increased the potential for cost effectiveness at lower WTP thresholds.

This analysis is consistent with an earlier analysis based on clinical data from the Multi-Ethnic Study of Atherosclerosis, which found managing to LDL-P, either alone or in combination with LDL-C, to be less expensive and to increase quality-adjusted life-years in comparison with LDL-C−only management.[12] Similarly, using the detailed Archimedes simulation model of disease progression and health care delivery, LDL-P−guided statin therapy was estimated to reduce the risk of CVD events to a greater extent than therapy guided by LDL-C alone and to be cost effective or cost saving for high-risk patients.[13]

The present analysis provides new insights that may be helpful in clinical practice. Multiple societies have issued recommendations to aid clinicians in the management of their patients' LDL-related CVD risk.[14−20] All involve assessment of CVD risk status, initiation of therapy using clinically proven drugs (i.e., statins), followed by varying recommendations to monitor LDL response to therapy. Concern exists that individual care may not be optimized if management is viewed as complete after the initiation of statin therapy. Because of frequent discordance between cholesterol and particle number measurements of LDL quantity,[21−24] and given that CVD risk tracks with LDL-P rather than LDL-C in the setting of discordance,[22,24,25] several groups have endorsed the use of LDL-P to judge response and optimize individual therapy, even if LDL-C and non−HDL-C are at target levels.[16−20] Our previous findings from a real-world population of patients with CVD showed LDL-P−guided therapy is associated with a reduction in CVD events.[1] The present analysis suggests this approach is likely to be cost effective as well, providing information that can be critical for the decision-making of physicians, payers, and patients.

We await the results of clinical trials evaluating the effect of proprotein convertase subtilisin/kexin type 9 inhibitors on CVD events.[26] Currently, these agents are indicated for use

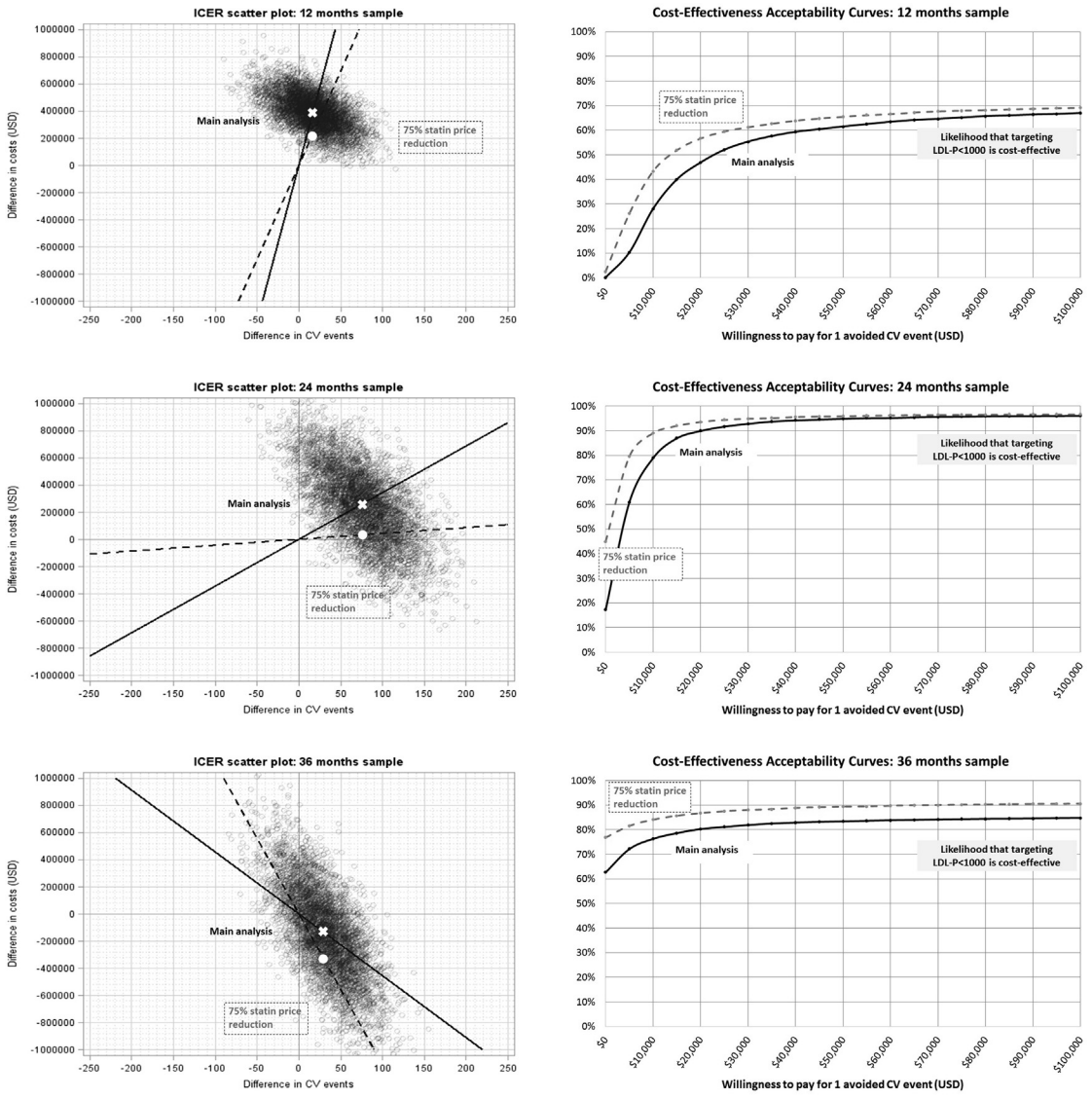

Figure 1. ICER scatter plots and cost-effectiveness acceptability curves.

in patients with clinical CVD or familial hypercholesterolemia who, on maximally tolerated statin therapy, are deemed to need further LDL reduction. This requires LDL monitoring to select eligible patients and to adjudicate response to therapy. If PCSK9 inhibitors demonstrate significant reduction in CVD risk, there is a potential for LDL-P assessments to be valuable in optimizing individual therapy. A similar opportunity exists based on the expected availability and therefore greater utilization of a generic form of Zetia (ezetimibe) in the United States starting in late 2016.[27]

Limitations of this analysis include the following: The study sample was taken from 1 large US commercial health plan, and results may not be generalizable to patients enrolled in different plans or outside the United States. Propensity score matching was used to simulate randomization into treatment cohorts based on observed characteristics; it is possible selection bias based on unobservable variables remained. In particular, because the study used a claims database, no information was available on several factors which could influence patient selection and outcomes (e.g., race, family history of CVD, smoking status, weight, diet, exercise, socioeconomic status, physician preferences, overall clinical quality of care). However, many 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. Variations in patient medication adherence to either lipid-lowering drugs or other cardioprotective medicines between cohorts were not assessed. This analysis was limited to direct costs; indirect costs, such as lost productivity, were not included.

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Disclosures

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Supplementary data

Supplementary data associated with this article can be found, in the online version at http://dx.doi.org/10.1016/j.amjcard.2016.10.028.

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