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Cardiovascular Disease, Mortality Risk, and Healthcare Costs by Lipoprotein(a) Levels According to Low-density Lipoprotein Cholesterol Levels in Older High-risk Adults

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ABSTRACT

Background: The value of lipoprotein(a) (Lp[a]) for predicting cardiovascular disease (CVD) across low-density lipoprotein cholesterol (LDL-C) is uncertain.

Hypothesis: In older high-risk adults, higher LDL and Lp(a) combined would be associated with higher CVD risk and more healthcare costs.

Methods: We included 3251 high-risk subjects (prior CVD, diabetes, or 10-year Framingham CVD risk >20%) age ≥65 years from the Cardiovascular Health Study and examined the relation of Lp(a) tertiles with incident CVD, coronary heart disease (CHD), and all-cause mortality within LDL-C strata (spanning <70 mg/dL to ≥160 mg/dL). We also examined 1-year all-cause and CVD healthcare costs from Medicare claims.

Results: Over a 22.5-year follow-up, higher Lp(a) levels predicted CVD and total mortality (both standardized hazard ratio [HR]: 1.06, $P < 0.01$), whereas higher LDL-C levels predicted higher CHD (standardized HR: 1.09, $P < 0.01$) but lower total mortality (standardized HR: 0.94, $P < 0.001$). Adjusted HRs in the highest (vs lowest) tertile of Lp(a) level were 1.95 ($P = 0.06$) for CVD events and 2.68 ($P = 0.03$) for CHD events when LDL-C was <70 mg/dL. One-year all-cause healthcare costs were increased for Lp(a) ($771 per SD of 56 μg/mL [$P = 0.03$], $1976 for Lp(a) 25–64 μg/mL vs <25 μg/mL [$P = 0.02$], and $1648 for Lp(a) ≥65 μg/mL vs <25 μg/mL [$P = 0.054$]) but not LDL-C.

Conclusions: In older high-risk adults, increased Lp(a) levels were associated with higher CVD risk, especially in those with LDL-C <70 mg/dL, and with higher healthcare costs.

Introduction

Elevated low-density lipoprotein cholesterol (LDL-C) in predicts cardiovascular disease (CVD) events.[1] Data also support an important role for lipoprotein(a) (Lp[a]) in coronary heart disease (CHD) risk, especially when LDL-C levels are elevated.[1] Moreover, Lp(a) adds to risk prediction

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over standard lipid and nonlipid risk factors[2] and predicts stroke, CVD death, and death from all causes in older adults free of prior CVD.[3] However, most prior studies were done in the general population or in specific high-risk populations such as patients with diabetes mellitus (DM)[4] or CHD.[5] The role of Lp(a) for CVD remains unclear in those with lower LDL-C,[5] and few studies have examined Lp(a) and LDL-C together. There are also limited data regarding the prognostic significance and healthcare costs associated with increased Lp(a) levels among older persons with known CVD or other high-risk conditions for CVD.

We examined in older adults enrolled in the prospective Cardiovascular Health Study (CHS) of older adults with preexisting CVD or other high-risk conditions subsequent CVD events, CHD events, all-cause death, and CVD healthcare costs in relation to Lp(a) according to LDL-C levels.

Methods

A total of 5201 participants age 65 to 102 years were initially recruited from 4 US communities (Washington County, MD; Allegheny County, PA; Forsyth County, NC; and Sacramento County, CA) in 1989–1990, and 687 African Americans were enrolled in 1992–1993. All participants provided informed consent. Detailed protocols of CHS have been published.[6]

Risk-Factor Assessment

Baseline exam data consisted of medical and personal history, physical examination, and laboratory tests. Standard questionnaires included smoking status, family history of CHD, medications, and medical history. Height and weight were measured and body mass index (BMI) calculated. Two sitting blood pressures were measured and averaged. Fasting total serum cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) were measured with an Olympus Demand system (Olympus Corp., Lake Success, NY) and standardized according to the US Centers for Disease Control and Prevention.[7] The LDL-C was calculated according to the Friedewald equation.[8] Lipoprotein(a) was measured with a monoclonal antibody–based enzyme-linked immunosorbent assay (Genentech, San Francisco, CA), isoform independent sensitive to react with all Lp(a) isoforms, at the second-year examination of the original cohort; therefore, the African American cohort did not have Lp(a) data[9] and was not included in the current analysis.

Sample Selection

We included 3251 CHS participants with high CVD risk requiring ≥1 of the following at baseline examination[1]: prior CVD,[2] DM,[3] and10-year Framingham risk score (FRS) for all CVD >20%.[10] Prior CVD included prior myocardial infarction (MI), angina pectoris, stroke (includes both ischemic and hemorrhagic stroke and unknown reason), transient ischemic attack, congestive heart failure (HF), coronary artery bypass surgery (CABG) or angioplasty, claudication or peripheral arterial disease (ankle-brachial index <0.9 or ≥1.5). Diabetes mellitus was defined as a fasting glucose ≥7.0 mmol/L or taking hypoglycemic therapy (oral medication or insulin). Subjects were excluded if they had missing key risk-factor data at baseline, including lipid measures, DM, blood pressure, or smoking status, or if they had incomplete follow-up data.

Ascertainment of Follow-up Events

The CHS Cardiovascular Events and Stroke Committees reviewed and classified all potential MI and stroke events, respectively, from follow-up through May 2011. "All incident CHD" included MI, angioplasty, CABG, angina, and death caused by "atherosclerotic CHD." "All incident CVD" was defined as MI, angioplasty, CABG, angina, stroke (ischemic, hemorrhagic, and unknown reason), claudication, HF, and CVD death. An incident event referred to the first qualifying event defined above. The corresponding follow-up time was either that of the earliest event or the censored date when the participant died of a non-CVD event, dropped out of the study, or did not experience any CVD events till the last day of follow-up.

Ascertainment of Follow-up Medical Costs

The CHS clinical event data were retrospectively linked to Medicare claims data beginning in 1996–1997 based on unique match-key information. Medical costs were determined based on the sum of the reimbursements paid out for fee-for-service medical claims. Baseline was set as the exam at which the Lp(a) measures were taken. Due to unavailability of cost data, 841 participants enrolled in health maintenance organizations or without Medicare claims were not included. We calculated all-cause costs, as well as CVD costs based on lead *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code of 390–459 and 745–747 for CVD.[11] We also captured healthcare cost information for all types of claims, including total as well as inpatient, outpatient, and other claims (including carrier claims, skilled nursing facility claims, home health claims, and hospice claims), separately.

Statistical Analysis

The LDL-C levels were stratified into 5 groups (<70 mg/dL, 70–99 mg/dL, 100–129 mg/dL, 130–159 mg/dL, and ≥160 mg/dL), as adapted from the National Cholesterol Education Program guidelines.[12] The Lp(a) levels were divided into tertiles (<25 μg/mL, 25–64 μg/mL, and ≥65 μg/mL). We then calculated rates of new CVD events, CHD events, and all-cause mortality (per 1000 person-years) according to Lp(a) tertiles and the above LDL-C categories. Cox regression was performed after adjustment for age, sex, triglycerides, HDL-C, systolic blood pressure, diastolic blood pressure, hypertension medication status, lipid medication status, smoking status, DM status, BMI, and family history of CHD. Analyses examining the relation of LDL-C with CVD events were adjusted additionally for Lp(a), and those involving Lp(a) were adjusted for LDL-C. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) for LDL-C, Lp(a), and combined LDL-C/Lp(a) categories using the lowest as the reference category. Standardized HRs were also provided for LDL-C and Lp(a) measured continuously to directly compare LDL-C and Lp(a) in predicting incident events. These analyses

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were done for incident CVD and CHD events and all-cause mortality. Analyses were also done in subgroups of those with prior CVD, DM without prior CVD, and FRS risk >20% but without prior CVD and DM; and secondary analyses examined components of CVD other than CHD (HF, claudication, and hemorrhagic stroke). Finally, we calculated the continuous net reclassification improvement (NRI) for CVD and CHD by adding LDL-C and/or Lp(a) to risk factors alone in logistic models, or by adding Lp(a) to risk factors plus LDL-C.

Analyses for medical costs (in 2011 dollars) involved linear regression with robust CIs to account for the high prevalence of outliers in cost data.[9] We focused on total costs over 1 year, but also considered type of medical claim (inpatient, outpatient, and other including carrier claims, skilled nursing facility claims, home health claims, and hospice claims). Costs adjusted for age, sex, and the risk factors used in the outcomes analyses above are presented to account for confounding that may be present in unadjusted costs. We used SAS 9.4 software for the above analysis (SAS Institute, Inc., Cary, NC); a P value < 0.05 was considered statistically significant.

Results

Our cohort at baseline averaged 73.8 years and was 57.6% male and 94% white. Out of our sample, 1620 (49.8%) had prior CVD, 985 (30.3%) had prior CHD, and 751 (23.1%) had DM at baseline. The 10-year Framingham calculated risk of CVD was >20% in 97.7% of those without CVD. Mean systolic/diastolic blood pressure was 140.9/71.3 mm Hg, BMI was 26.7 kg/m^2, LDL-C was 131.2 mg/dL, HDL-C was 50.2 mg/dL, Lp(a) was 55.4 μg/mL, and 10-year Framingham CVD risk averaged 25.5%. At baseline, 57.1% and 5.4% of participants were on antihypertensive and lipid-lowering medications, respectively, and 13.5% were current smokers.

Participants had up to 22.5 years of follow-up, with a mean follow-up of 8.4 years for CVD events (and a mean follow-up of 11.5 years in those who did not experience events), during which there were 2260 incident CVD events, including 1502 CHD events. The Figure shows the joint association of LDL-C and Lp(a) categories with the event rates for (Figure 1A) all incident CVD, (Figure 1B) all incident CHD, and (Figure 1C) all-cause death per 1000 person-years. Although there are modestly higher event rates across tertiles of Lp(a) for most categories of LDL-C, there is a substantially higher event risk observed in those with LDL-C <70 mg/dL for those in the highest tertile of Lp(a) for all 3 endpoints. Incident CVD and CHD events did not vary consistently with higher LDL-C categories, and the incidence of all-cause mortality was lower with increasing LDL-C categories.

Table 1 displays HRs per SD increase of LDL-C and Lp(a) separately, adjusted for other risk factors including Lp(a) in LDL-C analyses and LDL-C in Lp(a) analyses. Higher levels of Lp(a) were associated with greater risks for all CVD events and for all-cause mortality, whereas higher levels of LDL-C were associated with higher risks for all CHD events, but lower risks for all-cause mortality. A similar pattern was observed in analyses examining categories of LDL-C and Lp(a). Among those with LDL-C ≥160 mg/dL, adjusted HRs for CHD events were 1.64 (95% CI: 1.16 to 2.32, $P = 0.005$) and for all-cause mortality 0.80 (95% CI: 0.64 to 0.99, $P = 0.040$) compared with LDL-C <70 mg/dL. Those in the highest tertile of Lp(a) had adjusted HRs of 1.11 (95% CI: 1.00 to 1.23, $P = 0.047$) for CVD events and 1.11 (95% CI: 1.01 to 1.22, $P = 0.025$) for all-cause mortality.

In sensitivity analyses excluding nonischemic stroke, HF, and claudication from the CVD endpoint, relationships were attenuated for both LDL-C (HR: 1.35, 95% CI: 1.01 to 1.80, $P < 0.05$ for those with LDL-C ≥160 mg/dl) and Lp(a) (HR: 1.05, 95% CI: 0.94 to 1.18). Of interest, among individual endpoints, in fully adjusted analyses higher LDL-C (per SD) was associated with lower hemorrhagic stroke risk (HR: 0.78 per SD, 95% CI: 0.62 to 0.99) and higher Lp(a) (per SD) with higher risks for both claudication (HR: 1.16, 95% CI: 1.04 to 1.28) and hemorrhagic stroke (HR: 1.17, 95% CI: 1.00 to 1.37).

Table 2 shows the joint association, adjusted for other risk factors, of LDL-C and Lp(a) categories with the risk of all CVD events, all CHD events, and all-cause mortality. Compared with those in the lowest LDL-C group (<70 mg/dL) and first tertile of Lp(a) levels, adjusted HRs were highest for those who were in the highest tertile of Lp(a) accompanied by an LDL-C <70 mg/dL (2.68 [95% CI: 1.11 to 6.46, $P = 0.028$] for CHD events and 2.43 [95% CI: 1.36 to 4.34, $P = 0.003$] for all-cause mortality). LDL-C levels of ≥100 mg/dL were also associated with modest increases in CHD events regardless of Lp(a) levels, but increases in CVD events only when Lp(a) was in the highest tertile. No increases in risk of all-cause mortality were observed among those with higher levels of LDL-C regardless of Lp(a) levels, however. Sensitivity analyses for CVD events excluding those with congestive HF, nonischemic stroke, and claudication showed the highest risk to persist in those in the highest tertile of Lp(a) when LDL-C was <70 mg/dL (HR: 2.21, 95% CI: 1.03 to 4.73, $P < 0.05$) relative to those with LDL-C <70 mg/dL and the first tertile of Lp(a). LDL-C levels of ≥100 mg/dL were associated with significantly greater risks for CVD events (HR: 1.30-1.74, $P < 0.01$ to $P < 0.05$), regardless of Lp(a) level.

Table 3 shows the association of LDL-C or Lp(a) with CVD events, CHD events, and total mortality in specific high risk subgroups (prior CVD, DM, or >20% FRS CVD risk). An increment of 1 SD of LDL-C was associated with a 14% higher CVD risk in those with DM without prior CVD. Although LDL-C was not predictive for CHD events in the overall sample, it was specifically associated with CHD in those with prior CVD. LDL-C was a protective factor for all-cause death for both those with prior CVD and those with high FRS, but not for those with DM. Lp(a) was only predictive for all CVD events and total death in those with prior CVD.

Finally, calculation of NRI showed little or no added risk prediction for CVD from the addition of LDL-C to models with age, sex, and risk factors; however, there was a modest (0.26, 95% CI: −0.12 to 0.63) but nonstatistically significant NRI from the addition of Lp(a) to models with risk factors and LDL-C in those with an LDL-C <70 mg/dL. For CHD events, the single addition of LDL-C to model with risk factors had an NRI of 0.11 (95% CI: 0.05 to 0.18, $P = 0.001$),

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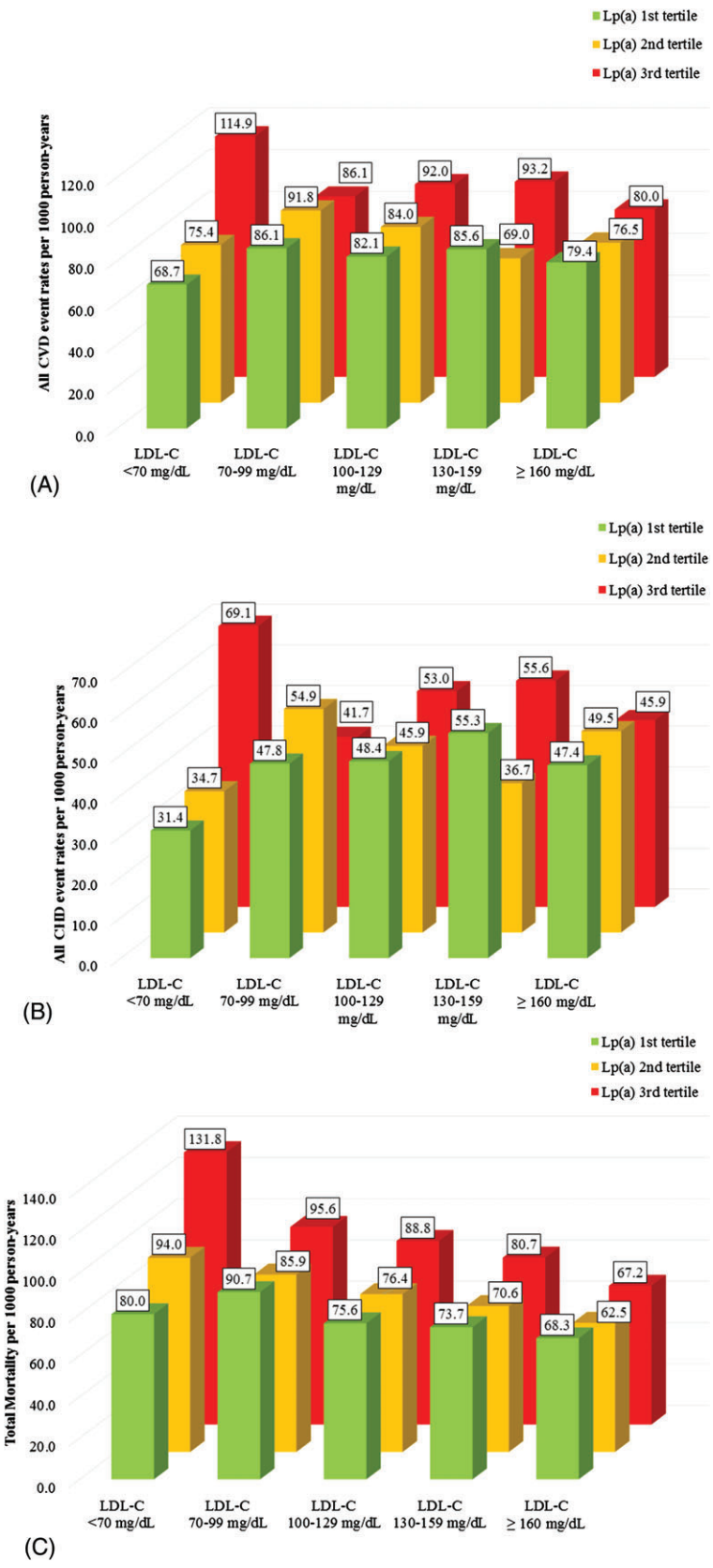

Figure 1. Average event rates of all (A) CVD, (B) CHD, and (C) all-cause death stratified by LDL-C groups and Lp(a) tertiles (first tertile, 0–24 μg/mL; second, 25–64 μg/mL; third, ≥65 μg/mL). Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

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Table 1. Adjusted Standardized HRs and 95% CIs of All CVD, All CHD, and All-Cause Death Relating LDL-C and Lp(a)

	All CVD Events		All CHD Events		All-Cause Death	
	HR	95% CI	HR	95% CI	HR	95% CI
LDL-C, mg/dL						
Per 1 SD	1.02	0.98 to 1.07	1.09	1.03 to 1.15[a]	0.94	0.90 to 0.98[b]
<70	1.00	Ref	1.00	Ref	1.00	Ref
70–99	1.17	0.90 to 1.52	1.34	0.94 to 1.90	0.93	0.75 to 1.15
100–129	1.27	0.99 to 1.63	1.51	1.08 to 2.12[c]	0.89	0.72 to 1.10
130–159	1.23	0.95 to 1.58	1.54	1.09 to 2.16[c]	0.84	0.68 to 1.04
≥160	1.23	0.95 to 1.60	1.64	1.16 to 2.32[a]	0.80	0.64 to 0.99[c]
Lp(a) tertile, μg/mL						
Per 1 SD	1.06	1.01 to 1.10[a]	1.04	0.99 to 1.10	1.06	1.02 to 1.09[a]
0–24	1.00	Ref	1.00	Ref	1.00	Ref
25–64	0.97	0.88 to 1.08	0.93	0.82 to 1.05	0.97	0.89 to 1.06
≥65	1.11	1.00 to 1.23[c]	1.07	0.94 to 1.22	1.11	1.01 to 1.22[c]

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); Ref, reference; SD, standard deviation.
[a] $P < 0.01$. [b] $P < 0.001$. [c] $P < 0.05$.

whereas the addition of Lp(a) did not show significant NRI either to the model with risk factors or to the model with risk factors plus LDL-C. These findings are consistent with our results showing LDL-C best predicted CHD events, whereas Lp(a) best predicted total CVD events in those with LDL-C <70 mg/dL.

One-year per capita all-cause and CVD healthcare costs (in 2011 dollars) for Lp(a) and LDL-C levels per SD and in categories (in fully adjusted analyses, relative to the lowest category of each) are shown in Table 4. One-year all-cause total healthcare costs per SD of Lp(a) were $771 ($P = 0.03$) higher, with no significant difference in costs for LDL-C. Costs were significantly higher only for those with Lp(a) levels 25 to 64 μg/mL (difference $1976, $P = 0.02$) with a borderline relation for those with levels of ≥65 μg/mL (difference $1648, $P = 0.054$). All-cause total healthcare costs were not significantly different by increasing LDL-C levels or by combined LDL-C plus Lp(a) categories. There were also greater all-cause inpatient costs associated with Lp(a) levels of 25 to 64 μg/mL (difference $1558, $P = 0.01$) and ≥65 μg/mL (difference $1050, $P = 0.09$). No patterns of either increasing or decreasing all-cause healthcare costs were observed for total, inpatient, outpatient, or other costs across LDL-C or combined LDL-C and Lp(a) categories, however. Similar patterns were observed for CVD healthcare costs.

Discussion

We show in older higher-risk adults higher Lp(a) levels to be associated with increases in CVD event risk, being most significant for those with baseline LDL-C levels (eg, <70 mg/dL). Among individual CVD endpoints, increased Lp(a) levels are most consistently related to an increased risk of claudication and nonischemic stroke. Moreover, we show higher levels of Lp(a) to be significantly related to increased all-cause healthcare costs independent of LDL-C levels.

The value of increased Lp(a) levels in risk prediction is well recognized. The Emerging Risk Factors Collaboration among 24 prospective studies showed Lp(a) to significantly improve both discrimination and reclassification for CVD events.[2] Also, the relation of Lp(a) with CHD events was homogenous across tertiles of total as well as non–HDL-C.[13] In the Nurses' Health Study, CVD events were greatest when LDL-C was >121 mg/dL and Lp(a) was above the 90th percentile (HR: 1.81).[14] In our study, total mortality was actually lower in those with high LDL-C (influenced by an inverse association of LDL-C with nonischemic stroke). A recent study on the predictive role of Lp(a) in long-term (15 years) CVD outcomes in the general community showed 40% of intermediate-risk subjects were reclassified in their risk from the addition of Lp(a), indicating the utility of Lp(a) in risk assessment.[15]

We show residual risk associated with increased Lp(a) in older higher-risk adults is greatest in those with ideal LDL-C (<70 mg/dL), suggesting residual risk remains despite well-controlled LDL-C levels. Others have shown that Lp(a) remains a significant predictor for future CVD despite statin therapy,[16,17] and lipoprotein apheresis targeting Lp(a) may reduce risk.[18] Also, in post–percutaneous coronary intervention patients who achieved LDL-C <100 mg/dL, survival was worse in those with Lp(a) levels of ≥30 mg/dL vs <30 mg/dL.[19] And in the 4S trial (Scandinavian Simvastatin Survival Study) subgroup of 4402 high-risk men, both deaths and coronary events were significantly higher in those elevated Lp(a) levels.[20] Finally, the recent Atherothrombosis Intervention in Metabolic Syndrome

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Table 2. Adjusted HRs of All CVD Events, All CHD Events, and All-Cause Death by Combined LDL-C Groups and Lp(a) Tertiles

		Lp(a) Tertile, μg/mL					
		0–24		25–64		≥65	
	LDL-C, mg/dL	No. of Events/ No. of Patients	HR (95% CI)	No. of Events/ No. of Patients	HR (95% CI)	No. of Events/ No. of Patients	HR (95% CI)
All CVD events	0–69	36/56	1.00 (Ref)	22/38	1.09 (0.64 to 1.85)	10/15	1.95 (0.96 to 3.96)
	70–99	147/219	1.32 (0.91 to 1.90)	120/170	1.30 (0.89 to 1.89)	84/130	1.32 (0.89 to 1.95)
	100–129	248/352	1.34 (0.94 to 1.90)	243/342	1.42 (1.00 to 2.02)	253/358	1.55 (1.09 to 2.20)[a]
	130–159	200/278	1.46 (1.02 to 2.08)[a]	208/325	1.20 (0.84 to 1.72)	244/334	1.54 (1.08 to 2.20)[a]
	160+	107/155	1.35 (0.92 to 1.97)	167/229	1.38 (0.96 to 1.98)	171/250	1.49 (1.03 to 2.14)[a]
All CHD events	0–69	18/56	1.00 (Ref)	12/38	1.05 (0.51 to 2.19)	7/15	2.68 (1.11 to 6.46)[a]
	70–99	95/219	1.55 (0.94 to 2.57)	82/170	1.68 (1.01 to 2.80)[a]	46/130	1.42 (0.82 to 2.45)
	100–129	166/352	1.71 (1.05 to 2.79)[a]	154/342	1.68 (1.03 to 2.74)[a]	169/358	1.95 (1.19 to 3.18)[b]
	130–159	147/278	2.07 (1.27 to 3.39)[b]	129/325	1.39 (0.85 to 2.29)	168/334	2.06 (1.26 to 3.36)[b]
	160+	73/155	1.80 (1.07 to 3.02)[a]	121/229	2.03 (1.23 to 3.35)[b]	115/250	1.96 (1.18 to 3.23)[b]
All-cause death	0–69	51/56	1.00 (Ref)	35/38	1.22 (0.79 to 1.87)	15/15	2.43 (1.36 to 4.34)[b]
	70–99	210/219	1.19 (0.87 to 1.61)	157/170	0.97 (0.71 to 1.33)	120/130	1.17 (0.84 to 1.63)
	100–129	323/352	0.96 (0.71 to 1.29)	305/342	1.03 (0.76 to 1.39)	337/358	1.22 (0.90 to 1.64)
	130–159	248/278	1.03 (0.76 to 1.39)	285/325	0.97 (0.72 to 1.31)	305/334	1.03 (0.76 to 1.39)
	160+	132/155	0.98 (0.71 to 1.35)	194/229	0.90 (0.66 to 1.23)	211/250	1.02 (0.75 to 1.39)

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); Ref, reference; SBP, systolic blood pressure; TG, triglycerides.
The HRs for LDL-C were adjusted for Lp(a), age, sex, race, SBP, DBP, BMI, TG, HDL-C, hypertension medication, lipid-lowering medication, smoking status, heart disease family history, and DM status; HRs for Lp(a) were adjusted for LDL-C and other risk factors mentioned above.
[a] $P < 0.05$. [b] $P < 0.01$.

With Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) trial showed that both baseline and on-study Lp(a) predicted CVD events in both simvastatin-plus-placebo and simvastatin-plus-niacin groups.[17] These studies support our findings of residual risk remaining from elevated Lp(a) levels in individuals with well-controlled LDL-C.[21]

There remain significant gaps in the treatment of dyslipidemia; in US adults, only two-thirds of those treated were at goal for LDL-C or non–HDL-C; in those with known CVD, only 34.7% and 42.5%, respectively, were at goal.[22] Though it has been recently suggested that Lp(a) measurement may be considered for intermediate- or higher-risk patients (and reasonable for many with recurrent events or a premature family history of CVD),[23] evidence of benefit for lowering CVD risk from therapies known to lower Lp(a) beyond any LDL-C lowering effect is still lacking and needed. Newer therapies such as proprotein convertase subtilisin-like kexin type 9 monoclonal antibodies (PCSK9 mAb) substantially reduce LDL-C by about 60% beyond statins, as well as reduce Lp(a) 25% and have the potential to further reduce CVD events,[24,25] including in those with remaining residual risk from elevated Lp(a) levels despite well-controlled LDL-C, as well as in statin-intolerant patients.[26,27] Although niacin, mipomersen, estrogen-replacement therapy, and lipoprotein apheresis also lower Lp(a) levels, their clinical utility in lowering CVD events remains unclear.[28] In addition to lipid-lowering drugs, tibolone, a synthetic steroid, as well as the nutraceutical L-carnitine also lower Lp(a) levels, although further investigation is needed on whether this has an effect on CVD events.[29,30]

Study Limitations

Our study has strengths and limitations. We included Medicare beneficiaries from 4 field sites in the United States with standardized recruitment, laboratory and data collection, and CVD event adjudication. As our subjects were largely untreated at entry into the study and duration and dosages of lipid therapy were unavailable, our findings should not be generalized to treated patients. Our study is also the first to examine healthcare costs associated with elevated Lp(a) levels. However, because we excluded participants who are HMO-enrolled and/or without Medicare claims due to unavailability of cost data in those persons, our cost estimates cannot be extrapolated to these groups. Nevertheless, in 2010, 76% of Medicare beneficiaries were covered under traditional fee

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Table 3. Adjusted Standardized HRs and 95% CIs of All CVD, All CHD, and All-Cause Death Relating LDL-C and Lp(a) in Each High-risk Group

	All CVD Events			All CHD Events			All-Cause Death		
	No. of Events	HR	95% CI	No. of Events	HR	95% CI	No. of Events	HR	95% CI
LDL-C per 1 SD									
Prior CVD; n = 1620	1189	1.03	0.97 to 1.09	790	1.12	1.04 to 1.20[a]	1517	0.93	0.89 to 0.98[b]
DM without CVD; n = 398	276	1.14	1.01 to 1.28[b]	181	1.13	0.97 to 1.30	354	1.00	0.89 to 1.12
FRS >20% but no DM or prior CVD; n = 1233	795	0.97	0.90 to 1.06	531	1.01	0.92 to 1.12	1057	0.92	0.86 to 0.99[b]
Lp(a) per 1 SD									
Prior CVD; n = 1620	1189	1.08	1.07 to 1.14[b]	790	1.05	0.98 to 1.13	1517	1.06	1.01 to 1.12[b]
DM without CVD; n = 398	276	1.07	0.90 to 1.26	181	1.08	0.88 to 1.32	354	0.98	0.85 to 1.13
FRS >20% but no DM or prior CVD; n = 1233	795	1.04	0.97 to 1.11	531	1.01	0.93 to 1.11	1057	1.04	0.98 to 1.10

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; FRS, Framingham risk score; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); SBP, systolic blood pressure; SD, standard deviation; TG, triglycerides.
The HRs for LDL-C were adjusted for Lp(a), age, sex, race, SBP, DBP, BMI, TG, HDL-C, hypertension medication, lipid-lowering medication, smoking status, heart disease family history, and DM status; HRs for Lp(a) were adjusted for LDL-C and other risk factors mentioned above.
[a] $P < 0.01$. [b] $P < 0.05$.

Table 4. One-Year All-Cause and CVD Costs Associated With LDL-C and Lp(a) Levels in 2011 US$

	All-Cause Healthcare Costs				CVD Healthcare Costs			
	Total	Inpatient	Outpatient	Other	Total	Inpatient	Outpatient	Other
LDL-C, mg/dL								
Per 1 SD	−154 ($P = 0.79$)	10 ($P = 0.98$)	−22 ($P = 0.49$)	−142 ($P = 0.28$)	−132[a] ($P = 0.04$)	−90 ($P = 0.05$)	0 ($P = 0.52$)	−42 ($P = 0.06$)
<70	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
70–99	4010 ($P = 0.85$)	3 ($P = 0.99$)	162 ($P = 0.30$)	244 ($P = 0.70$)	175 ($P = 0.69$)	70 ($P = 0.83$)	5 ($P = 0.07$)	101 ($P = 0.47$)
100–129	497 ($P = 0.81$)	103 ($P = 0.94$)	168 ($P = 0.25$)	227 ($P = 0.71$)	−40 ($P = 0.91$)	−34 ($P = 0.90$)	4[a] ($P = 0.01$)	−10 ($P = 0.93$)
130–159	−1301 ($P = 0.53$)	−973 ($P = 0.52$)	23 ($P = 0.87$)	−351 ($P = 0.55$)	−166 ($P = 0.62$)	155 ($P = 0.56$)	9[a] ($P = 0.03$)	−21 ($P = 0.83$)
160+	−704 ($P = 0.74$)	−567 ($P = 0.72$)	70 ($P = 0.64$)	−208 ($P = 0.74$)	346 ($P = 0.30$)	256 ($P = 0.34$)	3 ($P = 0.14$)	−93 ($P = 0.32$)
Lp(a), μg/mL								
Per 1 SD	771[a] ($P = 0.03$)	465 ($P = 0.07$)	64 ($P = 0.13$)	242[a] ($P = 0.03$)	40 ($P = 0.65$)	33 ($P = 0.60$)	0 ($P = 0.52$)	7 ($P = 0.78$)
0–24	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
25–64	1976[a] ($P = 0.02$)	1558[a] ($P = 0.01$)	−101 ($P = 0.14$)	519[a] ($P = 0.04$)	−267 ($P = 0.11$)	−157 ($P = 0.18$)	1 ($P = 0.06$)	−111 ($P = 0.06$)
≥65	1648 ($P = 0.05$)	1050 ($P = 0.09$)	118 ($P = 0.21$)	480 ($P = 0.06$)	55 ($P = 0.82$)	43 ($P = 0.79$)	1 ($P = 0.59$)	10 ($P = 0.90$)

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); Ref, reference; SBP, systolic blood pressure; SD, standard deviation; TG, triglycerides.
Sample size included in cost analyses: 2410. CVD costs were based on lead ICD-9-CM codes 390–459 and 745–747.
Estimates for LDL-C were adjusted for Lp(a), age, sex, race, SBP, DBP, BMI, TG, HDL-C, hypertension medication, lipid-lowering medication, smoking status, heart disease family history, and DM status; HRs for Lp(a) were adjusted for LDL-C and other risk factors mentioned above.
Other healthcare cost include carrier claims, skilled nursing facility claims, home health claims, and hospice claims.
1 SD of LDL-C = 36.4 mg/dL; 1 SD of Lp(a) = 55.7 μg/mL.
[a] $P < 0.05$.

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for service.[31] Importantly, our cohort is primarily Caucasian, so it has limited generalizability to other ethnic groups.

Conclusion

We show in higher-risk older adults a modest increase in risk of CVD events and increased 1-year all-cause healthcare costs associated with higher Lp(a); the residual risk from increased Lp(a) levels was greatest with LDL-C <70 mg/dL. This information is potentially valuable in the targeting of newer therapies to address elevated Lp(a) levels, especially in cohorts where LDL-C may already be well controlled.

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