Lipoprotein(a) and Coronary Artery Calcium for Predicting Atherosclerotic Cardiovascular Disease Risk

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Background

- Lipoprotein (a) [Lp(a)] and coronary artery calcium (CAC) are associated with increased risk for atherosclerotic cardiovascular disease (ASCVD)[1-3]
- Recent guidelines consider Lp(a) as a risk enhancer and CAC as a decision making tool for statin initiation in primary prevention[4]
- The independent and joint association of Lp(a) and CAC for predicting incident ASCVD is unknown

Hypothesis

- Lp(a) and CAC are independent and additive predictors of ASCVD in a primary prevention multi-ethnic cohort

Methods

Study Population

- ASCVD-free participants (n=5,862, age 56 ± 10 years) with Lp(a) and CAC data from two primary prevention multi-ethnic cohorts
  - DHS: n=2,199; mean age= 45±10; 48% male
  - MESA: n=3,663; mean age= 62±10; 44% male

Lp(a) Measurement

- DHS: Lp(a) plasma levels (nmol/L) measured by a sandwich enzyme-linked immunosorbent assay[5]
- MESA: Lp(a) mass concentration (mg/dL) measured by a latex-enhanced turbidimetric immunoassay[6]
- Both assays were insensitive to apolipoprotein(a) size[4,5]
- Race-specific quintiles were created to homogenize the sample

CAC Measurement

- Phantom adjusted CAC scores were measured similarly in both cohorts and reported in Agatston units (AU)[5,7]
- Each participant underwent two scans, and the average Agatston score was reported
- Three groups were created based on guideline recommended CAC categories: 0, 1 – 100, and > 100

Events

- ASCVD: non-fatal myocardial infarction, coronary heart disease related death, non-fatal stroke, and fatal stroke

Statistical Analysis

- Association of race-specific Lp(a) quintile 5 and ASCVD events was tested using Cox proportional hazards models using quintiles 1–4 as referent group
- Association of CAC score 1–100, and > 100 with ASCVD was tested using Cox proportional hazards models using CAC score 0 as referent group
- Models adjusted for traditional ASCVD risk factors and Lp(a) x CAC interactions were tested

Results

Table 1. Baseline characteristics of the pooled cohort stratified by race-specific Lp(a) quintiles

	Lp(a) quintile 1 n=1,173	Lp(a) quintile 2 n=1,175	Lp(a) quintile 3 n=1,170	Lp(a) quintile 4 n=1,174	Lp(a) quintile 5 n=1,170	p value
Age (years)	55 ± 13	55 ± 13	55 ± 13	56 ± 13	56 ± 13	NS
Men (n)	590	581	523	537	452	<0.01
DHS (n)	437	444	438	440	440	NS
BMI (kg/m²)	29 ± 6	29 ± 6	27 ± 6	29 ± 6	29 ± 6	NS
SBP (mmHg)	127 ± 19	127 ± 20	126 ± 20	126 ± 20	126 ± 19	0.04
DBP (mmHg)	75 ± 10	75 ± 10	74 ± 11	74 ± 11	74 ± 10	NS
Diabetes (n)	125	109	108	111	105	NS
Smoking (n)	218	207	238	224	193	NS
Lp(a)–DHS (mg/dL)	6 [3 – 23]	19 [12 – 51]	36 [25 – 79]	97 [48 – 116]	178 [150 –218]	<0.01
Lp(a)–MESA (nmol/L)	4 [2 – 5]	9 [7 – 20]	15 [12 – 31]	27 [21 – 45]	77 [51 – 96]	<0.01
LDL-C (mg/dL)	107 ± 33	111 ± 31	115 ± 32	120 ± 33	126 ± 33	<0.01
HDL-C (mg/dL)	50 ± 15	50 ± 15	51 ± 15	51 ± 14	52 ± 16	<0.01
Total Cholesterol (mg/dL)	183 ± 37	187 ± 37	190 ± 36	194 ± 36	202 ± 37	<0.01
Triglycerides (mg/dL)	111 [75 – 165]	107 [73 – 160]	99 [69 – 151]	101 [72 – 143]	101 [74 – 144]	<0.01
CAC score (AU)	1 [0 – 38]	1 [0 – 33]	0 [0 – 33]	0 [0 – 37]	0 [0 – 37]	NS

Table 2. Baseline characteristics of the pooled cohort stratified by CAC

	CAC = 0 (n = 2956)	CAC 1 – 100 (n = 1894)	CAC > 100 (n = 1012)	p value
Age (years)	52 ± 112	55 ± 13	66 ± 10	<0.01
Men (n)	1097	950	636	<0.01
DHS (n)	1037	986	176	<0.01
Blacks (n)	1052	788	275	0.01
Whites (n)	1000	608	465	<0.01
Hispanics (n)	692	372	178	<0.01
Chinese (n)	212	126	94	NS
BMI (kg/m²)	28 ± 6	31 ± 6	29 ± 6	<0.01
SBP (mmHg)	122 ± 19	130 ± 19	134 ± 21	<0.01
DBP (mmHg)	73 ± 10	77 ± 10	74 ± 11	<0.01
Diabetes (n)	184	218	156	<0.01
Smoking (n)	525	372	183	NS
Lp(a) – DHS (nmol/L)	47 [20 – 111]	50 [17 – 106]	64 [24 – 125]	NS
Lp (a) – MESA (mg/dL/L)	19 [9 – 43]	18 [9 – 39]	16 [7 – 40]	0.02
LDL-C (mg/dL)	113 ± 33	116 ± 33	121 ± 34	<0.01
HDL-C (mg/dL)	53 ± 15	49 ± 14	50 ± 15	<0.01
Total Cholesterol (mg/dL)	190 ± 36	191 ± 37	197 ± 38	<0.01
Triglycerides (mg/dL)	117 ± 74	129 ± 87	130 ± 80	<0.01

- In the pooled cohort: 21 % were White, 36 % Black, 21 % Hispanics, and 7 % Chinese
- For both cohorts higher levels of Lp(a) were noted among Blacks, followed by Whites, Hispanics, and Chinese
- There were 440 incident ASCVD events over mean 11.9 years follow-up

Table 3. Independent association of race-specific Lp(a) and CAC with incident ASCVD among pooled cohort participants

	ASCVD† n=440	
	HR (95 % CI)	p value
Lp(a) quintile 5	1.37 (1.10 – 1.71)	0.01
Lp(a) quintile 1 – 4	*Referent*	
CAC > 100	2.96 (2.24 – 3.90)	< 0.01
CAC 1 – 100	1.93 (1.48 – 2.53)	< 0.01
CAC = 0	*Referent*	

Cox proportional hazard regression models for age, sex, race, diabetes, smoking, systolic BP, anti-hypertensive use, total cholesterol, HDL-C, triglycerides, and BMI.
†No significant interaction was seen for Lp(a) and CAC categories

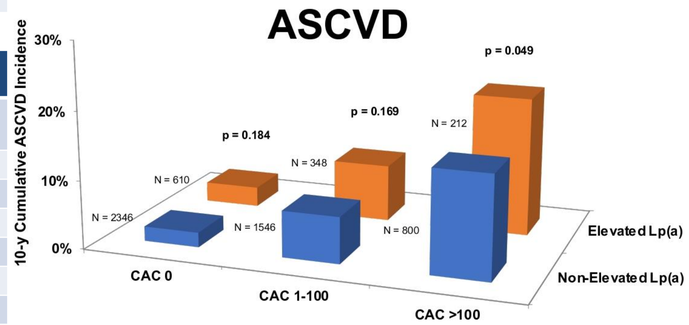

Figure 1. Ten-year cumulative incidence (95 % confidence interval) of ASCVD across pooled cohort participants CAC and Lp(a) groups

	CAC = 0	CAC 1 – 100	CAC > 100
Elevated Lp(a)	2.9 (1.6 - 4.3)	8.4 (5.4 - 11.4)	20.3 (14.7 - 26.0)
Non-elevated Lp(a)	2.2 (1.6 - 2.8)	6.8 (5.5 - 8.1)	15.0 (12.4 - 17.6)

Models adjusted for age, sex, race, BMI, diabetes, smoking, systolic blood pressure, diastolic blood pressure, anti-hypertensive use, total cholesterol, LDL-C, HDL-C, triglycerides, and family history of MI

Summary

- Female predominance was noted among the highest race-specific Lp(a) quintiles
- No difference was noted in CAC scores across race-specific Lp(a) quintiles
- High Lp(a) defined as race-specific quintile 5, was independently associated with ASCVD
- CAC 1 – 100, and CAC > 100 were independently associated with ASCVD
- No Lp(a) x CAC interaction was observed for ASCVD
- For participants with CAC > 100, the 10-year ASCVD cumulative incidence was higher in those with Lp(a) quintile 5 compared with Lp(a) quintile 1 – 4

Conclusions

- In this multiethnic, population-based cohort of individuals free of CVD, both high Lp(a), and CAC were independently associated with incident ASCVD
- There is a possible additive association of elevated Lp(a), and CAC score > 100 with increased ASCVD risk
- For individuals with CAC=0 or 1-100, the ASCVD risk does not appear higher when having concomitant elevated Lp(a) levels

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Disclosures

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