Poster 20

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First Demonstration by Cardiac Computed Tomography That Elevated Lipoprotein(a) Is Associated With High-Risk Partially Calcified Plaque, Extensive Plaque Burden, and Luminal Stenosis, Independent of Apolipoprotein B Levels

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KEY FINDINGS & CONCLUSIONS

- We found that Lp(a) was significantly associated with partially calcified plaque, the highest risk plaque type, and not non-calcified plaque or calcified plaque types
  - Increasing Lp(a) was also associated with more extensive coronary plaque burden as well as increasing prevalence of obstructive CAD, independent of ApoB levels
- Given that partially calcified plaque is most strongly associated with adverse cardiovascular events compared with non-calcified and calcified plaque types,[1] our study provides novel insight that Lp(a) may drive premature cardiovascular events through its association with qualified high-risk partially calcified plaque types
- In a long-term, prospective, observational study, it was shown that the low molecular weight apo(a) phenotype was the most important risk factor for the development of myocardial infarction in patients with premature coronary heart disease[2]
  - Elevated Lp(a) is considered a cause of premature and accelerated cardiovascular disease[3]
- These findings are consistent with the hypotheses that Lp(a)-driven CAD is characterized by more extensive plaque burden assessed by CT-Leaman score versus non-Lp(a)-driven CAD and that Lp(a)-driven CAD is a unique and high-risk CAD phenotype for any level of circulating ApoB
  - Importantly, there is currently a lack of management strategies for risk mitigation in patients with high Lp(a); however, maintaining a healthy heart lifestyle can reduce overall risk, and targeted Lp(a)-lowering therapies are in development[4]
- The Lp(a) subanalysis of the GLOBAL study is ongoing to discern high-risk phenotypic features in patients with Lp(a)-driven CAD, which could help to identify those with this condition that may be eligible for treatment with Lp(a)-lowering therapies should they become available in the future

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INTRODUCTION

- Cardiovascular diseases are the leading cause of mortality worldwide[5]
- Elevated Lp(a) is a common genetic cause of CAD and is emerging as a causal driver of myocardial infarction, stroke, peripheral arterial disease, calcific aortic valve disease, and heart failure[6]
- Elevated Lp(a) drives the progression of high-risk coronary plaque types[7] and is associated with an increased risk of both premature and accelerated cardiovascular disease[8,9]
  - An estimated 1.5 billion people have elevated Lp(a) levels ≥125 nmol/L (≥50 mg/dL),[10] a condition with a prevalence of up to 30% and potentially higher in patients with cardiovascular diseases[6]
  - While multiple clinical practice guidelines, including NLA, recommend Lp(a) testing at least once in all adults, universal adoption has yet to be realized[4]
- CCTA facilitates deep phenotyping of individual coronary plaques to aid cardiovascular risk assessment, and previous studies have shown CCTA to be superior to invasive coronary angiography for determining phenotypic plaque features[11]
  - Computed tomography-derived classifications of partially calcified plaque are observed in CAD and are associated with higher cardiovascular event rates compared with non-calcified plaque and calcified plaque[1]
- The GLOBAL study (NCT01738828) utilized multiomics analyses and deep phenotyping of coronary atherosclerosis via CCTA to unravel the underlying pathology of atherosclerotic CAD
  - The ongoing Lp(a) subanalysis of the GLOBAL study seeks to characterize the coronary plaque and phenotypic features associated with Lp(a)-driven CAD and to affirm the causal role of Lp(a) in cardiovascular disease
- We hypothesize that Lp(a) driven CAD, defined as CAD in the presence of increased Lp(a) regardless of other lipid/lipoprotein parameters, represents a unique, high-risk phenotype compared with non-Lp(a) driven CAD

OBJECTIVES

- The objective of this analysis was to determine the prevalence of high-risk (partially calcified plaque) versus non-calcified and calcified plaques, coronary plaque burden, and prevalence of luminal stenosis in patients enrolled in the Lp(a) subanalysis of the GLOBAL study, based on qualitative analysis

METHODS

- Data were analyzed from patients enrolled in the GLOBAL clinical study who were referred for coronary CCTA with suspected CAD
- Lp(a) mass was analyzed using a latex-enhanced immunoturbidimetric assay, and Lp(a) molar concentration (nmol/L) was measured using isoform independent ELISA
- Lp(a) cholesterol was measured using gel electrophoresis, and Lp(a) KIV_2 repeats and percentage of small versus large apo(a) isoforms (≤24 KIV_2 vs >24 KIV_2 repeats) were analyzed via western blot
- ApoB was measured using an antigen–antibody turbidimetric assay
- Coronary plaque type, plaque burden, and prevalence of obstructive luminal stenoses (≥70%) were assessed by CCTA in a core laboratory
- Plaque type was evaluated using the modified AHA 17-segment classification and defined as non-calcified plaque, partially calcified plaque, or calcified plaque in each segment using CAD-RADS 2.0 visual qualitative classification
- Measures of coronary plaque burden, i.e., SIS and CT-Leaman score, were determined by CCTA
- Statistical associations between Lp(a) measurements and the number of non-calcified plaque, partially calcified plaque, and calcified plaque per patient, as well as coronary plaque burden were determined by Pearson's correlation test
  - The test for the comparison between PCP and the combined NCP/CAP categories was planned
  - ANOVA was used to compare Lp(a) measurements across patients with predominant non-calcified plaque, partially calcified plaque, or calcified plaque
  - CT-Leaman score was compared across Lp(a) quartiles by ANOVA
- The association between Lp(a) measurements and luminal stenosis was determined by Welch's t-test
- ApoB was the strongest predictor of atherosclerosis; therefore, the effect of Lp(a) measurements conditioned on ApoB was determined by generalized covariance test

RESULTS

Patient characteristics

- In total, 340 patients were enrolled in the Lp(a) subanalysis of the GLOBAL study, of whom 62% had 'normal'/non-obstructive plaque, 10% had 1-vessel disease, 2% had 2-vessel disease, 17% had 3-vessel disease, and 9% had 4-vessel disease
  - 53% were female, and mean age was 55.6±9.8 years
  - Median Lp(a) concentration was 24.9 (IQR 73.3) nmol/L and median Lp(a) mass was 11.0 (IQR 22.1) mg/dL
  - Median ApoB concentration was 88.6 mg/dL and median LDL-C was 106.4 mg/dL
  - Mean total cholesterol was 179.2 mg/dL and mean HDL-C was 59.7 mg/dL
  - The mean number of partially calcified, non-calcified, and calcified plaques was 0.96, 0.26, and 1.09, respectively
  - Overall, 338 patients had available symptomatic status, of which ~2/3 (n=227) of patients were symptomatic and ~1/3 (n=111) were asymptomatic

Association between Lp(a) parameters and coronary plaque types

- Lp(a) molar concentration was significantly associated with partially calcified plaque (rho 0.153, P=0.005) but not with non-calcified plaque (rho 0.096, P=0.076) or calcified plaque (rho 0.078, P=0.153; **Figure 1A**)
- Similarly, Lp(a) mass and cholesterol, and small apo(a) isoforms were significantly associated with partially calcified plaque (rho 0.176, P=0.001; rho 0.179, P=0.001; rho 0.163, P=0.003, respectively; **Figure 1B**, **C**, and **D**) but not with non-calcified plaque or calcified plaque (all P>0.05)

Association between Lp(a) and coronary plaque type across the range of ApoB

- Across the range of ApoB (27.15–184.05 mg/dL), the association between Lp(a) molar concentration and coronary plaque was strongest for partially calcified plaque (rho 0.248, P<0.001) compared with non-calcified plaque (rho −0.036, P<0.001) or calcified plaque (rho 0.124, P<0.001; **Figure 2A**)
  - Similar results were observed for Lp(a) mass, Lp(a) cholesterol, and small apo(a) isoforms, with the strongest associations observed for partially calcified plaque versus non-calcified plaque and calcified plaque (all P<0.001; **Figure 2B**, **C**, and **D**)

Association between Lp(a) and predominant plaque type

- Lp(a) cholesterol was highest in patients with predominantly partially calcified plaque compared with non-calcified plaque and calcified plaque (4.27, 3.79, and 3.4 mg/dL, respectively; one-sided ANOVA P=0.018; **Figure 3A**)
- Small apo(a) isoforms were also significantly higher in patients with predominant partially calcified plaque versus the combined non-calcified plaque and calcified plaque categories (10.29, 3.68, and 2.77 nmol/L, respectively; one-sided ANOVA P=0.02; **Figure 3B**)

Correlation between SIS and Lp(a)

- SIS was significantly correlated with Lp(a) molar concentration (rho 0.16, P=0.003), Lp(a) mass (rho 0.18, P=0.001), Lp(a) cholesterol (rho 0.16, P=0.003), and small apo(a) isoforms (rho 0.14, P=0.009; **Figure 4**)

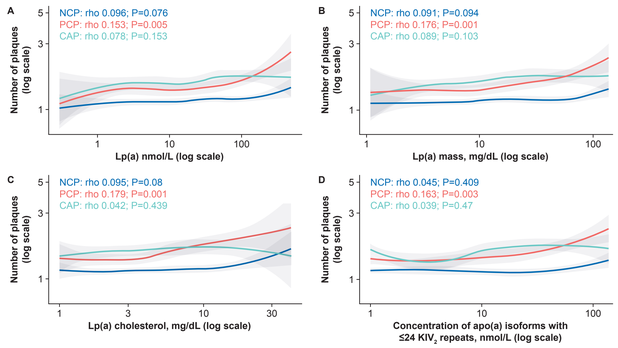
Correlation between CT-Leaman score and Lp(a)

- CT-Leaman score was significantly correlated with Lp(a) mass when expressed as a continuous variable (rho 0.17, P=0.002; **Figure 5A**) or Lp(a) mass quartiles (ANOVA P=0.03; **Figure 5B**)
  - When modeled over the range of ApoB (27.15–184.05 mg/dL), Lp(a) mass was a significant predictor of CT-Leaman score (rho 0.75, P<0.001; **Figure 5C**)

Association between luminal stenosis and Lp(a)

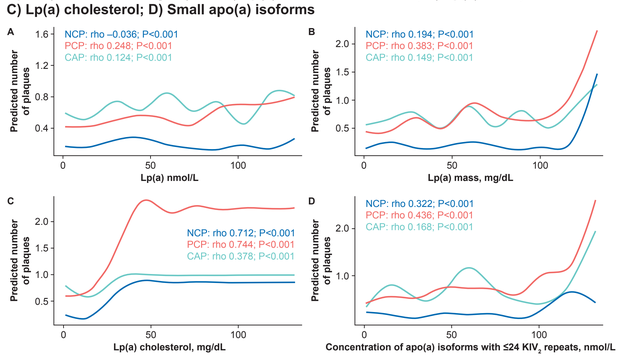
- Patients with ≥70% (n=71, 21%) versus <70% (n=269, 79%) luminal stenosis had:
  - Significantly higher Lp(a) molar concentration (44.75 vs 22.1 nmol/L, ANOVA P=0.015; **Figure 6A**)
  - Significantly higher levels of small (≤24 KIV_2) apo(a) isoforms (8.74 vs 4.18 nmol/L, ANOVA P=0.034; **Figure 6B**)
  - Significantly higher Lp(a) mass (17.8 vs 10.39 mg/dL, ANOVA P=0.011; **Figure 6C**)
  - A significantly higher percentage of ApoB carried by Lp(a) particles (3.8% vs 3.2%, ANOVA P=0.004; **Figure 6D**)
- Across the range of ApoB (27.15–184.05 mg/dL), Lp(a) molar concentration, Lp(a) mass, and small apo(a) isoforms were associated with ≥70% stenosis (rho: 0.8, 1.0, and 1.0, respectively)

Figure 1. Association between coronary plaque types and A) Lp(a) molar concentration; B) Lp(a) mass; C) Lp(a) cholesterol; D) Small apo(a) isoforms



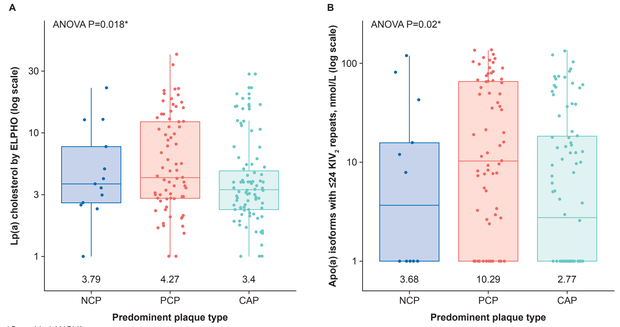
Apo(a), apolipoprotein(a); CAP, calcified plaque; KIV, kringle IV; Lp(a), lipoprotein(a); NCP, non-calcified plaque; PCP, partially calcified plaque.

Figure 2. Association between coronary plaque phenotypes across the range of ApoB (27.15–184.05 mg/dL) and A) Lp(a) molar concentration; B) Lp(a) mass; C) Lp(a) cholesterol; D) Small apo(a) isoforms



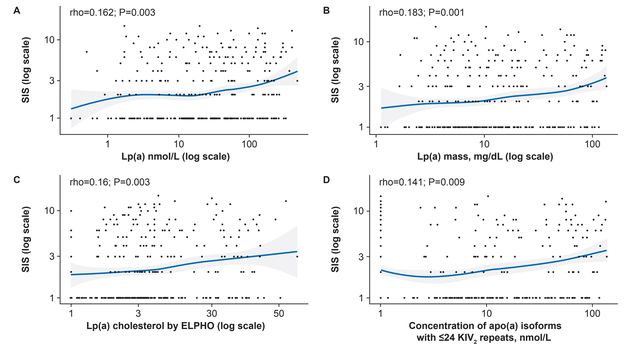
Apo(a), Apolipoprotein a; ApoB, apolipoprotein B; CAP, calcified plaque; KIV, kringle IV; Lp(a), lipoprotein(a); NCP, non-calcified plaque; PCP, partially calcified plaque.

Figure 3. Association between predominant coronary plaque type and A) Lp(a) cholesterol; B) Small apo(a) isoforms



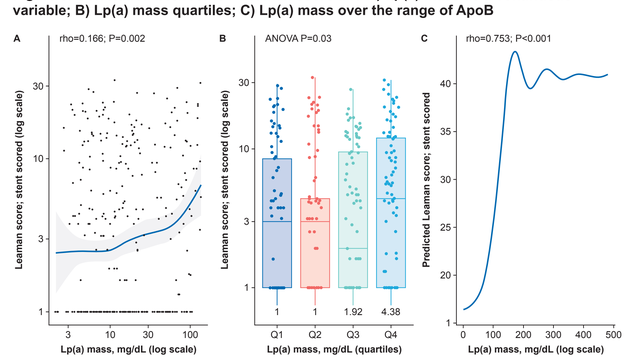
*One-sided ANOVA.
ANOVA, analysis of variance; apo(a), apolipoprotein a; CAP, calcified plaque; ELPHO, electrophoresis; KIV, kringle IV; Lp(a), lipoprotein(a); NCP, non-calcified plaque; PCP, partially calcified plaque.

Figure 4. A Correlation between SIS and A) Lp(a) molar concentration; B) Lp(a) mass; C) Lp(a) cholesterol; D) Small apo(a) isoforms



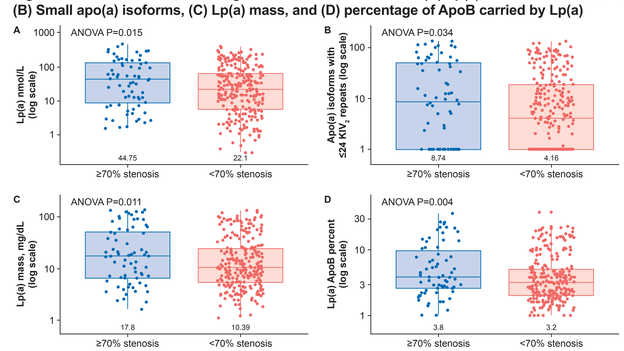
Apo(a), apolipoprotein a; ELPHO, electrophoresis; Lp(a), lipoprotein(a); SIS, segment involvement score.

Figure 5. Correlation between CT-Leaman score and A) Lp(a) mass as a continuous variable; B) Lp(a) mass quartiles; C) Lp(a) mass over the range of ApoB



ANOVA, analysis of variance; ApoB, apolipoprotein B; CT, computed tomography; Lp(a), lipoprotein(a).

Figure 6. Association between degree of luminal stenosis and (A) Lp(a) molar concentration, (B) Small apo(a) isoforms, (C) Lp(a) mass, and (D) percentage of ApoB carried by Lp(a)



ANOVA, analysis of variance; apo(a), apolipoprotein a; ApoB, apolipoprotein B; KIV, kringle IV; Lp(a), lipoprotein(a).

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Abbreviations

AHA, American Heart Association; ANOVA, analysis of variance; apo(a), apolipoprotein a; ApoB, apolipoprotein B; CAD, coronary artery disease; CAD-RADS, Coronary Artery Disease-Reporting and Data System; CAP, calcified plaque; CCTA, coronary computed tomography angiography; CT, computed tomography; ELISA, enzyme-linked immunosorbent assay; ELPHO, electrophoresis; GLOBAL, Genetic Loci and the Burden of Atherosclerotic Lesions; HDL-C, high density lipoprotein; IQR, interquartile range; KIV, kringle IV; LDL-C, low density lipoprotein; Lp(a), lipoprotein(a); NCP, non-calcified plaque; NLA, National Lipid Association; PCP, partially calcified plaque; SIS, segment involvement score.

Disclosures

SV and **BOB** are employees of G3 Therapeutics, Midlothian, VA, USA; **WB**, **DPY**, and **AL** are employees of Novartis; **DSW**, **MR**, and **SR** have nothing to disclose; **MRD** has received speaker fees from Pfizer, Radcliffe Cardiology, Amarin, Bristol Myers Squibb, Edwards, and Novartis and has received consultancy fees from Novartis, Jupiter Bioventures, AstraZeneca, Beren, and Silence Therapeutics; **AAQ** has received grants from the National Institutes of Health.

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