Poster 43

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Elevated Lipoprotein(a) Is Associated With Myocardial Infarction and Extent of Myocardial Infarct, Particularly in Premature Atherosclerosis

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KEY FINDINGS & CONCLUSIONS

- In this Lp(a) subanalysis of patients from the GLOBAL clinical study, we found that intermediate and elevated Lp(a) levels were significantly associated with both the presence of MI identified by CT and history of myocardial infarction
- To our knowledge, this is the first study to demonstrate an independent, causal association between elevated Lp(a) and infarct extent in premature atherosclerosis
  - These findings are consistent with previous data showing Lp(a) levels (>30 mg/dL) are associated with increased risk of myocardial infarction[1,2]
  - Smaller isoforms (≤24 KIV_2 repeats) were more strongly associated with presence of MI, reinforcing previous findings demonstrating that smaller isoforms confer higher plasma levels of Lp(a)[3]
  - Our data showed clinical correlation between increasing levels of Lp(a) and the extent of MI in patients with premature atherosclerosis, especially when Lp(a) levels were greater than ~70 mg/dL
- Although the impact of Lp(a) on infarct size is poorly understood, evidence from previously published studies supports a causal role of Lp(a) in premature ASCVD[4,5]
- Our data support previously published findings showing that Lp(a) is an independent, causal risk factor for premature and accelerated CVD
  - We propose that improved Lp(a) screening in clinical practice could facilitate identification of at-risk individuals with elevated Lp(a) who may benefit from strategies to reduce their overall risk[6]
- The ongoing Lp(a) subanalysis of the GLOBAL study aims to better understand risk stratification by evaluating high-risk phenotypic features associated with Lp(a)-driven ASCVD in individuals with elevated Lp(a) and to help identify patients who may potentially benefit from future Lp(a)-lowering pharmacotherapies

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INTRODUCTION

- Lp(a) is an apoB-containing lipoprotein that contains an apoB molecule covalently attached to an apo(a) particle[7]
- Apo(a) contains multiple KIV domains (termed KIV_1 to KIV_{10})[3]
  - Copy number variation in KIV_2 causes differing apo(a) isoform sizes between individuals, and smaller isoform sizes are associated with higher Lp(a) levels[3]
- Elevated Lp(a) (≥50 mg/dL) is an independent, genetic, causal risk factor for CVD that drives the progression of premature CV events[8,9,10]
  - The risk associated with Lp(a) has been shown to increase slightly at levels of 30 to 50 mg/dL (62 to 105 nmol/L) and become clinically relevant at >50 mg/dL (>105 nmol/L)[11]
  - Data show that elevated Lp(a) levels are estimated to occur in ~20% of the global population[10] and in approximately one-third of patients with premature ASCVD[12]
- Previous studies have shown that increasing infarct size is associated with worse clinical outcomes and may be a negative prognostic factor in patients with CVD[13,14]
  - Although individuals with intermediate (30 to 50 mg/dL) and elevated (≥50 mg/dL) Lp(a) levels are known to have an increased risk of myocardial infarction,[1,2] the impact of Lp(a) on infarct size has not been fully determined
- The Genetic Loci and the Burden of Atherosclerotic Lesions (GLOBAL) study (NCT01738828) utilized multiomics analyses and deep phenotyping of coronary atherosclerosis via CCTA to evaluate the pathology of ASCVD, including the underlying molecular pathways driving disease progression[15]
- The ongoing Lp(a) subanalysis of the GLOBAL study hypothesizes that Lp(a)-driven ASCVD represents a unique, high-risk phenotype compared with non–Lp(a)-driven ASCVD[16]

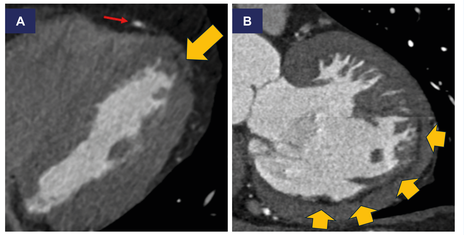
OBJECTIVE

- To evaluate whether intermediate (30 to 50 mg/dL) or elevated (≥50 mg/dL) Lp(a) is associated with the presence and extent of MI and to determine whether Lp(a) is an independent, causal factor in the extent of MI in patients with premature atherosclerosis, defined as <55 and <65 years of age in men and women, respectively

METHODS

- We analyzed data from patients referred for CCTA who were enrolled in the Lp(a) subanalysis of the GLOBAL clinical study
  - The study was approved by institutional review boards and ethics committees
- Lp(a) was measured at the time of CCTA between 2012 and 2014, and samples were later reanalyzed and Lp(a) data validated
  - Cases were defined as patients with a history of myocardial infarction (termed 'clinical myocardial infarction') vs those without a history of myocardial infarction (controls)
  - Patients were also evaluated based on the presence or absence of a visible infarct by cardiac CT (termed 'infarct by CT')
- Infarct extent was measured by contrast-enhanced CT and analyzed by a central imaging core laboratory
  - The left ventricle was analyzed visually based on a 17-segment model[17]
  - Infarct extent was determined as the number of segments with detectable infarct (**Figure 1**)
- Lp(a) mass (mg/dL) was measured using a latex-enhanced immunoturbidimetric assay, and apoB (mg/dL) was measured by antigen–antibody reaction via a turbidimeter
- Lp(a) KIV_2 repeats, percentage, and circulating concentration of small vs large apo(a) isoforms (≤24 KIV_2 vs >24 KIV_2 repeats) were measured by western blot
- Partial dependence plots were used to determine the independent association of Lp(a) across the apoB range
- The association between Lp(a) and extent of infarct was determined by Spearman's correlation
- One-sided t-tests were performed to evaluate whether Lp(a) was higher in cases vs controls
- Lp(a) data were non-normally distributed and highly skewed; therefore, we present Lp(a) concentration on a log scale for improved visualization
- Data were adjusted for age, sex, and apoB levels

Figure 1. Infarct Sizing by CT



A) Small apical infarct involving only one segment of the myocardium in a patient with an Lp(a) level of 103 nmol/L (the yellow arrow indicates location of infarct and the red arrow shows the left anterior descending artery);
B) Large infarct spanning five myocardial segments in a 42-year-old female with an Lp(a) level of 232 nmol/L and premature atherosclerosis (arrows indicate location of infarct).
CT, computed tomography; Lp(a), lipoprotein(a).

RESULTS

Patient Characteristics

- In total, 800 patients from the GLOBAL study were included (**Table 1**)
  - Median age (range) was 61.0 (55.0 to 68.0) and 57.0 (52.0 to 65.0) years for cases (n=400) and controls (n=400), respectively

Table 1. Demographics and Baseline Disease Characteristics

Variable	Total N=800
Male sex, %	74.8
Median Lp(a), (IQR; upper limit of Q1, Q3)	
Lp(a) mass, mg/dL	11.1 (41.1; 5.3, 46.4)[a,b]
Lp(a) thresholds, n	
<30 vs ≥30 mg/dL	549 vs 251
<50 vs ≥50 mg/dL	609 vs 191
Premature status, n	
Premature atherosclerosis	323
Nonpremature atherosclerosis	477

[a]Lp(a) levels were comparable to previously published data.[9,18] [b]Median Lp(a) mass across Q1 to Q4: 2.9, 7.9, 20.3, and 76.2 mg/dL, respectively.
IQR, interquartile range; Lp(a), lipoprotein(a); Q, quartile.

The Association Between Lp(a) Mass and Both History of Myocardial Infarction and Presence of Infarct by CT

- Median Lp(a) mass levels were significantly higher in patients with MI by CT vs those without (19.6 vs 10.5 mg/dL, *P*=0.015) as shown in **Figure 2A**
  - Similar results were observed in patients with a history of myocardial infarction vs controls (14.5 vs 9.8 mg/dL, *P*<0.001), **Figure 2B**

Rate of Infarct by CT and Clinical Myocardial Infarction in Patients With Lp(a) Levels ≥30 mg/dL vs <30 mg/dL, and ≥50 mg/dL vs <50 mg/dL

- The proportion of patients with MI by CT was significantly higher for patients with Lp(a) levels ≥30 vs <30 mg/dL (23.1% vs 16.0%, *P*=0.011) and for patients with a clinical history of myocardial infarction and Lp(a) levels ≥30 vs <30 mg/dL (60.2% vs 45.4%, *P*<0.001) as shown in **Figure 3A** and **B**, respectively
  - Similar findings were observed for patients with Lp(a) levels ≥50 vs <50 mg/dL (MI by CT: 23.6% vs 16.6%, *P*=0.021, and clinical myocardial infarction: 63.4% vs 45.8%, *P*<0.001, respectively), **Figure 3C** and **D**

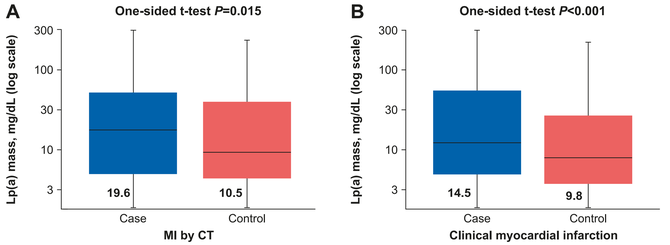
Differences in Total Small and Large Lp(a) Isoform in Patients With or Without Infarct by CT or Clinical Myocardial Infarction

- Total small isoform Lp(a) (≤24 KIV_2 repeats) was significantly higher in patients with the presence of MI by CT vs in patients without detectable MI (9.4 vs 5.9 nmol/L, *P*=0.038) as shown in **Figure 4A**
  - Similarly, total small isoform Lp(a) was significantly higher in patients with a clinical history of myocardial infarction vs those without (8.5 vs 4.5 nmol/L, *P*<0.001), **Figure 4B**
  - Total large isoform Lp(a) (>24 KIV_2 repeats) was not significantly different in patients with presence of MI by CT vs those without or by presence or absence of a clinical history of myocardial infarction, **Figure 4C** and **D**

Association Between Lp(a) and Extent of Infarct Across the Range of ApoB by Age

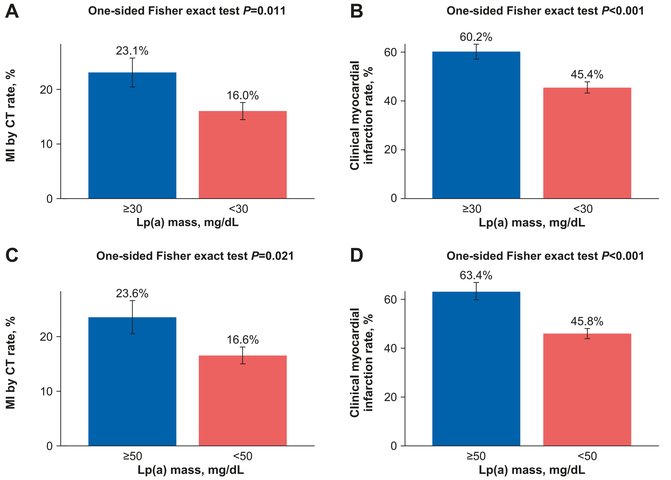
- The generalized covariance measure, evaluated across the entire range of apoB, indicates that Lp(a) is a causal factor driving the extent of MI in patients with premature atherosclerosis (rho 0.707) but not in patients with nonpremature atherosclerosis (rho −0.029, **Figure 5**)
  - In patients with premature atherosclerosis, there was a sharp increase in the number of myocardial segments involved when Lp(a) levels exceeded 70 mg/dL

Figure 2. Lp(a) Mass in Patients A) With and Without Infarct by CT, and B) With and Without a Clinical History of Myocardial Infarction



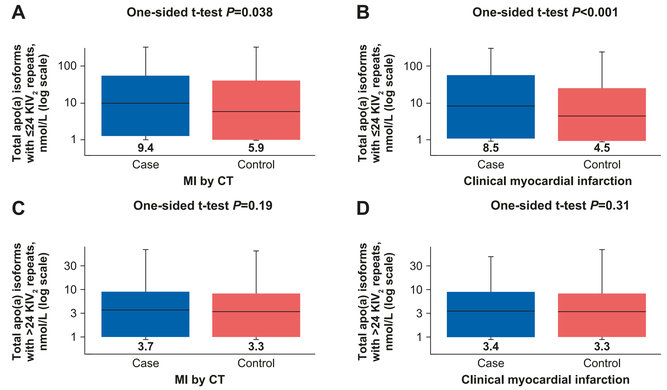
CT, computed tomography; Lp(a), lipoprotein(a); MI, myocardial infarct.

Figure 3. Rate of Infarct by CT and Clinical Myocardial Infarction by Lp(a) Levels ≥30 mg/dL vs <30 mg/dL (A and B), and ≥50 mg/dL vs <50 mg/dL (C and D)



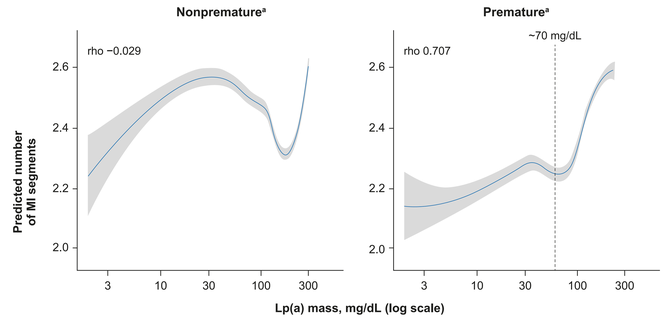
A) Rate of MI by CT and B) rate of clinical myocardial infarction in patients with Lp(a) levels ≥30 vs <30 mg/dL; C) Rate of MI by CT and D) rate of clinical myocardial infarction in patients with Lp(a) levels ≥50 vs <50 mg/dL.
CT, computed tomography; Lp(a), lipoprotein(a); MI, myocardial infarct.

Figure 4. Differences in Total Small and Large Lp(a) Isoform Levels in Patients With or Without Infarct by CT or History of Clinical Myocardial Infarction



A) Patients with or without MI by CT and total small Lp(a) isoform levels; B) Patients with or without clinical myocardial infarction and total small Lp(a) isoform levels; C) Patients with or without MI by CT and total large Lp(a) isoform levels; D) Patients with or without clinical myocardial infarction and total large Lp(a) isoform levels.
apo(a), apolipoprotein a; CT, computed tomography; KIV, kringle IV; Lp(a), lipoprotein(a); MI, myocardial infarct.

Figure 5. Association Between the Extent of MI and Lp(a) Mass Across the Range of ApoB in Patients With Nonpremature and Premature Atherosclerosis



Spearman's correlation across the range of apoB, showing a positive association between increasing Lp(a) levels and extent of MI in patients with premature atherosclerosis.
[a]Premature atherosclerosis was defined as <55 and <65 years of age in men and women, respectively.
apoB, apolipoprotein B; Lp(a), lipoprotein(a); MI, myocardial infarct.

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Abbreviations

apo(a), apolipoprotein a; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CCTA, coronary computed tomography angiography; CT, computed tomography; CV, cardiovascular; CVD, cardiovascular disease; GLOBAL, Genetic Loci and the Burden of Atherosclerotic Lesions; IQR, interquartile range; KIV, kringle IV; Lp(a), lipoprotein(a); MI, myocardial infarct; Q, quartile.

Disclosures

SV and **MRB** are employees of G3 Therapeutics. **WB** and **DPY** are employees of Novartis. **DSW**, **SJR**, and **ZF** have nothing to disclose. **HSB** has received consultancy fees from Novartis, Kaneka Corporation, Arrowhead Pharmaceuticals, New Amsterdam, and Abbott. **FR** has received consulting fees from Novartis, Novo Nordisk, Esperion Therapeutics, Movano Health, Kento Health, Edwards, Arrowhead Pharmaceuticals, Heartflow, iRhythm, Amgen, and Cleerly Health. **TD** has received consulting fees from New Amsterdam.

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