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ORIGINAL ARTICLE
Valvular heart disease

Impact of C-reactive protein levels on lipoprotein(a)-associated aortic stenosis incidence and progression

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Aims

Elevated lipoprotein(a) [Lp(a)] levels are associated with the risk of coronary artery disease (CAD) and calcific aortic valve stenosis (CAVS). Observational studies revealed that Lp(a) and C-reactive protein (CRP) levels, a biomarker of systemic inflammation, may jointly predict CAD risk. Whether Lp(a) and CRP levels also jointly predict CAVS incidence and progression is unknown.

Methods and results

We investigated the association of Lp(a) with CAVS according to CRP levels in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study ($n = 18\,226$, 406 incident cases) and the UK Biobank ($n = 438\,260$, 4582 incident cases), as well as in the ASTRONOMER study ($n = 220$), which assessed the haemodynamic progression rate of pre-existing mild-to-moderate aortic stenosis. In EPIC-Norfolk, in comparison to individuals with low Lp(a) levels (<50 mg/dL) and low CRP levels (<2.0 mg/L), those with elevated Lp(a) (>50 mg/dL) and low CRP levels (<2.0 mg/L) and those with elevated Lp(a) (>50 mg/dL) and elevated CRP levels (>2.0 mg/L) had a higher CAVS risk [hazard ratio (HR) = 1.86 (95% confidence intervals, 1.30–2.67) and 2.08 (1.44–2.99), respectively]. A comparable predictive value of Lp(a) in patients with vs. without elevated CRP levels was also noted in the UK Biobank. In ASTRONOMER, CAVS progression was comparable in patients with elevated Lp(a) levels with or without elevated CRP levels.

Conclusion

Lp(a) predicts the incidence and possibly progression of CAVS regardless of plasma CRP levels. Lowering Lp(a) levels may warrant further investigation in the prevention and treatment of CAVS, regardless of systemic inflammation.

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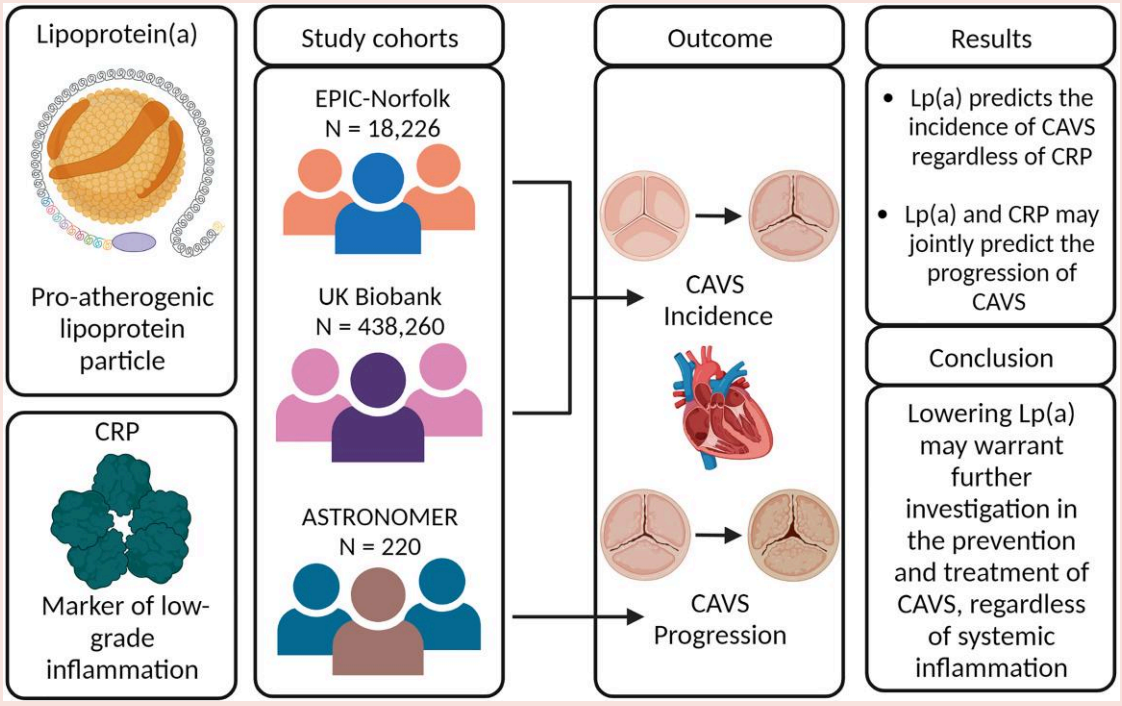
Graphical Abstract



Keywords Calcific aortic valve stenosis • Lipoprotein(a) • C-reactive protein

Introduction

Atherosclerotic cardiovascular diseases, including coronary artery disease (CAD) and stroke, are the leading causes of morbidity and mortality worldwide, whereas calcific aortic valve stenosis (CAVS) is the most common form of valvular heart disease in the Western world.[1,2] Interestingly, atherosclerosis and CAVS share similar risk factors including hypertension, dyslipidaemia, and smoking.[3] For both CAD and CAVS, accumulating evidence supports an additional role for lipoprotein(a) [Lp(a)], and genetic studies have confirmed that this association is likely to be causal.[4–7] Numerous prospective population studies have also identified C-reactive protein (CRP), an established biomarker of systemic inflammation, as a risk marker for CAD,[8] but this is not the case for CAVS. A small cross-sectional study showed that CRP levels were higher in CAVS patients than in matched controls.[9] Also, several small-scale prospective studies in CAVS patients showed that CRP levels were higher among those who showed a faster haemodynamic progression.[10–12] In contrast, a Swedish retrospective study showed that CRP levels did not differ between people who underwent surgery for CAVS compared with matched controls.[13] A prospective study, the ASTRONOMER trial, showed that CRP levels were not associated with CAVS severity or haemodynamic progression.[14] The large prospective Cardiovascular Health Study also observed a lack of association between CRP levels and prevalent or incident CAVS.[15]

In addition to the unresolved role of CRP in CAVS, it is also unclear whether the degree of systemic inflammation interacts with Lp(a) to predict the risk of CAVS. For the risk of CAD in patients with established vascular disease, such an interaction has been shown in the ACCELERATE trial, where elevated Lp(a) levels were related to the risk of cardiovascular death, myocardial infarction, and stroke if CRP levels were $\geq$2 mg/L, but not among those with CRP < 2 mg/L.[16] A similar interaction was shown in primary prevention in the prospective Multi-Ethnic Study of Atherosclerosis where Lp(a) and CRP jointly predicted the incidence of cardiovascular diseases.[17] We hypothesised that CRP and Lp(a) levels may jointly affect the incidence of CAVS and the haemodynamic progression of aortic stenosis. We tested this hypothesis in the EPIC-Norfolk prospective population study, the UK Biobank, and the ASTRONOMER trial.

Methods

Study populations

The design, methods, and baseline patient characteristics of the EPIC-Norfolk prospective population study have previously been described.[18] In brief, this cohort included 25 663 participants aged between 45 and 79 years residing in the region of Norfolk, UK.[19] Participants were recruited from the age–sex registers of general practices of Norfolk. They completed a detailed health and lifestyle questionnaire at baseline, between 1993 and 1997, and were followed for approximately 20 years. All relevant baseline characteristics were available in 18 226 study participants.

The study design and population of the UK Biobank have previously been reported.[20] UK Biobank includes more than 500 000 participants between 40 and 69 years of age who were recruited from the United Kingdom's National Health Service (NHS) central registers between 2006 and 2010. Assessment for diseases and serological tests for these participants were done in 22 assessment centres during the same period. Data collection included a self-report questionnaire, physical measures, and blood, urine, and

saliva sample collection. Analyses in the UK Biobank were conducted under the data application number 25205. Participants in both EPIC-Norfolk and UK Biobank gave signed and informed consent for their participation in these respective studies. Furthermore, UK Biobank has been approved by the North West Multi-Center Research Committee. A total of 438 260 UK Biobank participants and Lp(a) measurements available were included in the current analysis. Patients with CAVS at baseline (self-reported and/or who met the diagnostic criteria for CAVS) in EPIC-Norfolk and UK Biobank were excluded from the present study (*Figure 1*).

The design and rationale of the ASTRONOMER trial (NCT00800800) has previously been described.[21] This study included 269 participants between 18 and 82 years of age with mild-to-moderate CAVS at baseline [peak aortic jet velocity (V_{peak}) between 2.5 and 4.0 m/s]. Participants were recruited between 2002 and 2005 at 23 Canadian sites. Patients diagnosed with severe or symptomatic AS, severe aortic regurgitation, symptomatic CAD, significant mitral valve disease (stenosis or regurgitation), congestive heart failure, low-density lipoprotein cholesterol (LDL-C)-lowering therapy, or diabetes were excluded from the trial. Participants were randomly assigned to either rosuvastatin 40 mg or a placebo in a study protocol approved by the institutional review boards of all participating centres. Participants gave written signed informed consent for the study. For the current analysis, we included 220 participants.

Laboratory measurements

Participants in the EPIC-Norfolk study completed a detailed health and lifestyle questionnaire at the baseline survey, between 1993 and 1997, which included questions on the presence of existing diseases and cigarette smoking. The height and weight of participants were measured in light clothes and with shoes removed; height was measured using a stadiometer and rounded to the nearest 0.1 cm; weight was measured using Salter scales model 975 and rounded to the nearest 100 g. Blood pressure was measured using an Accutor non-invasive blood pressure monitor in the right arm of seated participants after a 5 min rest. Lipids were measured using serum taken from blood samples taken by venipuncture and by using the RA 1000 (Bayer Diagnostics, Basingstoke, UK). LDL-C levels were calculated using the Friedwald formula.[22] Blood creatinine levels were measured using a Dade-Behring Dimension AR analyser. Blood CRP levels were measures using an Olympus AU460 Chemistry Immuno Analyzer device. Lp(a) levels were measured with an immunoturbidimetric Olympus AU640 assay based on polyclonal antibodies that target apolipoprotein(a) epitopes.[23] Participants in UK Biobank also completed a detailed lifestyle questionnaire. Participants height was measured using a Seca 202 height measure, while weight was measured using the Tanita BC-418 MA body composition analyser on participants without shoes and with only light clothing. Blood pressure was measured using an Omron HEM-7015IT digital blood pressure monitor on seated participants after 1 min of rest. Blood samples were taken from participants using a 21G Safety Lok butterfly needle connected to a vacutainer barrel. LDL-C levels were measured from these samples using a direct homogeneous Beckman assay. Blood creatinine levels were measured by enzymatic analysis using a Beckman Coulter AU5800. Blood CRP levels were measured by immunoturbidometric assay on the same device.[20] Lp(a) levels of participants in the UK Biobank were measured by immunoturbidometric analysis on a Randox AU5800. Participants who had Lp(a) levels below the detectable minimum (3.8 nmol/L) were assigned the value 2.88 nmol/L. Those with Lp(a) levels above the upper level of detection (189 nmol/L) were included in the high Lp(a) group. Clinical measurements for the ASTRONOMER trial were performed in plasma samples collected from 220 out of 269 trial participants. These measurements included plasma levels of glucose, total cholesterol, LDL-C, high-density lipoprotein cholesterol, triglycerides, apolipoprotein B (apoB), and creatinine, and were done using techniques automated and standardised by the Canadian reference laboratory. Lp(a) was measured using a chemiluminescent immunoassay, as previously described.[24–27] Participants with CRP levels higher than 20 mg/L were excluded in all three cohorts.

Outcomes ascertainment

Cases of CAVS in the EPIC-Norfolk study were identified by hospital admission codes through their unique NHS number linked with ENCORE (East Norfolk Health Authority Database). Hospital admission codes were determined by trained professionals in accordance with the International Classification of Diseases version 10 (ICD-10) guidelines. CAVS cases were identified by patient hospitalizations or deaths with CAVS as an underlying cause. A total of 406 CAVS cases were reported according to this outcome definition within EPIC-Norfolk, whereas 17 820 participants did not develop CAVS over a median follow-up time of 16 years. In the UK Biobank, the CAVS outcome was defined using ICD-10 identification codes. Such cases were defined as patients with ICD codes I35.0 or I35.2. Patients with codes related to rheumatic fever or rheumatic heart disease, as defined by ICD-10 codes I00, I02, I05, and I09, were excluded from the CAVS outcome. All other patients except for those with self-reports of CAVS were included in the analysis. This definition of CAVS allowed for the inclusion of 4582 CAVS cases and 433 678 without CAVS from the UK Biobank. Median follow-up time for participants in the UK Biobank was of 12.5 years. The CAVS outcome in the ASTRONOMER trial was the progression rate of aortic valve stenosis as measured by the annual change of peak aortic jet velocity (V_{peak}) over a median follow-up of 3.5 years, an established measure of CAVS progression.[28] Measurement methods employed for clinical and Doppler echocardiographic data in the ASTRONOMER study were described previously[29] and allowed to measure V_{peak} and calculate aortic valve area. This change was calculated and annualised to account for different follow-up times of participants by dividing the calculated difference between the last follow-up and the baseline by the time between these two visits.

Statistical analyses

Continuous variables were reported as mean and SD values for normally distributed variables and as median and interquartile range for non-normally distributed variables. Normality was assessed through visual examination of graphical representation of the data. Categorical data were expressed as percentages of the total study cohort. Participants were categorised according to their blood Lp(a) levels in EPIC-Norfolk, the UK Biobank, and ASTRONOMER. A threshold of 50 mg/dL was set in EPIC-Norfolk and patient were classified as having a circulating Lp(a) level either superior or equal or lower than this threshold. This same stratification was done using a threshold of 125 nmol/L in the UK Biobank. In ASTRONOMER, patients were stratified into tertiles of the Lp(a) distribution and comparison was done between patients from the 3rd tertile (Lp(a) $\geq$ 58.5 mg/dL) or patients from the two lower tertiles (Lp(a) < 58.5 mg/dL) as previously described.[30] In all three cohorts, patients were additionally classified according to CRP levels (<2 mg/L vs. $\geq$ 2 mg/L). Multivariable Cox proportional hazard models adjusted for age, sex, BMI, blood pressure, LDL cholesterol levels, circulating creatinine, and smoking status were used to assess the association between Lp(a) levels and incidence of CAVS in participants with low or high CRP levels and hazard ratios (HRs) and corresponding 95% confidence intervals (95% CI) in EPIC-Norfolk and the UK Biobank were obtained. Assumptions of the Cox proportional hazard models were assessed though visual inspection of the Schoenfeld residuals. Goodness-of-fit was evaluated by computing the concordance of the predicted model with the observed data. Two-way analyses of variance followed by Tukey and Dunnett *post-hoc* tests were used to assess the effect of Lp(a) levels on annualised changes in V_{peak} in ASTRONOMER. All statistical analyses were performed using the computational software R version 4.1.3 (R Foundation for Statistical Computing) along with the packages 'survival', 'rstatix', and 'multcomp'. Figures were created using the 'ggplot2' and 'ggsignif' packages.

Results

Characteristics of study participants at baseline

Characteristics at baseline of participants in the EPIC-Norfolk study according to Lp(a) and CRP levels are reported in Supplementary material online, *Table S1*. In both studies, the baseline characteristics of the study participants were comparable to that of the general population although with a lower proportion of smokers. Median levels of Lp(a) and CRP were 11.5 mg/dL and 1.50 mg/L, respectively. A total of 2080 patients (11.4% of the cohort) had Lp(a) levels $\geq$50 mg/dL, while

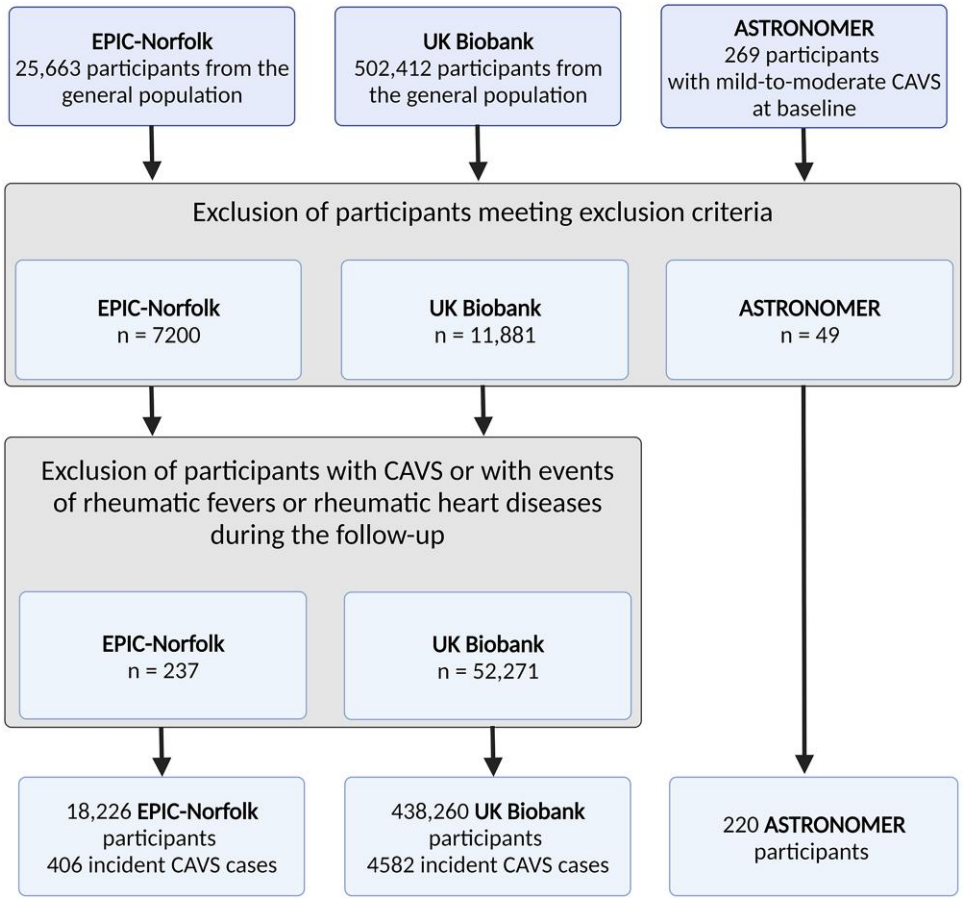


Figure 1 Flowchart presenting the patient selection strategy.

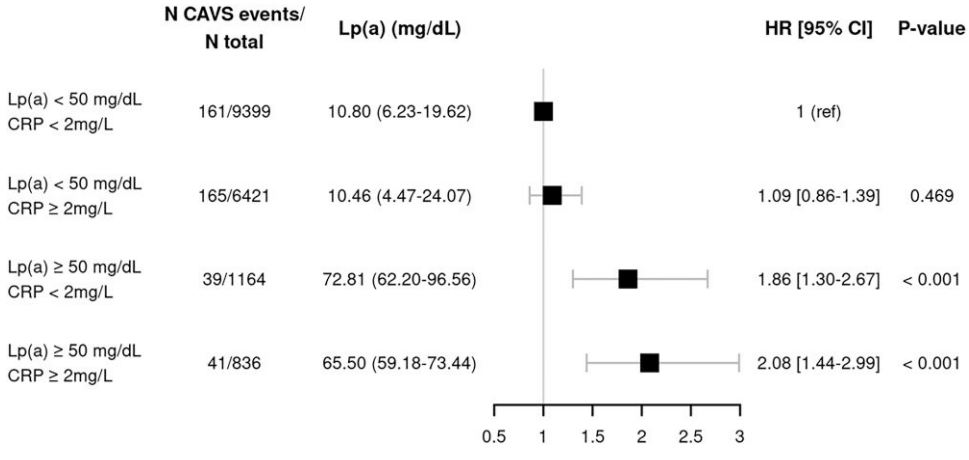


Figure 2 Hazard ratios for calcific aortic valve stenosis (bars) in participants from EPIC-Norfolk with higher vs. lower lipoprotein(a) and C-reactive protein levels. Multivariable Cox proportional hazard models were adjusted for age, sex, BMI, blood pressure, LDL cholesterol levels, circulating creatinine, and smoking status. Median (interquartile range) Lp(a) levels are also shown for each group. Error bars represent the 95% confidence interval.

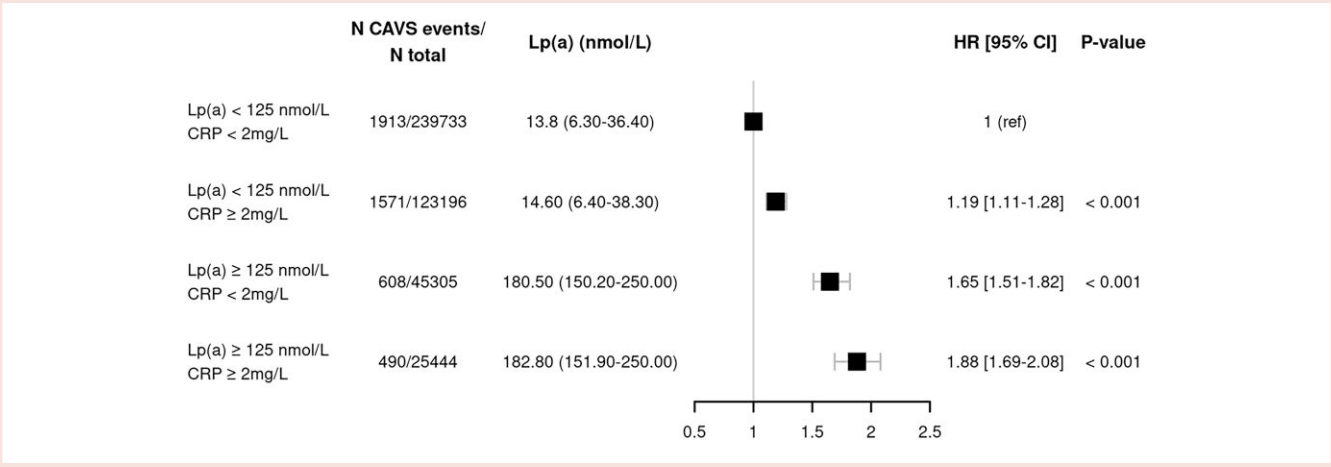


Figure 3 Hazard ratios for calcific aortic valve stenosis (bars) in participants from UK Biobank with higher vs. lower lipoprotein(a) and C-reactive protein levels. Multivariable Cox proportional hazard models were adjusted for age, sex, BMI, blood pressure, LDL cholesterol levels, circulating creatinine, and smoking status. Median (interquartile range) Lp(a) levels are also shown for each group. Error bars represent the 95% confidence interval.

Table 1 Calcific aortic valve stenosis event rates in EPIC-Norfolk and the UK Biobank by lipoprotein(a) and C-reactive protein levels

	EPIC-Norfolk				UK Biobank			
Lp(a)	<50 mg/dL		≥50 mg/dL		<125 nmol/L		≥125 nmol/L	
CRP (mg/L)	<2	≥2	<2	≥2	<2	≥2	<2	≥2
n CAVS events/*n* total	161/9399	165/6421	39/1164	41/836	1913/239733	1571/123 196	608/45 305	490/25 444
CAVS event rate (%)	1.71	2.57	3.35	4.9	0.79	1.26	1.32	1.89

CAVS, calcific aortic valve stenosis.

7463 (40.9%) had CRP levels ≥2 mg/L. Baseline characteristics for participants in the UK Biobank cohort are presented in Supplementary material online, *Table S2* according to Lp(a) and CRP levels. The median Lp(a) level in the full cohort was 19.6 nmol/L, and 71 847 (16.4%) patients had a Lp(a) level ≥125 nmol/L. Median CRP was 1.30 mg/L, and 150 701 (34.4%) patients had a CRP level ≥2.0 mg/L. Baseline characteristics of patients in the ASTRONOMER study stratified based on Lp(a) and CRP levels are presented in Supplementary material online, *Table S3*. Overall median levels were 29.8 mg/dL and 1.8 mg/L, for Lp(a) and CRP, respectively. A total of 88 (40%) patients had CRP levels ≥2.0 mg/L in ASTRONOMER.

Lipoprotein(a), C-reactive protein, and incident aortic stenosis

In EPIC-Norfolk, high levels of Lp(a) were associated with incident CAVS, while CRP levels were not associated with CAVS. Compared with participants with low Lp(a) and low CRP levels, those with high Lp(a) and with either high or low CRP levels were at higher CAVS risk. As presented in *Figure 2*, participants in the group with high Lp(a) and high CRP levels were at the highest CAVS risk [HR = 2.08 (95%CI, 1.44–2.99)]. Participants with high Lp(a) and low CRP also had a higher risk [HR = 1.86 (95% CI, 1.30–2.67)]. Participants with low Lp(a) and high CRP were however not at higher CAVS risk [HR = 1.09 (95% CI, 0.86–1.39)]. In the UK Biobank, participants with high Lp(a) had a higher risk of CAVS. Compared with participants with low Lp(a) and low CRP levels, those with high Lp(a) and high CRP or high Lp(a) and low CRP were also at higher CAVS risk, as presented in *Figure 3* [HR = 1.88 (95% CI, 1.69–2.08) and 1.65 (1.51–1.82), respectively, for patients with high Lp(a) and high vs. low CRP levels]. Participants with low Lp(a) but high CRP were at a slightly higher CAVS risk [HR = 1.19 (95% CI, 1.11–1.28)]. Incidence rates of CAVS are presented for every patient category in *Table 1*.

Lipoprotein(a), C-reactive protein, and incident aortic stenosis progression

In ASTRONOMER, Lp(a) and CRP levels appeared to be jointly associated with the progression of CAVS. Although patients in the top Lp(a) tertile and with high CRP had a significantly faster V_{peak} progression rate than patients in the two bottom tertiles of Lp(a) and with low CRP (0.29 ± 0.12 m/s/yr vs. 0.15 ± 0.06 m/s/yr, $P = 0.03$), CAVS progression was comparable in patients with elevated Lp(a) levels with or without elevated CRP levels (*Figure 4*).

Discussion

We investigated the potential joint associations of Lp(a) and CRP, a biomarker of systemic inflammation, in increasing CAVS risk in two large prospective cohorts, EPIC-Norfolk, and the UK Biobank. Higher levels of Lp(a) were associated with an increased risk of developing CAVS in these studies. This association is expected as Lp(a) is a widely known risk factor for CAVS.[6] In both studies, although participants with high

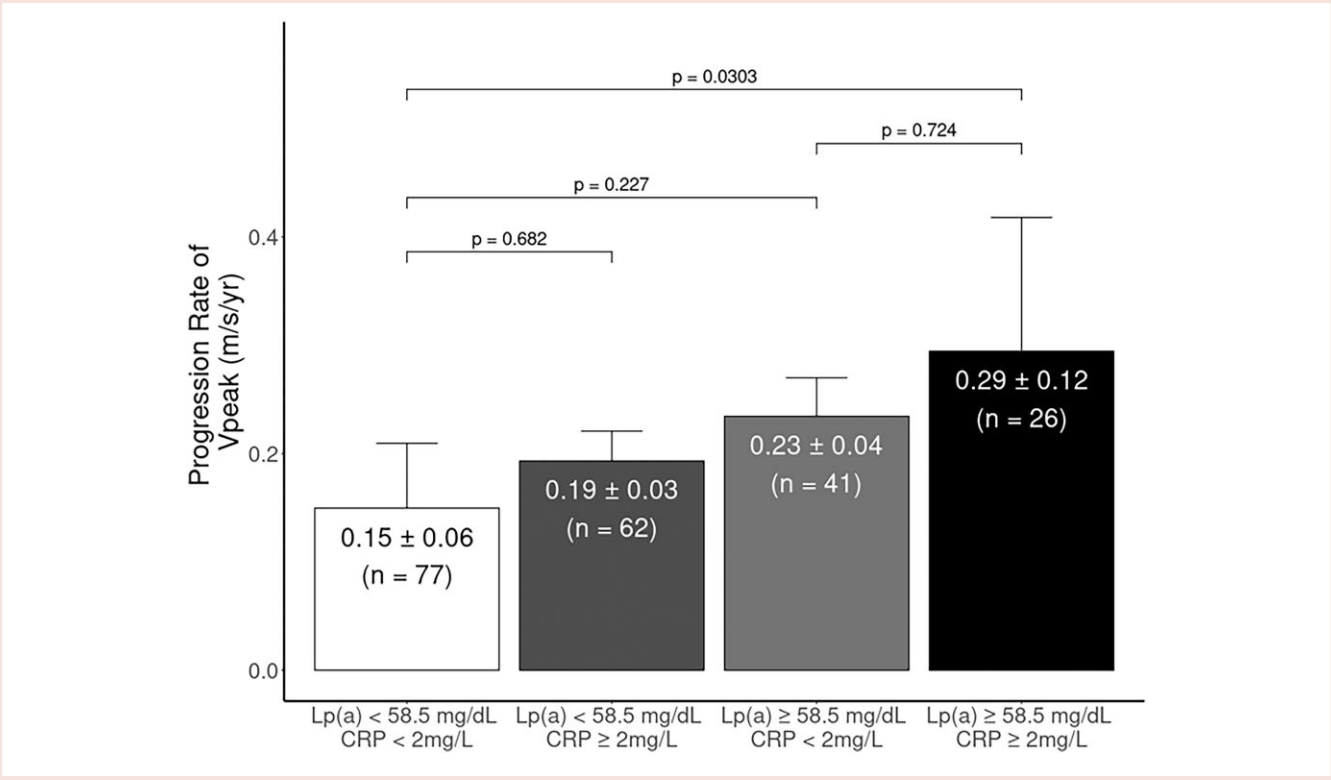


Figure 4 Progression rate of peak aortic jet velocity (bars) in m/s/yr for participants in the ASTRONOMER trial in patients with higher vs. lower lipoprotein(a) and C-reactive protein levels. The number of participants and *P*-value for statistical significance of change among groups is also presented. Error bars represent standard errors.

Lp(a) levels were at higher risk of CAVS, Lp(a) was associated with CAVS risk regardless of CRP levels. Analyses performed in the ASTRONOMER trial revealed that the fastest CAVS haemodynamic progression rate was observed in patients with both high Lp(a) and CRP levels. No significant difference was found between the progression rate of CAVS in patients with high Lp(a) and either low or high CRP. Altogether, our results provide evidence for an important effect of Lp(a) on CAVS incidence and possibly progression that is only modestly influenced by CRP levels.

It has previously been shown that elevated CRP levels were associated with higher cardiovascular risk in patients with high Lp(a), suggesting that adding CRP to the measurement of Lp(a) could provide a better risk-stratification assessment.[16,17] CRP levels were also recently shown to promote *de novo* aortic valve calcium accumulation, but not progression.[31] Lp(a) has been shown to elicit inflammatory pathways and promote macrophage activation and endothelial migration.[32,33] Systemic inflammation has long been known to play a role in the pathogenesis of CAD and possibly CAVS.[34–37] With regard to the incidence rate of CAVS, the present findings suggest that a marker of low-grade inflammation such as CRP does not provide additional information to the measurement of Lp(a) for predicting the incidence of CAVS. A previous analysis from ASTRONOMER, as well as a pooled analysis from the Ring of Fire and SALTIRE I studies revealed that Lp(a) was positively associated with the progression of CAVS.[38,39] However, though it warrants further investigation in larger studies, it is possible that CRP may help identify patients with a faster progression rate of CAVS in those with elevated Lp(a). Lp(a) was recently found to not predict aortic valve calcification in the general population.[40] Whether CRP could modulate the impact of Lp(a) in the general population is currently unknown.

To our knowledge, this study is the first to examine the predictive value of plasma Lp(a) levels in patients with and without elevated CRP levels in the context of CAVS. Our study however has limitations. The ASTRONOMER study was not designed to evaluate the respective contributions of Lp(a) and CRP to CAVS progression. Results of this *post-hoc* analysis should therefore be considered as hypothesis-generating. Although the joint effects of Lp(a) and CRP levels on CAVS incidence and progression might suggest that Lp(a) predicts risk more strongly in the context of systemic inflammation, CRP may simply be a marker of higher absolute CAVS risk. Many studies revealed an important effect of higher adiposity and metabolic dysfunction to be association with both higher CRP levels and CAVS risk.[41] Our study design does not enable us to conclude that patients with a slightly higher Lp(a)-mediated risk in the context of high CRP levels is due to systemic inflammation or higher absolute CAVS risk.[42] Also, no information on aortic valve phenotypes (bicuspid vs. tricuspid aortic valves or the presence of aortic sclerosis) was available in the prospective cohorts and the study populations were mostly of European ancestry. In population-based studies, the CAVS diagnosis was obtained from electronic health records and was not confirmed by echocardiography. Some CAVS cases could have been identified based on CAD diagnosis-driven symptoms or echocardiography. We recently reported that the predictive value of Lp(a) was similar in patients with vs. without CAD in multiple cohorts.[43] Whether the presence of CAD might influence the joint effect of CRP and Lp(a) on CAVS incidence is unknown. Finally, it should also be mentioned that our results on Lp(a) and CRP progression only applies to patients with CAVS.

In conclusion, in two large prospective studies, we found that higher Lp(a) levels were associated with higher CAVS risk in patients with low or high CRP levels. In the ASTRONOMER study, CAVS progression

was comparable in patients with high Lp(a) levels with high vs. low CRP levels. Future trials of Lp(a) lowering in the prevention or treatment of CAVS could further support our study conclusions by determining the valvular effect of drugs lowering Lp(a) in patients with vs. without evidence of systemic inflammation.

Lead author biography

Arnaud Girard received a bachelor's degree in biomedical sciences from Laval University in Quebec, Canada, and is currently pursuing a master's degree at the Quebec Heart and Lung Institute. His research project focuses on the identification of causal risk factors for the development of cardiovascular diseases using molecular epidemiology. Arnaud is passionate about human genetics and how it can be leveraged to improve patient-related outcomes in preventive cardiology.

Data availability

Access to UK Biobank data can be granted via the Access Management System of the UK Biobank (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access). Data access permission for this study was granted under UK Biobank application 25205. All other data produced in the present study are available upon reasonable request.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Conflict of interest: B.J.A. is a consultant for Novartis, Editas Medicine, and Silence Therapeutics and has received research contracts from Pfizer, Ionis Pharmaceuticals, and Silence Therapeutics. R.C. has received honorarium from Novartis. P.P. has received funding from Edwards Lifesciences, Medtronic, Pi-Cardia, and Cardiac Phoenix for echocardiography core laboratory analyses and research studies in the field of transcatheter valve therapies, for which he received no personal compensation. P.P. has received lecture fees from Edwards Lifesciences and Medtronic. S.T. is a co-inventor of monoclonal antibodies directed to Lp(a) owned by UCSD directed to Lp(a) and receives royalties from patents on oxidation-specific antibodies and of biomarkers related to oxidised lipoproteins and Lp(a) held by UCSD. S.T. is a cofounder and have an equity interest in Oxitope, Inc. and its affiliates ('Oxitope') as well as in Kleanthi Diagnostics, LLC ('Kleanthi'). The terms of this arrangement have been reviewed and approved by the UCSD, in accordance with its conflict-of-interest policies. S.T. has a dual appointment at University of California San Diego and Ionis Pharmaceuticals.

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