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Lipoprotein(a), venous thromboembolism and COVID-19: A pilot study

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ABSTRACT

Background and aims: Thrombosis is a major driver of adverse outcome and mortality in patients with Coronavirus disease 2019 (COVID-19). Hypercoagulability may be related to the cytokine storm associated with COVID-19, which is mainly driven by interleukin (IL)-6. Plasma lipoprotein(a) [Lp(a)] levels increase following IL-6 upregulation and Lp(a) has anti-fibrinolytic properties. This study investigated whether Lp(a) elevation may contribute to the pro-thrombotic state hallmarking COVID-19 patients.

Methods: Lp(a), IL-6 and C-reactive protein (CRP) levels were measured in 219 hospitalized patients with COVID-19 and analyzed with linear mixed effects model. The baseline biomarkers and increases during admission were related to venous thromboembolism (VTE) incidence and clinical outcomes in a Kaplan-Meier and logistic regression analysis.

Results: Lp(a) levels increased significantly by a mean of 16.9 mg/dl in patients with COVID-19 during the first 21 days after admission. Serial Lp(a) measurements were available in 146 patients. In the top tertile of Lp(a) increase, 56.2% of COVID-19 patients experienced a VTE event compared to 18.4% in the lowest tertile (RR 3.06, 95% CI 1.61–5.81; p < 0.001). This association remained significant after adjusting for age, sex, IL-6 and CRP increase and number of measurements. Increases in IL-6 and CRP were not associated with VTE. Increase in Lp(a) was strongly correlated with increase in IL-6 (r = 0.44, 95% CI 0.30–0.56, p < 0.001).

Conclusions: Increases in Lp(a) levels during the acute phase of COVID-19 were strongly associated with VTE incidence. The acute increase in anti-fibrinolytic Lp(a) may tilt the balance to VTE in patients hospitalized for COVID-19.

1. Introduction

Almost two years after the first outbreak in Wuhan, China, Coronavirus disease 2019 (COVID-19) is still driving one of the largest pandemics in the history of mankind. Infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) leads to a heterogeneous disease, varying from asymptomatic to acute respiratory distress syndrome requiring intensive care unit (ICU) admission. A hallmark of severe cases of COVID-19 is a cytokine storm [1], with interleukin-6 (IL-6) mainly produced by macrophages and dendritic cells serving as a principal cytokine driving inflammation [2]. COVID-19 is also associated with an increased propensity for thrombotic complications [3]. Approximately 21% of all hospitalized COVID-19 patients are found to have symptomatic venous thromboembolism (VTE) despite the use of...
2.3. Laboratory measurements
defered consent, patients or their legal representatives were informed about the biobank as soon as possible. To ensure all patients willfully participated in the biobank and provide a possibility to opt out from the biobank is a prospective cohort study containing clinical data and material from patients admitted with COVID-19 in both academic hospitals of Amsterdam UMC, between March 24 and May 23, 2020. All hospitalized patients ≥18 years with a positive SARS-CoV-2 polymerase chain reaction (PCR) test as well as those with a high clinical suspicion and unequivocal findings on CT-imaging without an alternative diagnosis were eligible for inclusion [11]. For the current analysis, COVID-19 patients were selected when a blood sample was available within 2 days of ward- or ICU-admission. Patients were treated according to the local protocol that included thromboprophylaxis, but did not include the use of remdesivir, hydroxychloroquine, azithromycin, convalescent plasma, corticosteroids or any other immunomodulatory therapy. Thromboprophylaxis consisted of low-molecular weight heparin (fraxiparin 5700 IE), once daily for patients <100 kg and twice daily for patients >100 kg. As of April 3, 2020, all ICU-admitted COVID-19 patients were also given the twice daily dose. Comprehensive clinical and outcome data were acquired from the CovidPredict cohort, as previously reported [12]. In short, this included daily reports, laboratory results and detailed clinical outcome data.

2.2. Ethical approval
Patients or their legal representatives received written information about the study and were asked to give written informed consent for participation. If direct informed consent of patients was not feasible, patients could be included with a deferred consent procedure. In case of deferred consent, patients or their legal representatives were informed about the biobank as soon as possible. To ensure all patients willfully participated in the biobank and provide a possibility to opt out from the biobank, comprehensive information and an opt-out form was sent to the patients three months after discharge. This study was approved by the Medical Ethical Committees of both Amsterdam UMC hospitals.

2.3. Laboratory measurements
Blood samples were routinely collected at the emergency department, ICU and hospital ward following hospitalization. Since we used biobank samples obtained in clinical practice, the number of blood withdrawal and time points of blood withdrawal varied across participants. The analysis was restricted to patients who had a first sample available within two days after admission. Plasma samples were stored at −80 °C after centrifugation. After thawing, Lp(a) levels were determined using an immunoturbidimetric (mass) assay (Quantia Lp(a), Architect, Abbott). This assay is calibrated for 5-points of apo(a) isoforms, which minimizes isoform sensitivity. IL-6 and CRP levels were determined using multiplex immunoassays (Bio-Plex 200, Biorad).

2.4. Primary and secondary outcomes
The primary outcome was incidence of VTE during hospitalization. VTE was defined as an objectively confirmed diagnosis of distal or proximal extremity DVT, pulmonary embolism (PE), or venous thrombosis at other sites including catheter-related thrombosis. Secondary outcomes were disease adverse outcomes defined as ICU admission and all-cause mortality during the first 21 days following hospital admission. All-cause mortality was defined as either mortality during admission or discharge for palliative care, either at home or at a palliative care facility. If the patient was discharged home from the hospital and no further follow-up data was available, we considered the patient to be event-free for the remaining study period.

2.5. Statistical analysis
Baseline characteristics are reported as mean ± standard deviation (SD) for normally distributed data, as medians with interquartile range (IQR) for non-normally distributed data, and as number with proportion for categorical data. Between-group differences were evaluated using the appropriate tests (Mann-Whitney U, Kruskal-Wallis, Chi-squared, respectively).
Baseline samples were defined as samples taken on the first or second day after admission. Baseline Lp(a), IL-6 and CRP levels were related to COVID-19 disease outcomes in a logistic regression analysis adjusted for age (continuous) and sex in COVID-19 patients. Next, we analyzed the time course of Lp(a), IL-6 and CRP levels in all COVID-19 patients with at least one measurement available following hospitalization using a linear mixed effects model with random intercept in the first 21 days following admission. In the linear mixed effects model, the relationship between log(Lp(a)), log(IL-6) and log(CRP) and time was modelled using cubic splines, of which the order was chosen based on the Akaike information criterion. Marginal means were depicted graphically with standard error (SE) interval. To quantify changes in these biomarkers, we calculated the maximum delta Lp(a), IL-6 and CRP; by subtracting minimum values from maximum values of each biomarker for each of the COVID-19 patients with more than one measurement available. The correlation between delta Lp(a), delta IL-6 and delta CRP was calculated using Pearson’s correlation coefficient. In addition, the correlation between delta Lp(a) and the traditional biomarker D-dimer was assessed, also using Pearson’s correlation coefficient. We then assessed the relation between delta Lp(a) and the COVID-19 disease outcomes using a logistic regression analysis with adjustment for delta IL-6, delta CRP and the number of measurements. To test for multicollinearity, the Variance Inflation Factor (VIF) was calculated for the delta values in the regression model. The relationship between VTE and the different tertiles of delta Lp(a) was determined using a Kaplan Meier analysis for the first 21 days following admission. For the linear mixed effects model, correlation, delta and Kaplan Meier analyses, log-transformed values of Lp(a), IL-6 and CRP were used. All statistical analyses were conducted with RStudio version 3.6.1 (R Foundation, Vienna, Austria).

3. Results
3.1. Patient selection and characteristics
In the first two months of the COVID-19 pandemic in the Netherlands, a total of 403 COVID-19 patient admissions were registered.
Of these patients, 219 provided informed consent and had samples available in which concentrations of Lp(a), IL-6 or CRP levels were measured, resulting in 800 time points analyzed for Lp(a), IL-6 and CRP levels. The mean age of the included COVID-19 patients was 63 ± 12 years, and 34% of patients were female (Table 1). One or more VTE events occurred in 67 (31%) patients admitted for COVID-19. Categorized by type of thrombosis, 31 (46%) of patients with a VTE developed an extremity DVT during admission, 42 (62%) patients experienced a pulmonary embolism and 11 (5%) patients had a VTE located elsewhere (Table 2). During hospitalization, 121 of the 219 (56%) COVID-19 patients were admitted to the ICU and 54 (25%) patients died (Table 2).

### Table 1

Baseline characteristics of included hospitalized COVID-19 patients. COVID-19, coronavirus disease 2019; SD, standard deviation; BMI, body mass index; ICU, intensive care unit; VTE, venous thromboembolism; ATE, arterial thromboembolism.

|                          | All patients | Patients with serial Lp(a) measurements available |
|--------------------------|--------------|--------------------------------------------------|
| n                        | 219          | 146                                              |
| Age (years, mean (SD))   | 63 (12)      | 63 (11)                                          |
| Women                    | 74 (33.9)    | 41 (27.6)                                        |
| BMI (kg/m², mean (SD))   | 28.9 (6.3)   | 28.7 (6.2)                                       |
| Active smoking           | 70 (33.3)    | 37 (26.4)                                        |
| Chronic cardiac disease  | 53 (24.3)    | 28 (19.3)                                        |
| Hypertension             | 102 (47.0)   | 62 (43.1)                                        |
| Chronic pulmonary disease| 26 (11.9)    | 17 (11.7)                                        |
| Chronic kidney disease   | 18 (8.3)     | 7 (4.9)                                          |
| Diabetes                 | 67 (30.7)    | 42 (29.0)                                        |
| Malignancy               | 12 (5.6)     | 7 (4.9)                                          |
| Baseline Lp(a) (mg/dl)   | 15.6 [6.3–35.7] | 14.9 [5.5–29.9]                                  |
| Baseline IL-6 (ng/l)     | 33.2 [15.3–58.6] | 35.2 [20.1–61.5]                                |
| Baseline CRP (mg/l)      | 41.3 [36.2–44.7] | 42.2 [37.4–44.6]                                |

Baseline characteristics of included hospitalized COVID-19 patients. COVID-19, coronavirus disease 2019; SD, standard deviation; BMI, body mass index; ICU, intensive care unit; VTE, venous thromboembolism; ATE, arterial thromboembolism.

### Table 2

Primary and secondary outcomes in COVID-19 patients. Shown are absolute numbers (percentages). COVID-19, coronavirus disease 2019; BMI, body mass index; ICU, intensive care unit; VTE, venous thromboembolism; ATE, arterial thromboembolism.

| Patient group           | COVID-19 patients n = 219 |
|-------------------------|--------------------------|
| VTE during admission    | 67 (30.6)                |
| Extremity DVT           | 31 (14.2)                |
| PE                      | 42 (19.2)                |
| Other                   | 11 (5.0)                 |
| ICU admission           | 121 (55.5)               |
| All-cause mortality     | 54 (24.8)                |

Primary and secondary outcomes in COVID-19 patients. Shown are absolute numbers (percentages). COVID-19, coronavirus disease 2019; BMI, body mass index; ICU, intensive care unit; VTE, venous thromboembolism; ATE, arterial thromboembolism.

### 3.2. Baseline Lp(a) levels and increase during hospital admission in COVID-19 patients

The median baseline Lp(a) level was 15.6 mg/dl [IQR 6.3, 35.7], in the COVID-PREDICT database. Of these patients, 219 provided informed consent and had samples available in which concentrations of Lp(a), CRP or IL-6 were measured, resulting in 800 time points analyzed for Lp(a), IL-6 and CRP levels. The mean age of the included COVID-19 patients was 63 ± 12 years, and 34% of patients were female (Table 1). One or more VTE events occurred in 67 (31%) patients admitted for COVID-19. Categorized by type of thrombosis, 31 (46%) of patients with a VTE developed an extremity DVT during admission, 42 (62%) patients experienced a pulmonary embolism and 11 (5%) patients had a VTE located elsewhere (Table 2). During hospitalization, 121 of the 219 (56%) COVID-19 patients were admitted to the ICU and 54 (25%) patients died (Table 2).
whereas the median baseline IL-6 level was 33.2 pg/ml [IQR 20.8, 157.7]. The median baseline CRP level was 41.3 mg/l [IQR 36.2, 44.7] (Fig. 1). The linear mixed effects model showed a significant change of all three markers over time. In the linear mixed effects model, Lp(a) levels increased almost threefold on average during the first three weeks after hospital admission (10.1–27.0 mg/dl; Fig. 2; p < 0.001). IL-6 and CRP levels increased in the first days after admission, followed by a decrease after the first week following admission (Fig. 2; p < 0.001).

3.3. Change in Lp(a) is associated with VTE and adverse events in COVID-19 patients

In the entire cohort, baseline Lp(a), IL-6 and CRP levels were not associated with VTE incidence. Baseline IL-6 levels were associated with ICU admission (Supplemental Table 1). We then calculated the maximum delta for Lp(a) and IL-6 in all patients with multiple measurements available. These 146 patients had an average of 4 measurements per patient. Patients who suffered from VTE were characterized by higher increase in Lp(a) compared with patients without VTE (7.4 mg/dl [IQR 3.5, 17.0] vs 4.0 mg/dl [IQR 1.8, 8.3], p < 0.001). In a logistic regression model adjusted for age, sex, delta IL-6 and number of measurements, delta Lp(a) was significantly associated with VTE incidence (OR 3.77, 95% CI 1.38–10.31, p = 0.007, Table 3). In the same model, delta IL-6 was not associated with VTE (OR 1.16, 95% CI 0.79–1.71, p = 0.441, Table 3). For the VTE-free survival analysis, patients were divided into tertiles of delta Lp(a) levels. In patients in the top tertile, Lp(a) levels increased by an average of 20.1 mg/dl, compared with 5.1 mg/dl in the lowest tertile. In the top tertile 56.2% of patients experienced a VTE, compared to 18.4% in the lowest tertile during the first 21 days after admission (RR 3.06, 95% CI 1.61–5.81; p < 0.001; Fig. 3). The Kaplan Meier analysis showed a significant association between delta Lp(a) tertiles and VTE event free survival in the first 21 days after admission (p < 0.001, Fig. 3).

In addition, we compared COVID-19 patients who were admitted to the ICU or died following hospitalization to those who were not admitted to the ICU or who survived. As expected, higher delta Lp(a) levels were observed in the patients admitted to the ICU (6.3 mg/dl [IQR 3.1, 13.7] vs 3.0 mg/dl [IQR 1.2, 6.6], p < 0.001). This correlation disappeared after adjustment for age, sex, delta IL-6 and number of measurements (Table 3). However, a trend was observed for the association between delta Lp(a) and ICU admission (OR 2.22, 95% CI 0.97–5.09, p = 0.061, Table 3). No differences in delta Lp(a) levels were observed in COVID-19 patients who died compared to those who survived (6.9 mg/dl [IQR 2.7, 12.6] vs 5.2 mg/dl [IQR 2.5, 10.2], p = 0.323) nor in the adjusted model (Table 3). In all models, additional adjustment for delta CRP did not materially change the findings. There were no signs of multicollinearity; the VIFs were 1.20 and 1.38 for delta Lp(a) and delta IL-6, respectively.

3.4. Increase in Lp(a) is associated with increase in IL-6, but not with CRP

Lastly, we compared associations between the delta values of the three biomarkers during admission. Delta IL-6 was strongly correlated with delta Lp(a) (r = 0.44, 95% CI 0.30–0.56, p < 0.001) and with delta CRP (r = 0.18, 95% CI 0.01–0.34, p = 0.040). Conversely, delta CRP was not correlated with delta Lp(a) (p = 0.580). In addition, there was a modest association between delta Lp(a) and delta D-dimer (r = 0.19; 95% CI 0.01–0.37; p = 0.04).

4. Discussion

This study demonstrates that in patients hospitalized with COVID-19 Lp(a) levels rise threefold during the hospitalization. Although Lp(a) levels upon admission were not predictive of VTE, the patients in the highest tertile of Lp(a) increase during admission, representing absolute increases of 20 mg/dl, experience a 56% incidence of VTE despite the use of VTE prophylaxis. In contrast, the change in the inflammatory biomarkers IL-6 and CRP was not associated with VTE incidence. Lp(a) is an anti-fibrinolytic particle, it is pro-inflammatory and also a known acute phase reactant [13]. Collectively, these data imply an integrated impact of Lp(a) in conjunction with the heightened inflammatory and prothrombotic state on VTE incidence in hospitalized COVID-19 patients.

Lp(a) levels are primarily genetically determined with more than 80% of plasma levels mediated by variations in kringe IV type 2 (KIV2) isomorl number and various single nucleotide polymorphisms in the coding region of the LPA gene [13]. However, during acute inflammatory episodes, Lp(a) has been found to be transiently elevated and persisting for 3–4 months. This increase has been partly attributed to an IL-6 response element in the LPA gene [14]. Indeed, we substantiate that Lp(a) levels are upregulated in the course of a SARS-CoV-2 infection, with an up to three-fold increase of Lp(a) levels in 21 days following hospital admission. In line with this, we show that the day 4 peak of IL-6 levels, which likely already increase from baseline before admission, precedes the Lp(a) increase, supporting Lp(a) changes following the IL-6 increase (r = 0.44).

We also observed that patients with the highest Lp(a) increase during COVID-19 have a striking increase in VTE incidence (Central Illustration). In contrast, CRP increase, a well-known acute phase reactant also regulated by IL-6,[15] was not associated with VTE incidence. The discordant impact of Lp(a) versus IL-6 and CRP on VTE incidence may imply a direct pathophysiological role of Lp(a) elevation in eliciting a thrombogenic potential. A likely explanation for this effect is the high homology of apolipoprotein(a) to plasminogen, and this explanation was further supported by an association between Lp(a) increase and D-dimer increase, which has also been previously documented [16]. Apolipoprotein(a) lacks protease activity but has similar lysine binding activity to plasminogen allowing accumulation of Lp(a) to the same sites of exposed lysines, such as in denuded endothelium, where it may interfere with plasminogen activation [17]. In some but not all studies,

| Table 3 |
| --- |
| Multiple logistic regression models in COVID-19 patients. |
| | Model 1: Venous thromboembolism | Model 2: ICU admission | Model 3: Mortality |
| | OR | 95% CI | p-value | OR | 95% CI | p-value | OR | 95% CI | p-value |
| Age | 1.001 | (0.967–1.037) | 0.964 | 0.923 | (0.866–0.984) | 0.014 | 1.019 | (0.979–1.059) | 0.358 |
| Female sex | 0.902 | (0.365–2.227) | 0.823 | 0.231 | (0.056–0.948) | 0.042 | 0.891 | (0.341–2.327) | 0.814 |
| delta log(Lp(a)) | 3.251 | (1.224–8.369) | 0.018 | 10.903 | (0.632–188.041) | 0.100 | 1.968 | (0.858–4.515) | 0.110 |
| delta log(IL-6) | 1.245 | (0.849–1.825) | 0.262 | 2.215 | (0.965–5.084) | 0.061 | 1.296 | (0.891–1.885) | 0.176 |
| N of measurements | 1.517 | (1.109–2.173) | 0.014 | 3.251 | 1.319–8.011) | 0.010 | 1.131 | (0.813–1.572) | 0.465 |

Logistic regression for the effect of age, sex, delta Lp(a), delta IL-6 and number of measurements on venous thromboembolism during hospitalization (model 1), ICU admission (model 2) and mortality (model 3) in the first 21 days following admission in COVID-19 patients. ICU, intensive care unit; Lp(a), lipoprotein(a); IL-6, interleukin-6; N, number.
Lp(a) has been shown to attenuate fibrinolysis, thereby promoting thrombus growth [14]. The pro-thrombotic effect of Lp(a) in clinical studies has been controversial, with substantiation in some observational studies with a preponderance of elevated Lp(a) levels in VTE patients compared with controls [15]. In 20% of VTE patients compared with 7% in controls; 95% CI 1.9–5.3, p < 0.001] [18]. However, genetic studies [19] and in vitro studies failed to support a causal role [20]. Lp(a) concentrations in the UK biobank were also not associated with thromboembolic events in COVID-19 patients [21]. Part of these inconsistent results may relate to the fact that Lp(a) by itself is not a pro-thrombotic factor; it is anti-fibrinolytic and thus predominantly may cause clot-propagation in pre-existing thrombi as ‘second hit’ agent. This ‘second hit’ mechanism could already be activated in relatively low Lp(a) levels, even below the ASCVD risk threshold of 50 mg/dl from the 2019 ESC/EAS guidelines. In the case of COVID-19, severe endothelial injury and ongoing active coagulation may be particularly sensitive to Lp(a) tipping the balance to clot propagation and clinical expression of VTE. Besides an anti-fibrinolytic effect, Lp(a) also activates pro-inflammatory pathways in endothelial cells and monocytes, which may further enhance the pro-thrombotic state [22]. Recent findings emphasized that oxidized phospholipids carried by Lp(a) may be the main cause of this pro-inflammatory effect [23]. Collectively, these data lend further support to a direct effect of Lp(a) on thrombogenesis, contributing to the disproportionately enhanced VTE incidence in COVID-19 patients hallmarkd by Lp(a) increase during the infectious episode.

In absence of available interventions to reduce Lp(a), multiple studies have investigated the effect of tocilizumab, a monoclonal anti-body inhibiting IL-6, in COVID-19 patients. To date, the majority of these studies have not shown a reduction in disease severity or complication rates [24–27]. However, randomized administration of tocilizumab in 389 early-disease COVID-19 patients showed a 44% reduction of the composite endpoint of mechanical ventilation and death [28]. Unfortunately, this study did not report the effect of either Lp(a) levels or VTE incidence in COVID-19 patients.

4.1. Clinical implications

Current guidelines recommend routine VTE prophylaxis with low-molecular weight heparin (LMWH) in hospitalized patients with COVID-19, which we adhered to in the present study [29]. Our findings lend support to a marked contribution of Lp(a) increase in augmenting the pro-thrombotic state in COVID-19 patients. In view of the more than threefold increase in VTE incidence in the upper tertile compared to the lowest tertile of Lp(a) increase, a switch towards therapeutically dosed low-molecular weight heparin may be advised in patients in whom marked increases in Lp(a) are observed during hospitalization. Identification of COVID-19 patients with high VTE risk is of particular importance since standard use of therapeutic anticoagulation is associated with increased risk of bleeding complications, without an overall reduction of VTE [30]. However, future studies are required to prospectively evaluate Lp(a) and VTE incidence in COVID-19 patients before using this regimen. It is tempting to speculate whether a single administration of the apo(a) antisense oligonucleotide pelacarsen, which reduces Lp(a) levels by more than 80% [31], or lipid apheresis which can acutely remove Lp(a) and oxidized phospholipids [32], may also be of clinical value to reduce VTE incidence in severe COVID-19 patients.

4.2. Study limitations

The number and timing of samples differed between patients and there were no pre- or post-admission Lp(a) levels available. Included patients were already in a disease state requiring hospital admission, and no Lp(a) levels in the healthy state nor long-term Lp(a) changes could be assessed in this study. Since every patient was in a different disease stage both at and during admission, we were unable to analyze these measurements using traditional statistical methods. These differences in disease stage also complicated analysis of baseline Lp(a) values. Therefore, we analyzed delta Lp(a) levels after log transformation, presuming maximal change in Lp(a) levels reflects the disease-mediated increase in Lp(a). Due to the limited power of this study, we could not account for the exact temporality of changes in Lp(a). To adjust for the potential influence of duration of admission on the number of Lp(a) measurements and possible immortal time bias, we adjusted for the number of measurements in the logistic regression model. Second, the limited sample size could also explain the fact that we did not find a significant correlation between baseline Lp(a) levels and adverse outcomes. Larger studies routinely measuring Lp(a) serially in hospitalized patients will be required to substantiate these findings. Third, a relatively large proportion of the hospitalized study population was admitted to the ICU and almost half of patients were from non-Caucasian descent, which makes it difficult to extrapolate our results to the overall COVID-19 population and could explain the relatively low baseline Lp
In conclusion, the increase of Lp(a) levels during COVID-19 hospitalization is associated with a high incidence of VTE. Further studies are needed to determine whether interventions reducing Lp(a) elevation will be able to reduce the VTE incidence in severe COVID-19 patients.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2021.12.008.

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