Prognostic Value of Elevated Lipoprotein(a) In Patients With Acute Coronary Syndromes

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Abstract

Background

Minimal lipoprotein(a) [Lp(a)] target values are advocated for high-risk cardiovascular patients. We investigated the prognostic value of Lp(a) in the acute setting of patients with acute coronary syndromes (ACS).

Methods

Plasma levels of Lp(a) were collected at time of angiography from 1711 patients hospitalized for ACS in a multicenter Swiss prospective cohort. Associations between elevated Lp(a) ≥ 30 mg/dL (cut-off corresponding to the 75th percentile of the assay) or Lp(a) tertiles at baseline, and major adverse cardiovascular events (MACE) at 1-year, defined as a composite of cardiac death, myocardial infarction or stroke were assessed using hazard ratios (HR) and 95% confidence intervals (CI) adjusting for traditional cardiovascular risk factors (age, sex, smoking, diabetes, hypertension, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C] and triglycerides.

Results

Lp(a) levels range between 2.5 mg/dL to 132 mg/dL with a median value of 6 mg/dL and a mean value of 14.2 mg/dL. A total of 276 patients (23.0%) had Lp(a) plasma levels ≥ 30 mg/dL). Patients with elevated Lp(a) were more likely to be of female gender, and to have higher levels of total cholesterol, LDL-C, HDL-C and triglycerides. Higher Lp(a) was associated with failure to reach the LDL-C target < 1.8 mmol/l at 1-year (HR 1.71, 95% CI 1.13-2.58, P=0.01). No association was found between elevated Lp(a) and MACE at 1 year (HR 1.05, 95% CI 0.64-1.73), nor for Lp(a) tertiles (HR 0.82, 95% CI 0.52-1.28, P >0.20) or standardized continuous variables (0.98, 95% CI 0.82-1.19 for each increase of standard deviation).

Conclusions

Our real-world data suggest high Lp(a) levels at time of angiography are not predictive for cardiovascular outcomes in patients otherwise medically well controlled, but might be useful to identify patients who would not be on LDL-C targets one year after ACS.

Introduction

Lipoprotein(a) [Lp(a)] is a particle constituted of a low-density lipoprotein (LDL) with apolipoprotein B-100 (ApoB) bound to its surface and bound by a disulfide bridge to Apolipoprotein A (ApoA).[1] Although the physiological function of Lp(a) has not been elucidated, mechanistic studies have shown it to play a pathogenic role in the process of atherothrombosis.[2] Epidemiological and Mendelian randomization studies provide support for a causal association between Lp(a) levels and cardiovascular disease (CVD).[3, 4] It is estimated that 20% of the population has Lp(a) levels above 50 mg/dL and that the risk for CVD is increased by 2- to 2.5-fold in individuals with levels above the 90th percentile.[5] However, the cut-off is assay dependant and some studies suggested a cut-off of 24 mg/dL or 36 mg/dL in populational studies. [6]

The *European Society of Cardiology* (ESC) guidelines recommend measuring Lp(a) levels in selected patients at intermediate or high risk of CVD and associate values above the cut-off of 50 mg/dL with a very high cardiovascular (CV) risk.[7] Patients presenting with acute coronary syndromes (ACS) are at high risk of recurrent CVD events and need intensive lipid-lowering therapies to lower LDL cholesterol (LDL-C) and improve their prognosis.[7] This is especially true for patients with familial hypercholesterolemia (FH) who have a higher risk for recurrence of CVD events after an ACS. [8] In the secondary prevention setting, available data suggest a possible increase of CVD events with higher levels of Lp(a), but it remains unclear whether Lp(a) is a predictor independent of LDL-C or other prognostic factors.[9] In addition, previous studies have not measured Lp(a) levels in the acute phase of ACS nor the prevalence of elevated Lp(a) levels in this specific high-risk setting. One of the main reasons has been the inability of traditional lipid-lowering agents, including statin and ezetimibe, to effectively lower Lp(a).[1] Nevertheless, the more recent lipid-lowering monoclonal antibodies that inhibit proprotein convertase kexin/subtilisin 9 (PCSK9) have led to a 20–30% reduction in Lp(a) levels, as well as a lowering of the incidence of CVD events after ACS, suggesting that Lp(a) could represent an appealing biomarker of residual CV risk amenable to therapy. [10]

Despite these encouraging results, the clinical relevance of Lp(a) for clinical purposes has been questioned and its measurement is not widely applied in clinical practice. More data are needed in the ACS setting to clarify whether measuring Lp(a) could be helpful beyond the currently recommended

markers. Therefore, we evaluated the prevalence of elevated Lp(a) levels and investigated their prognostic value in a contemporary cohort of patients after ACS.

Methods

Study Population

The Special Programme University Medicine Acute Coronary Syndromes and Inflammation (SPUM-ACS) cohort consists of patients with a primary diagnosis of ACS referred for an angiography to one of four Swiss academic centers (Bern, Geneva, Lausanne, and Zürich, NCT01000701). [11] For the analysis of plasma Lp(a) measurements we extracted data from patients enrolled between December 2009 and October 2012, as in our previous publications. [11, 12] Inclusion criteria comprised all females and males aged 18 years and older presenting within 5 days (preferably within 72 h) after pain onset associated with either one of the following primary diagnoses: ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) or unstable angina. Patients had to present symptoms compatible with angina pectoris (chest pain and dyspnea) and fulfill at least one of the following criteria: (i) persistent ST-segment elevation or depression, T-inversion, or dynamic electrocardiogram (ECG) changes, new left bundle branch block (LBBB); (ii) evidence of positive troponin by local laboratory reference values (with a rise and/or fall in serial troponin levels); (iii) known coronary artery disease, specified as status after myocardial infarction, coronary artery bypass grafting (CABG), or percutaneous coronary intervention (PCI) or newly documented, ≥50% stenosis of an epicardial coronary artery during initial catheterization. Exclusion criteria comprised severe physical disability, inability to comprehend the study or <1 year of life expectancy (for non-cardiac reasons). Follow-up was performed at 1 year (clinical visit) with events adjudicated by three independent experts using pre-specified adjudication forms.

Familial hypercholesterolemia classification

Based on a previous study, we used the validated Dutch Lipid Clinic Network algorithm for FH classification.[13] In this algorithm, FH was considered possible when scoring 3–5 points, probable for 6–8 points and definite for >8 points.[17] The diagnosis of possible FH required both an elevated LDL cholesterol >4.9 mmol/L along with a family or personal history of premature atherosclerosis. Lipid-lowering therapy included statin, fibrates, niacin, ezetimibe or resins.

Biomarker measurements

Blood was drawn from the arterial sheath at coronary angiography (time-point 1, [T1]) and centrifuged at $2700 \times g$ for 10 min at room temperature to obtain plasma, and then frozen and stored in aliquots at −80°C. Aliquots were measured blinded to patients' data by means of numbered codes and then merged with the clinical dataset. Plasma Lp(a) levels were determined by means of particle-enhanced immunonephelometry (Siemens BN ProSpec™ analyzer). The inter-assay coefficient of variation was <3.9%, the limit of detection (LoD) 2.5 mg/l and the limit of quantitation (LoQ) 100 mg/l. For cases below the LoD, we imputed the minimal value as 2.5 mg/l (N= 509 patients). PCSK9 levels were measured in each patient using ethylenediaminetetraacetic acid (EDTA) plasma by colorimetric enzyme-linked immunosorbent assay from R&D Systems (Minneapolis, MN, USA) according to the manufacturer's instructions. The minimal limit of detection was 0.625 ng/mL, the mean intra- and inter-assay coefficient of variation was at the accepted threshold of <8%. The cut-off of 30 mg/dL for this essay corresponds to the 75th percentile in male Caucasian reference population. High-sensitive cardiac troponin T (hs-TnT), N-terminal-pro B-type natriuretic peptide (NT-proBNP) and high-sensitive C-reactive protein (hs-CRP) were measured in one serum aliquot per patient at the Zürich Core Laboratory using a electrochemiluminescence immunoassay on a cobas e 602[®] reader (all Roche Diagnostics, Mannheim, Germany), with assay characteristics as reported by the manufacturer.[14]

Study endpoints

The primary endpoint was a composite of major adverse cardiovascular events (MACE) defined as cardiac death, myocardial infarction or stroke. The secondary clinical endpoints comprised all-cause death, cardiac death, myocardial infarction, cerebrovascular events (ischemic or hemorrhagic stroke including transient ischemic attack) and clinically indicated coronary revascularization. Clinical endpoints were adjudicated by a panel of independent experts (three certified cardiologists) blinded to the results of Lp(a). Participants were first followed up at 30 days by telephone by a trained study nurse and were then asked to attended a clinical visit at one-year post-ACS. If patients were unable to attend the clinic visit, follow-up was performed using either of the following alternatives, listed by order of preference: (i) phone call, (ii) postal mail or email, (iii) through family members, or (iv) via the primary care physician or cardiologist.

Statistical methods

The data were expressed as medians ± interquartile range for continuous variables and as numbers and percentages for categorical variables. The correlation between Lp(a) levels and other biomarkers was evaluated by a nonparametric test (Spearman rank correlation). Using logistic regression model

adjusted for previously tested confounding variables, [15] we evaluated the odds ratios (OR) and the 95% confidence intervals (95% CI) of the association between Lp(a) values at time of the angiography and the achievement of LDL-C targets one year after ACS. Continuous Lp(a) levels were categorized into tertiles to assess their association with clinical outcomes.[18] We also classified patients into two groups, according to whether their Lp(a) levels were elevated (≥ 30 mg/dL) or normal (< 30 mg/dL). The time-to-first event or composite events were analyzed censoring patients at 365 days, death, or last valid contact date. The univariable association of Lp(a) tertiles with all-cause death and secondary clinical outcomes was evaluated using Cox proportional hazards models and expressed with hazard ratios (HRs) and 95% confidence intervals (CI). We examined the proportionality of hazards using graphical methods and Schoenfeld residual tests. To increase statistical power, we additionally considered continuous Lp(a) concentrations, estimating the effect on clinical outcomes per 1 standard deviation (SD) increase. Effect estimates were presented as HR and 95% CI. In the multivariable model, we adjusted for traditional CV risk factors (age, sex, smoking, diabetes, hypertension, LDL-C, high-density lipoprotein cholesterol [HDL-C], triglycerides and body mass index). All hypothesis tests were two-sided and the significance level wa set at 5%. Statistical analyses were performed using STATA software® (Version 15, STATA Corp, College Station, TX, USA). Reporting of the study conforms to the STROBE statement along with references to the STROBE statement and the broader EQUATOR guidelines.[16]

Results

Among the 2168 patients recruited, 1711 had available data on Lp(a) plasma levels at baseline (T1), Figure 1 depicts the distribution of Lp(a) levels, the range was between 2.5 mg/dL to 132 mg/dL with a median value of 6 mg/dL and a mean value of 14.2 mg/dL. A total of 92 patients (5.4%) had Lp(a) plasma levels ≥ 50 mg/dL and 276 patients (23.0%) has plasma level ≥ 30 mg/dL. Patients with elevated Lp(a) values were more likely to be female, and have higher levels of total cholesterol, LDL-C and HDL-C PCSK9 (Table 1). Mean age was 63.9 ± 12.6 years, 15.2% had a history of MI, 31.3% were already on statin treatment and 2.3% on other lipid-lowering agents. The percentage of women significantly increased also across Lp(a) tertiles, passing from 17.0% in the lowest tertile to 25.2% in the highest tertile (P=0.003).

Baseline Lp(a) values were significantly and positively correlated with total cholesterol, LDL-C and HDL-C values, and negatively with triglycerides at one-year follow-up (Table 2). No correlation was found between Lp(s) values and cardiac biomarkers (HsTnT, CK, NT-pro BNP) or inflammation (hs CRP). In addition, no significant differences in Lp(a) were observed according to the duration of chest

pain prior to blood draw. Discharge therapies were similar for both elevated and normal Lp(a) groups (Supplemental Table 1).

At one-year follow-up, compliance to statin therapy was comparable between both groups (95% for patients with Lp(a) levels ≥ 30 mg/dL and 93% for Lp(a) levels < 30 mg/dL; P = 0.42, Supplemental Table 2), and the use of non-statin lipid-lowering agents was uncommon (5% vs. %, respectively; P = 0.55). Regarding the subgroup of patients with available data for LDL-C at one year (Supplemental Table 2), patients with elevated Lp(a) had significantly higher mean LDL-C levels one-year after ACS compared to normal Lp(a) values (2.4±0.7 mmol/l vs. 2.2±0.9 mmol/l, P=0.003). Furthermore, a significantly lower proportion of patients with elevated Lp(a) values reached the LDL-C target of < 1.8 mmol/l (24% vs. 38%, P=0.003). In the multivariate variables adjusting for potential confounding factors, high Lp(a) levels at time of ACS were associated with failure to reach LDL-C targets one year after ACS (Table 3, HR 1.71. 95% CI 1.13-2.58, P=0.011).

The rate of MACE was similar between both Lp(a) groups, as were the clinical outcomes in crude and adjusted Cox regression models (Table 4). MACE rates were 8.3% for the group with elevated Lp(a) levels vs. 8.6% for patients with normal Lp(a) (HR 1.05, 95% CI 0.64–1.73, P =0.84). Equally, HRs for highest vs. lowest Lp(a) tertiles did not differ significantly for any of the clinical outcomes, whether taken separately or as a composite endpoint (Table 5, Figure 2) Results were also similar when considering Lp(a) as a continuous standardized value (HR 0.98, 95% CI 0.82-1.19 for each increase in SD). In sensitivity analyses, no significant interactions were found relative to the presence FH (Supplemental Table 3) and HRs were similar for nonfatal outcomes when using all-cause death as a competitive risk in the model (Supplemental Table 4).

Discussion

This large prospective cohort study of patients with ACS adds new evidence to the prognostic role of circulating Lp(a) plasma levels in patients with ACS: (i) the prevalence of elevated Lp(a) plasma levels at initial presentation is about 16% and an important amount of patients had values below the limit of quantification; (ii) higher Lp(a) plasma levels were associated with higher LDL-C values, but not with inflammation or cardiac injury markers; (iii) Lp(a) plasma levels obtained at initial presentation were not significantly associated with all-cause mortality, cardiac mortality, recurrent myocardial infarction or stroke at 1 year; (iv) patients with elevated Lp(a) plasma levels at initial presentation were less likely to reach the recommended target of LDL-C <1.8 mmol (<70 mg/dL) at 1 year.

Our study is one of the largest to evaluate Lp(a) plasma levels specifically in ACS patients undergoing coronary angiography and, in most cases, primary percutaneous coronary intervention. Surprisingly, our findings indicate that assessing Lp(a) plasma levels in the acute ACS setting is likely to be devoid of clinical utility in terms of risk stratification. Compared to a primary prevention setting, the ACS population of the present cohort is characterized by very high use of statin, aspirin and P2Y12 inhibitors at discharge and at one year, which could potentially counteract the prothrombotic and proatherogenic properties of Lp(a). Furthermore, our data suggest that the acute condition of ACS might represent an pre-analytical factor able to substantially affect Lp(a) levels. However, we did not find any significant correlation between the levels of Lp(a) and the amount of inflammation or myocardial injury. Current evidence is controversial regarding the prognostic value of Lp(a) in secondary prevention and for patients on statin. In the *Rosuvastatin Versus Atorvastatin* (SATURN) trial, baseline and follow-up Lp(a) levels were not associated with changes in percent atheroma volume as measured with ultrasound.[17] LDL-C decreased from 114 mg/dL to 60 mg/dL, while Lp(a) remained unchanged (17.4 mg/dL and 16.5 mg/dL, respectively) with statin therapy. The cut-off of 50 mg/dl for Lp(a) was neither protective nor a risk factor for disease progression.[17] In a sub-analysis of the *Study of Dalcetrapib in Patients Hospitalized for an Acute Coronary Syndrome* (dal-OUTCOMES), no association was found between Lp(a) concentrations and major adverse outcomes including 4139 patients treated with statins: for a doubling of the dose of Lp(a), the level of risk for CVD was stagnant (HR 1.01, 95% CI 0.96-1.06, P=0.66).[18] Similar results were also reported in 3 different pooled studies with 6708 subjects known for coronary artery disease: the odds ratios (OR) were 1.03 (95% CI 0.96-1.11) for each increase in log-transformed standard deviation of Lp(a) or by quintile (highest vs. lowest OR 1.05, 95% CI 0.83-1.34).[9] Some other data suggested that the risk associated with Lp(a) in patients with premature ACS was predominantly observed in those with concomitant elevated LDL-C levels, and not for patients with low LDL-C. [19] Recently, an individual patient-data meta-analysis of 29,069 patients from statin outcome trials suggested that baseline Lp(a) levels, as well as Lp(a) values on statin therapy were both associated with CVD events, especially for values higher than 50 mg/dL after adjustment for confounding factors.[20] Therefore, the association between Lp(a) and major adverse cardiovascular events in a population already treated with statin, especially after ACS, is not consistent across literature.[9, 18] Along these lines, the association of Lp(a) with LDL-C is, however, well established and Lp(a) is also considered as a marker for the diagnosis of FH.[1, 5] Finally, we also observed that Lp(a) levels were higher in women, as recently reported in the FOURIER trial. [21]

Defining the Lp(a) cut-off for populations at risk is a source of controversy.[1] The cut-off of 50 mg/dL was mainly based on the fact that 20% of subjects from the general population have Lp(a) levels above 50 mg/dL.[5] Moreover, this threshold is assay-specific, as some studies have shown a significant risk increase already at Lp(a) levels above 30 mg/dL, as demonstrated for the assay used in this

study.[1] No randomized controlled trial has shown a positive correlation between the reduction of Lp(a) and CVD events. Statin therapy has not shown to significantly impact Lp(a) levels.[1] Niacin was also evaluated for reducing Lp(a) levels, but has since been withdrawn from the market following evidence of therapeutic futility.[22] More recently, trials testing monoclonal antibodies directed against PCSK9 have reported a significant 25–30% decrease in Lp(a) values, as shown in a pooled analysis from 1359 patients.[10] The reduction of Lp(a) was, however, significantly correlated with the percentage reduction of LDL-C and currently no evidence suggests that isolated reduction of Lp(a) could improve outcomes.[23] Recently, treatment with antisense oligonucleotides targeting Apo(a) has shown that it can lower Lp(a) levels by up to 80% in individuals with elevated Lp(a). [24] A clinical study with CVD outcomes is now required to evaluate the specific impact of reducing Lp(a) alone. Along these lines, the sub-analysis of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY) data would clarify whether achieving Lp(a) target values <50 mg/dL in secondary prevention would improve prognosis or change the effect of PCSK9 inhibition on clinical outcomes.

Strengths and limitations

The major strength of this study is that it consists of a large cohort of patients with ACS with complete one-year follow-up data and characterized by the measurement of Lp(a) values at the time of angiography. The study population was medically well controlled, as illustrated by the extensive use of recommended treatments including statin and antiplatelet therapy, thereby offering a real-world setting for the assessment of biomarkers. However, we cannot exclude that our follow-up period of one year was not sufficient to detect a possible association at mid- or long-term. The recently published sub-analysis from the FOURIER study including 25,096 high-risk stable patients reported an association between Lp(a) and major adverse cardiovascular events with a median follow-up of 3 years, and this independently of LDL-C.[21] Although our data were observational and not randomized, we also took into consideration key confounding factors, such as inflammation and cardiac biomarkers, as well as the GRACE score. Other limitations include potential underpowered statistical analyses for the elevated Lp(a) strata (≥30 mg/dL), which is the reason why we did not use a more stringent cut-off of ≥ 50 mg/dL. However, analyses evaluating tertiles or standardized continuous Lp(a) corroborated our observations. Although we did not compare Lp(a) values measured at baseline with sample values collected during follow-up, our data do not suggest that Lp(a) levels were associated with the amount of inflammation or cardiac injury; rather, their distribution tends towards lower values than usually described in the high-risk population. Moreover, ACS causes a rapid decline in LDL-C levels, making their interpretation 24 h post-MI unreliable for the steady-state

level.[25] Finally, as with all biomarker studies, pre-analytical (long-term stability of Lp(a) at −80°C is poorly known) as well as analytical aspects may have affected our findings. As samples were stored for 4-5 years prior to analysis, degradation of Lp(a) may have occurred.

Conclusions

Although Lp(a) is associated with proatherogenic and prothrombotic properties, the present study demonstrated that elevated Lp(a) values at time of angiography were not associated with worse clinical outcomes at one year in medically well controlled patients. However, measurement of Lp(a) might be useful to identify patients who would not be on LDL-C targets one year after ACS independently of other lipid particles.

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Disclosures

References

1. Gencer B, Kronenberg F, Stroes ES and Mach F. Lipoprotein(a): the revenant. *European heart journal*. 2017;38:1553-1560.
2. Schmidt K, Noureen A, Kronenberg F and Utermann G. Structure, function, and genetics of lipoprotein (a). *Journal of lipid research*. 2016;57:1339-59.
3. Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, Marcovina SM, Collins R, Thompson SG and Danesh J. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *Jama*. 2009;302:412-23.
4. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R and Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *Jama*. 2009;301:2331-9.
5. Nordestgaard BG, Chapman MJ, Ray K, Boren J, Andreotti F, Watts GF, Ginsberg H, Amarenco P, Catapano A, Descamps OS, Fisher E, Kovanen PT, Kuivenhoven JA, Lesnik P, Masana L, Reiner Z, Taskinen MR, Tokgozoglu L and Tybjaerg-Hansen A. Lipoprotein(a) as a cardiovascular risk factor: current status. *European heart journal*. 2010;31:2844-53.
6. Verbeek R, Boekholdt SM, Stoekenbroek RM, Hovingh GK, Witztum JL, Wareham NJ, Sandhu MS, Khaw KT and Tsimikas S. Population and assay thresholds for the predictive value of lipoprotein (a) for coronary artery disease: the EPIC-Norfolk Prospective Population Study. *Journal of lipid research*. 2016;57:697-705.
7. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Z, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WMM, Vlachopoulos C, Wood DA, Zamorano JL and Cooney MT. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *European heart journal*. 2016;37:2999-3058.
8. Nanchen D, Gencer B, Muller O, Auer R, Aghlmandi S, Heg D, Klingenberg R, Raber L, Carballo D, Carballo S, Matter CM, Luscher TF, Windecker S, Mach F and Rodondi N. Prognosis of Patients With Familial Hypercholesterolemia After Acute Coronary Syndromes. *Circulation*. 2016;134:698-709.
9. O'Donoghue ML, Morrow DA, Tsimikas S, Sloan S, Ren AF, Hoffman EB, Desai NR, Solomon SD, Domanski M, Arai K, Chiuve SE, Cannon CP, Sacks FM and Sabatine MS. Lipoprotein(a) for risk assessment in patients with established coronary artery disease. *Journal of the American College of Cardiology*. 2014;63:520-7.

10.   Raal FJ, Giugliano RP, Sabatine MS, Koren MJ, Langslet G, Bays H, Blom D, Eriksson M, Dent R, Wasserman SM, Huang F, Xue A, Albizem M, Scott R and Stein EA. Reduction in lipoprotein(a) with PCSK9 monoclonal antibody evolocumab (AMG 145): a pooled analysis of more than 1,300 patients in 4 phase II trials. *Journal of the American College of Cardiology*. 2014;63:1278-1288.

11.   Gencer B, Montecucco F, Nanchen D, Carbone F, Klingenberg R, Vuilleumier N, Aghlmandi S, Heg D, Raber L, Auer R, Juni P, Windecker S, Luscher TF, Matter CM, Rodondi N and Mach F. Prognostic value of PCSK9 levels in patients with acute coronary syndromes. *European heart journal*. 2016;37:546-53.

12.   Klingenberg R, Aghlmandi S, Liebetrau C, Raber L, Gencer B, Nanchen D, Carballo D, Akhmedov A, Montecucco F, Zoller S, Brokopp C, Heg D, Juni P, Marti Soler H, Marques-Vidal PM, Vollenweider P, Dorr O, Rodondi N, Mach F, Windecker S, Landmesser U, von Eckardstein A, Hamm CW, Matter CM and Luscher TF. Cysteine-rich angiogenic inducer 61 (Cyr61): a novel soluble biomarker of acute myocardial injury improves risk stratification after acute coronary syndromes. *European heart journal*. 2017;38:3493-3502.

13.   Nanchen D, Gencer B, Auer R, Raber L, Stefanini GG, Klingenberg R, Schmied CM, Cornuz J, Muller O, Vogt P, Juni P, Matter CM, Windecker S, Luscher TF, Mach F and Rodondi N. Prevalence and management of familial hypercholesterolaemia in patients with acute coronary syndromes. *European heart journal*. 2015;36:2438-45.

14.   Klingenberg R, Aghlmandi S, Raber L, Gencer B, Nanchen D, Heg D, Carballo S, Rodondi N, Mach F, Windecker S, Juni P, von Eckardstein A, Matter CM and Luscher TF. Improved risk stratification of patients with acute coronary syndromes using a combination of hsTnT, NT-proBNP and hsCRP with the GRACE score. *European heart journal Acute cardiovascular care*. 2018;7:129-138.

15.   Gencer B, Auer R, Nanchen D, Raber L, Klingenberg R, Carballo D, Blum M, Vogt P, Carballo S, Meyer P, Matter CM, Windecker S, Luscher TF, Mach F and Rodondi N. Expected impact of applying new 2013 AHA/ACC cholesterol guidelines criteria on the recommended lipid target achievement after acute coronary syndromes. *Atherosclerosis*. 2015;239:118-24.

16.   Simera I, Moher D, Hoey J, Schulz KF and Altman DG. A catalogue of reporting guidelines for health research. *European journal of clinical investigation*. 2010;40:35-53.

17.   Puri R, Ballantyne CM, Hoogeveen RC, Shao M, Barter P, Libby P, Chapman MJ, Erbel R, Arsenault BJ, Raichlen JS, Nissen SE and Nicholls SJ. Lipoprotein(a) and coronary atheroma progression rates during long-term high-intensity statin therapy: Insights from SATURN. *Atherosclerosis*. 2017;263:137-144.

18.   Schwartz GG, Ballantyne CM, Barter PJ, Kallend D, Leiter LA, Leitersdorf E, McMurray JJV, Nicholls SJ, Olsson AG, Shah PK, Tardif JC and Kittelson J. Association of Lipoprotein(a) With Risk of Recurrent Ischemic Events Following Acute Coronary Syndrome: Analysis of the dal-Outcomes Randomized Clinical Trial. *JAMA cardiology*. 2018;3:164-168.

19.   Afshar M, Pilote L, Dufresne L, Engert JC and Thanassoulis G. Lipoprotein(a) Interactions With Low-Density Lipoprotein Cholesterol and Other Cardiovascular Risk Factors in Premature Acute Coronary Syndrome (ACS). *J Am Heart Assoc*. 2016;5.

20.   Willeit P, Ridker PM, Nestel PJ, Simes J, Tonkin AM, Pedersen TR, Schwartz GG, Olsson AG, Colhoun HM, Kronenberg F, Drechsler C, Wanner C, Mora S, Lesogor A and Tsimikas S. Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials. *Lancet*. 2018;392:1311-1320.

21.   O'Donoghue ML, Fazio S, Giugliano RP, Stroes ESG, Kanevsky E, Gouni-Berthold I, Im K, Lira Pineda A, Wasserman SM, Ceska R, Ezhov MV, Jukema JW, Jensen HK, Tokgozoglu SL, Mach F, Huber K, Sever PS, Keech AC, Pedersen TR and Sabatine MS. Lipoprotein(a), PCSK9 Inhibition and Cardiovascular Risk: Insights from the FOURIER Trial. *Circulation*. 2018.

22.   Landray MJ, Haynes R and Armitage J. Niacin for reduction of cardiovascular risk. *The New England journal of medicine*. 2014;371:1943-4.

23.   Raal FJ, Giugliano RP, Sabatine MS, Koren MJ, Blom D, Seidah NG, Honarpour N, Lira A, Xue A, Chiruvolu P, Jackson S, Di M, Peach M, Somaratne R, Wasserman SM, Scott R and Stein EA. PCSK9

inhibition-mediated reduction in Lp(a) with evolocumab: an analysis of 10 clinical trials and the LDL receptor's role. *Journal of lipid research*. 2016;57:1086-96.

24.   Tsimikas S, Viney NJ, Hughes SG, Singleton W, Graham MJ, Baker BF, Burkey JL, Yang Q, Marcovina SM, Geary RS, Crooke RM and Witztum JL. Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study. *Lancet*. 2015;386:1472-83.

25.   Wattanasuwan N, Khan IA, Gowda RM, Vasavada BC and Sacchi TJ. Effect of acute myocardial infarction on cholesterol ratios. *Chest*. 2001;120:1196-9.

TABLES

Table 1. Baseline characteristics of 1711 patients with ACS			
	Lp(a) ≥ 30 mg/dL	Lp(a) < 30 mg/dL	p value
	(n=276)	(n=1435)	
Demographics			
Age, yr.	64.1±11.7	63.8±12.7	0.75
Woman, n (%)	36 (31.2)	284 (19.8)	**< 0.001**
BMI, kg/m^2	26.6 ± 5.0	27.2 ± 4.3	0.03
Hypertension, no. (%)	159 (57.6)	595 (41.5)	0.78
Diabetes, no. (%)	44 (15.9)	279 (19.4)	0.17
FH classification, no (%)			0.61
No FH	218 (80.8)	1146 (81.4)	
Possible or probable	54 (19.9)	262 (18.6)	
Current Smoking, no. (%)	98 (35.8)	580 (41.3)	0.08
Use of statin, no. (%)	97 (35.3)	435 (30.5)	0.12
History of MI, no (%)	39 (14.1)	221 (15.4)	0.59
History of malignancy, no (%)	27 (9.8)	106 (7.4)	0.17
Family history CAD, no (%)	79 (29.2)	349 (24.8)	0.13
Clinical presentation			
ACS[|] type			0.91
STEMI, no (%)	142 (51.5)	722 (50.3)	
NSTEMI, no (%)	124 (44.9)	655 (45.6)	
Unstable angina	10 (3.6)	58 (4.0)	
Killip classification			0.08
I, no. (%)	226 (81.9)	1247 (86.9)	
II, no. (%)	36 (13.0)	128 (8.9)	
III, no. (%)	8 (2.9)	24 (1.7)	
IV, no. (%)	6 (2.2)	36 (2.5)	
SBP, mmHg	131.0 ± 23.7	129.8 ± 23.0	0.40
DBP mmHg	75.0 ± 13.8	74.7 ± 14.9	0.72
Revascularization (PCI or CABG)	255 (92.4)	1347 (93.9)	0.36
Biochemical values			
Cholesterol (mmol/l)	5.1 ± 1.3	4.9 ± 1.3	0.01
LDL-C (mmol/l)	3.7 ± 1.1	3.3 ± 1.1	**< 0.001**
Triglycerides (mmol?l)	1.1 ± 0.8	1.4 ± 1.31	0.001
HDL-C (mmol/l)	1.3 ± 0.2	1.2 ± 0.4	**< 0.001**
PCSK9 (ng/ml)	341.3 ± 147.1	329.3 ± 145.9	0.22
CRP (mg/L)	9.5 ± 1.6	11.1 ± 0.7	0.35
Creatinine (mg/dl)	81.3 ± 27.1	84.3 ± 46.3	0.28
Glucose (mmol/l)	6.9 ± 2.2	7.1 ± 2.8	0.48

Data are expressed as mean ± standard deviation or number (no.) and percentages (%). Two-tailed Fisher's exact tests for dichotomous variables, larger Chi-squared test for [+]T-Test or Mann-Whitney-U tests for continuous variables, were utilized as appropriate. Abbreviations: ACS, acute coronary syndromes; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CRP, C-reactive protein; DBP, diastolic blood pressure; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NSTEMI, Non ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin kexin 9; PVD, peripheral vascular disease; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction

Table 2 Correlations between Lp(a) and other biomarkers		
Biomarkers	**Rho #**	**P-value**
LDL-C (mmol/l)	0.105	**<0.001**
HDL-C (mmol/l)	0.116	**<0.001**
Triglycerides (mmol/l)	-0.125	**<0.001**
PCSK9 (ng/ml)	0.027	0.259
Creatinine (mg/dl)	-0.013	0.600
hs-CRP (mg/l)	-0.024	0.359
Hs Troponin (µg/l)	-0.002	0.938
CK (U/l)	-0.004	0.889
NT-pro BNP (ng/l)	0.020	0.429
Glucose (mmol/l)	-0.031	0.235
# Spearman's rank correlation rho for continuous variables; Rho=1 denotes perfect positive correlation, rho=-1 denotes perfect negative correlation and Rho=0 absence of correlation. Abbreviations: CK, creatinine kinase; hs-CRP, high-sensitive C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NT-pro BNP, N-terminal-pro B-type natriuretic peptide; PCSK9 proprotein convertase subtilisin kexin 9.		

Table 3 Clinical Associated Factors With Failure to Achieve LDL-C Targets One Year After ACS		
	Odds Ratios (95% CI)	P-value
Lp(a) Tertile		
1st Tertile	1(Ref)	
2nd Tertile	1.03 (0.70-1.53)	0.864
3rd Tertile	1.71 (1.13-2.58)	0.011
Age (per year increase)	0.98 (0.97-1.00)	0.021
Sex (women)	1.33 (0.84-2.11)	0.218
Body mass index (per unit increase)	0.97 (0.93-1.01)	0.118
History of diabetes	1.35 (0.87-2.09)	0.183
Use of statin at one year	0.06 (0.01-0.3)	<0.001
LDL-C (per mmol/l increase)	2.21 (1.85-2.65)	<0.001
HDL-C (per mmol/l increase)	1.68 (1.00-2.85)	0.051
Triglycerides (per mmol/l increase)	1.16 (1.03-1.31)	0.016
Attendance to cardiac rehabilitation	0.68 (0.46-1.00)	0.047

Abbreviations: ACS, acute coronary syndromes; CI, confidence intervals; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), Lipoprotein (a);

Table 4 Association between elevated Lp(a) values and clinical outcomes at one year				
Clinical outcomes at 365 days	Lp(a) ≥ 30 mg/dl	Lp(a) < 30 mg/dl	HR (95% CI)	
	Number events/participants	Number events/participants	Unadjusted	Adjusted for age, sex and CVRF¶
Composite MACE#	23/276 (8.3%)	123/1435 (8.6%)	0.97 (0.62-1.51) *	1.05 (0.64-1.73) *
All-cause death	10/276 (3.6%)	75/1435 (5.2%)	0.69 (0.35-1.33) *	0.82 (0.39-1.73) *
Cardiac death	9/276 (3.3%)	60/1435 (4.1%)	0.77 (0.38-1.55) *	0.95 (0.43-2.13) *
MI	9/276 (3.3%)	50/1435 (3.5%)	0.93 (0.46-1.88) *	1.02 (0.47-2.19) *
Stroke	5/276 (1.8%)	21/1435 (1.5%)	1.23 (0.46-3.26) *	1.05 (0.35-3.16) *
Revascularization	16/276 (5.8%)	81/1435 (5.6%)	1.00 (0.59-1.72) *	1.07 (0.62-1.87) *

MACE was defined as a composite of cardiac death, MI and stroke events.

¶ CVRF was defined as smoking, history of hypertension, history of diabetes, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, triglycerides and body mass index. * P-value > 0.20. Abbreviations: CI, confidence intervals; CVRF, cardiovascular risk factor; HR, hazard ratio; Lp(a), Lipoprotein(a); MACE, major adverse cardiovascular events.

	1st Tertile (<2.5-3.1 mg/dL)	2nd Tertile (3.1-12.4 mg/dL)	3rd Tertile (12.5-132 mg/dL)	Per SD increase
Table 5 Association between Lp(a) tertiles and clinical outcomes at one year				
Composite MACE§				
Number events/participants	56/571 (9.8%)	49/572 (8.6%)	41/568 (7.2%)	
Crude HR and 95% CI	1 (Ref)	0.87 (0.59-1.27)	0.73 (0.49-1.09) ***	0.94 (0.79-1.12)
Adjusted HR and 95% CI	1 (Ref)	0.89 (0.59-1.35)	0.82 (0.52-1.28)	0.98 (0.82-1.19)
All-cause death				
Number events/participants	36/571 (6.3%)	31/572 (5.4%)	18/568 (3.2%)	
Crude HR and 95% CI	1 (Ref)	0.85 (0.53-1.38)	0.49 (0.28-0.87)	0.75 (0.56-0.99) *
Adjusted # HR and 95% CI	1 (Ref)	0.88 (0.52-1.50)	0.62 (0.33-1.16) ***	0.82 (0.60-1.12)
Cardiac death				
Number events/participants	31/571 (5.4%)	23/572 (4.0%)	15/568 (2.6%)	
Crude HR and 95% CI	1 (Ref)	0.74 (0.43-1.26)	0.48 (0.26-0.89) *	0.75 (0.55-1.02) **
Adjusted HR and 95% CI	1 (Ref)	0.79 (0.43-1.43)	0.66 (0.33-1.31)	0.86 (0.61-1.20)
Myocardial Infarction				
Number events/participants	22/571 (3.9%)	21/572 (3.7%)	16/568 (2.8%)	
Crude HR and 95% CI	1 (Ref)	0.95 (0.52-1.72)	0.72 (0.38-1.37)	0.89 (0.67-1.19)
Adjusted HR and 95% CI	1 (Ref)	0.91 (0.48-1.71)	0.75 (0.38-1.50)	0.91 (0.67-1.24)
Stroke				
Number events/participants	8/571 (1.4%)	6/572 (1.1%)	12/568 (2.1%)	
Crude HR and 95% CI	1 (Ref)	0.74 (0.26-2.14)	1.50 (0.61-3.66)	1.31 (0.99-1.74) **
Adjusted HR and 95% CI	1 (Ref)	0.60 (0.19-1.88)	1.09 (0.40-2.95)	1.24 (0.91-1.68) ***
Revascularization				
Number events/participants	38/571 (6.7%)	33/572 (5.8%)	26/568 (4.6%)	
Crude HR and 95% CI	1 (Ref)	0.86 (0.54-1.37)	0.66 (0.40-1.09) ***	0.92 (0.75-1.14)
Adjusted HR and 95% CI	1 (Ref)	0.87 (0.53-1.43)	0.71 (0.42-1.20) ***	0.95 (0.76-1.18)

Adjusted model included age, sex, smoking, history of hypertension, history of diabetes, low-density lipoprotein-cholesterol, high-density lipoprotein triglycerides and body mass index. * p value < 0.05, ** p value 0.05-0.10. *** p value 0.10–0.20. § MACE was defined as a composite of cardiac death, MI and stroke events. Abbreviations; CI, confidence intervals; HR, hazard ratio; SD, standard deviation
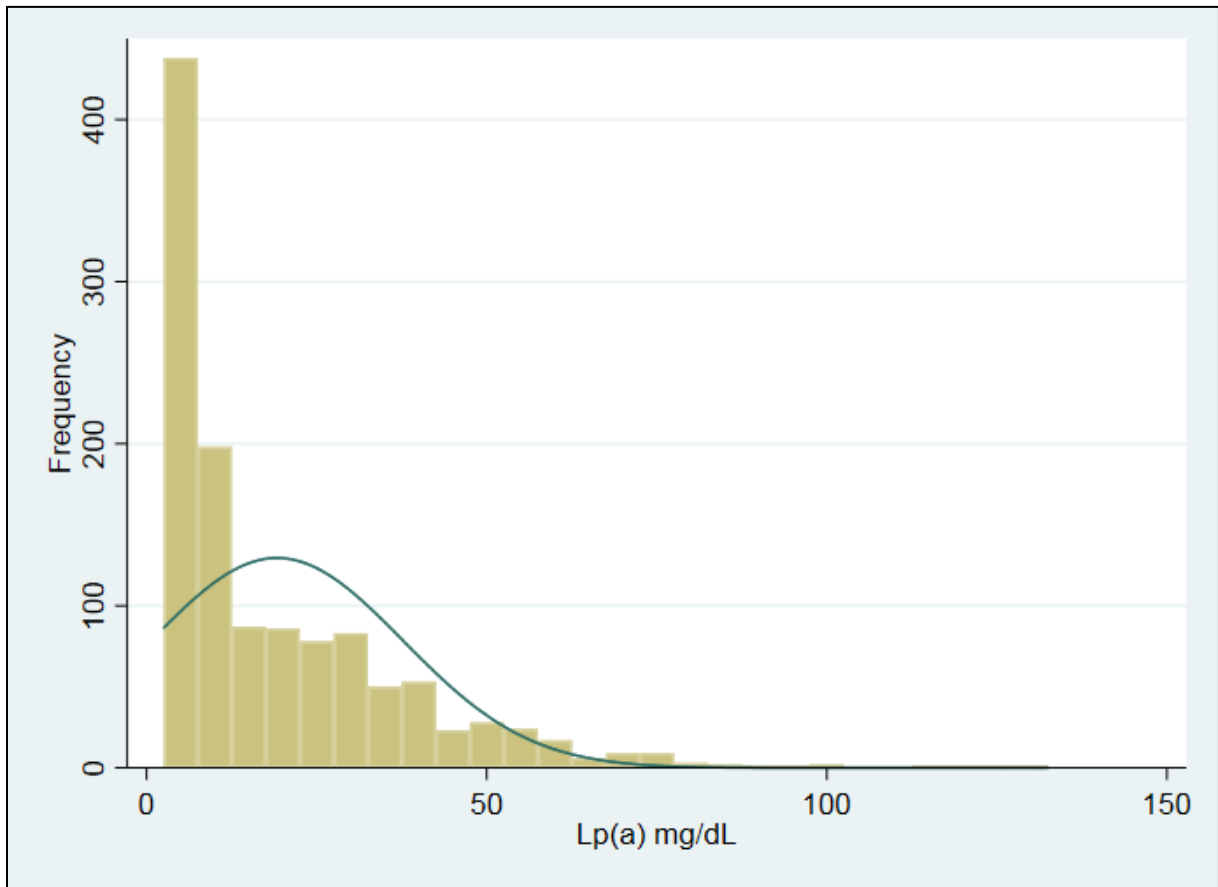
Figure 1 Distribution of Lipoprotein(a) Levels At Time of Angiography in Patients With Acute Coronary Syndrome.
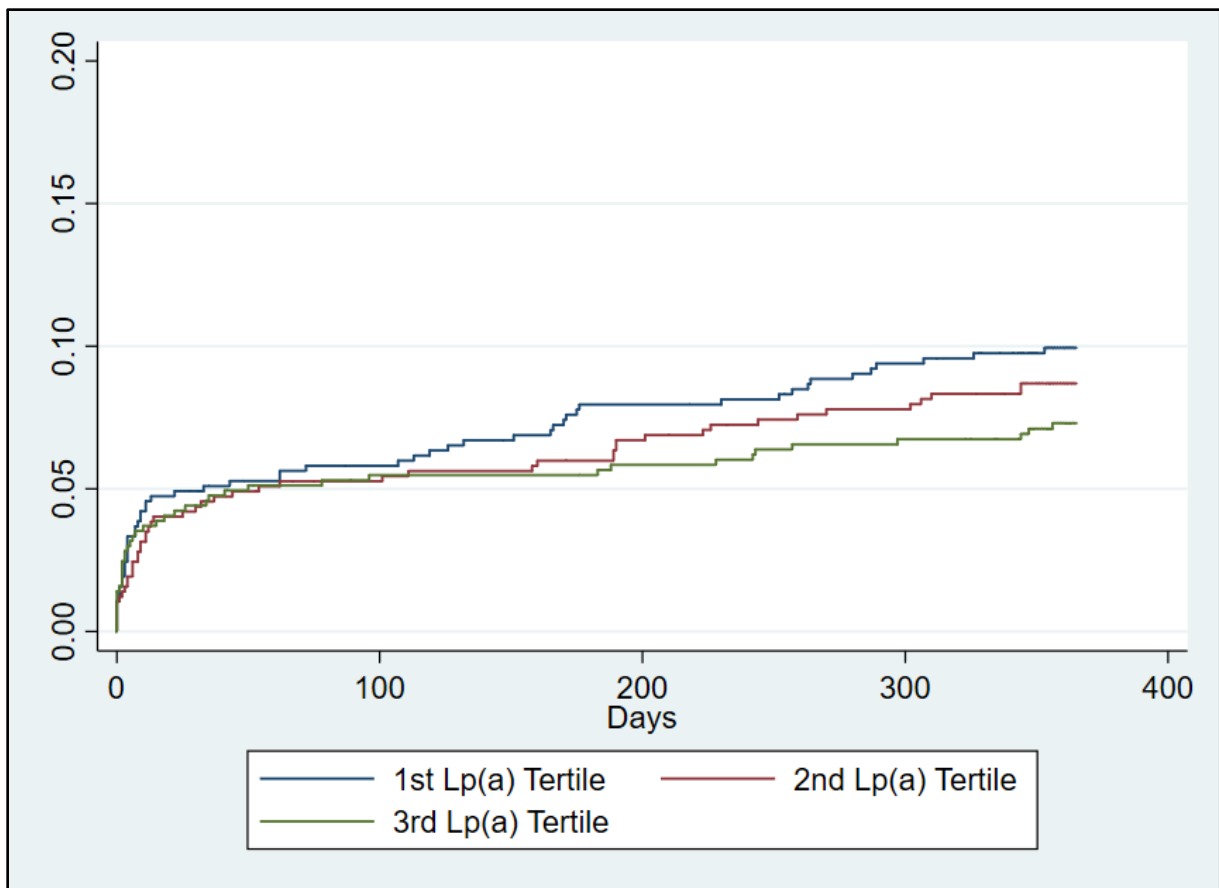
Figure 2 Kaplan-Meier curve for major adverse cardiac events according to Lp(a) tertiles.

Abbreviations: Lp(a), lipoprotein(a); MACE, major adverse cardiovascular events