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ORIGINAL RESEARCH

# Association of Lipoprotein (a) and Standard Modifiable Cardiovascular Risk Factors With Incident Myocardial Infarction: The Mass General Brigham Lp(a) Registry

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**BACKGROUND:** Lipoprotein (a) [Lp(a)] is a robust predictor of coronary heart disease outcomes, with targeted therapies currently under investigation. We aimed to evaluate the association of high Lp(a) with standard modifiable risk factors (SMuRFs) for incident first acute myocardial infarction (AMI).

**METHODS AND RESULTS:** This retrospective study used the Mass General Brigham Lp(a) Registry, which included patients aged ≥18 years with an Lp(a) measurement between 2000 and 2019. Exclusion criteria were severe kidney dysfunction, malignant neoplasm, and prior known atherosclerotic cardiovascular disease. Diabetes, dyslipidemia, hypertension, and smoking were considered SMuRFs. High Lp(a) was defined as >90th percentile, and low Lp(a) was defined as <50th percentile. The primary outcome was fatal or nonfatal AMI. A combination of natural language processing algorithms, *International Classification of Diseases* (*ICD*) codes, and laboratory data was used to identify the outcome and covariates. A total of 6238 patients met the eligibility criteria. The median age was 54 (interquartile range, 43–65) years, and 45% were women. Overall, 23.7% had no SMuRFs, and 17.8% had ≥3 SMuRFs. Over a median follow-up of 8.8 (interquartile range, 4.2–12.8) years, the incidence of AMI increased gradually, with higher number of SMuRFs among patients with high (log-rank $P$=0.031) and low Lp(a) (log-rank $P$<0.001). Across all SMuRF subgroups, the incidence of AMI was significantly higher for patients with high Lp(a) versus low Lp(a). The risk of high Lp(a) was similar to having 2 SMuRFs. Following adjustment for confounders and number of SMuRFs, high Lp(a) remained significantly associated with the primary outcome (hazard ratio, 2.9 [95% CI, 2.0–4.3]; $P$<0.001).

**CONCLUSIONS:** Among patients with no prior atherosclerotic cardiovascular disease, high Lp(a) is associated with significantly higher risk for first AMI regardless of the number of SMuRFs.

**Key Words:** acute myocardial infarction ■ atherosclerotic cardiovascular disease ■ lipoprotein (a) ■ standard modifiable risk factors



Despite significant progress in the diagnosis and treatment of coronary artery disease (CAD) and acute myocardial infarction (AMI), these conditions remain major causes of death worldwide with increasing social and economic burden.[1,2] Standard modifiable risk factors (SMuRFs), such as diabetes, hypertension, smoking, and dyslipidemia, are well-known risk factors for coronary heart disease, and are commonly used for risk stratification, especially among patients who do not have established cardiovascular

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## CLINICAL PERSPECTIVE

### What Is New?

- Among individuals without prior atherosclerotic cardiovascular disease, elevated lipoprotein (a) is associated with a significantly higher risk of acute myocardial infarction, independent of the presence or number of standard modifiable risk factors, with the additional risk being comparable to having 2 standard modifiable risk factors.

### What Are the Clinical Implications?

- These findings support the need for broader screening of lipoprotein (a), and suggest incorporating lipoprotein (a) alongside standard modifiable risk factors for enhanced risk stratification and therapeutic decision-making.
- Although there are currently no approved therapies for lowering lipoprotein (a), patients identified as having a higher risk should undergo aggressive management of all modifiable risk factors.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **Lp(a)** | lipoprotein (a) |
| **SMuRF** | standard modifiable risk factor |

disease.[3–6] However, up to 20% of patients with acute coronary syndrome have no SMuRFs, and paradoxically such patients have worse outcomes when compared with those who have at least 1 SMuRF.[7–19] Furthermore, a recent study by Chunawala et al[19] found a temporal trend of increase in the incidence of 28-day mortality following AMI for patients without SMuRFs, whereas it declined for those with ≥1 SMuRFs. This underscores the importance of identifying additional modifiable cardiovascular risk factors.

Lipoprotein (a) [Lp(a)] is a lipid-carrying particle composed of a low-density lipoprotein (LDL)–like moiety containing apolipoprotein B-100 linked by a disulfide bond to apolipoprotein (a).[20] Lp(a) has emerged as a causal risk factor for CAD, and in particular AMI.[21–23] This has prompted the development of new targeted therapies that effectively reduce Lp(a).[20,24] Although several such therapies that directly target Lp(a) production are being evaluated among individuals with prior cardiovascular disease,[24] there are presently no approved treatments for its lowering. Thus, for individuals with elevated Lp(a) levels, the therapeutic approach focuses on general risk reduction and the management of other modifiable risk factors.[4,25–27]

Although Lp(a) has been shown to have prognostic value among patients with acute coronary syndrome who do not have SMuRFs,[28] there is currently a scarcity of data on the interaction between Lp(a) and SMuRFs, especially among individuals without a history of atherosclerotic cardiovascular disease (ASCVD). There is also a paucity of data on Lp(a) within the United States.

Therefore, the objective of this study was to evaluate the risk of elevated Lp(a) levels in relation to SMuRFs for developing a first AMI.

## METHODS

### Study Design and Population

The patient population was derived from the Mass General Brigham Lp(a) Registry, as previously described.[29,30] In summary, this is a retrospective cohort study, which included all patients who had undergone Lp(a) testing as part of their routine care between January 2000 and July 2019 and was conducted at 2 large academic medical centers in Boston, Massachusetts (Brigham and Women's Hospital and Massachusetts General Hospital). The Mass General Brigham Lp(a) Registry was granted approval by the Institutional Review Board at Mass General Brigham, and the requirement for informed consent has been waived. All individuals aged ≥18 years with at least 1 Lp(a) result were screened for inclusion in the cohort. Exclusion criteria consisted of 2 factors: (1) severe kidney dysfunction, which was defined as stage 5 chronic kidney disease (estimated glomerular filtration rate <15 mL/min per $m^2$), prior renal transplant, or those receiving renal replacement therapy; or (2) the presence of a diagnostic *International Classification of Diseases* (*ICD*) (*ICD-9*, *ICD-10*) code for a malignant neoplasm during the covariate assessment window, except for nonmelanoma skin cancer. Additionally, for the current study, patients with a history of ASCVD, defined as a previous myocardial infarction, history of coronary revascularization, or a history of ischemic stroke, were also excluded.

### Data Sources and Definitions

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author.

Three primary sources were used to collect the data, including: (1) the RPDR (Research Patient Data Registry)[31] at Mass General Brigham, which provides demographic, laboratory, imaging, diagnostic, procedural, medication, vital status (based on the Social Security Administration Death Master File), and clinical documentation for individuals who meet specific

search criteria; and (2) *ICD*-coded death information from the National Death Index or the Massachusetts Office of Vital Statistics was used to establish the causes of death for each patient who passed away during the study period.

To determine the presence of cardiovascular risk factors, validated natural language processing (NLP) modules,[32] laboratory data, and diagnostic and procedural *ICD-9*, *ICD-10*, and Current Procedural Terminology codes were used, as previously described.[29]

The baseline covariate assessment period was established as the 12-month period before and 30 days after the Lp(a) measurement. For individuals with >1 Lp(a) test, their covariate assessment period was assessed relative to the first Lp(a) test. Any clinical covariate that occurred or was documented during this time was attributed to baseline characteristics.

The definitions used to define SMuRFs were as follows. Diabetes was classified on the basis of the presence of a combination of diagnostic *ICD* codes, NLP, and hemoglobin A1c results. Hypertension was defined on the basis of the presence of a combination of diagnostic *ICD* codes and NLP. Non-Lp(a) dyslipidemia was determined through NLP, treatment with a cholesterol-lowering medication, or laboratory values (median) that exceeded any 1 of the following thresholds during the covariate window: (1) total cholesterol ≥240 mg/dL, (2) LDL cholesterol (LDL-C) ≥160 mg/dL, (3) high-density lipoprotein cholesterol <40 mg/dL (men), (4) high-density lipoprotein cholesterol <50 mg/dL (women), or (5) total triglycerides ≥175 mg/dL. Smoking was classified as current, former, or never smoker by an NLP algorithm that was proven to be highly accurate in our institution.[33] Further details on the covariate assessment, ascertainment, and adjudication are found in Data S1.

## Lp(a) Assays

Lp(a) was measured as part of routine medical care using available immunochemical-based assays with reference ranges <30 mg/dL or <75 nmol/L.[34–36] All Lp(a) laboratory testing was performed at commercial laboratories over the study period using industry-standard assays. We converted all Lp(a) values to nmol/L using the following conversion formula: Lp(a) nmol=[2.18×Lp(a)-M]–3.83.[37,38] To avoid potential biases attributable to possible differences in Lp(a) testing techniques over the study period, percentile distributions for each assay were defined separately, as previously also performed by others.[37,39–41] Subsequently, Lp(a) percentiles were then combined across assay types.

Given the well-established distribution of Lp(a), a priori percentiles were determined and used in the present study: 1st to 50th, 51st to 70th, 71st to 90th, and 91st to 100th.[21,42,43] Accordingly, high Lp(a) was defined as a value >90th percentile in the cohort, and low Lp(a) was defined as a value <50th percentile.

## Primary Outcome

The primary outcome for the current study was the occurrence of AMI during the follow-up period. As previously described,[29] AMI was defined by the presence of a diagnostic *ICD* code in the primary hospital discharge position. This method has been thoroughly validated and is associated with high specificity, high positive predictive value, and reasonable sensitivity.[44–48]

## Statistical Analysis

Continuous variables are reported as medians, and categorical variables are reported as frequencies and percentages. Ordinal variables were compared using Jonckheere-Terpstra trend test. Cumulative incidence of AMI was compared according to the study variables using Kaplan-Meier approach. The relative risk of AMI was assessed with univariate and multivariable levels of Cox proportional hazard models, presented as hazard ratio (HR) and 95% CI. We evaluated multicollinearity among the independent variables using Spearman correlation coefficients. The correlations between variables were all <0.7, indicating no evidence of substantial multicollinearity in the multivariable model.

The proportional hazards assumption was tested using Schoenfeld residuals and found to be valid ($P$>0.05), indicating that the HRs for the covariates remained constant over time. Incidence rate ratios were calculated when comparing the rates of cardiovascular events between different levels of Lp(a). The $\chi^2$ goodness-of-fit test for multinominal data was used to calculate the $P$ values for low and high Lp(a). Patients were censored either upon their death or at the conclusion of the query period, which extended until July 2019. We used the Fine-Gray model to evaluate the potential for competing risks of death. Tests were 2 tailed and considered statistically significant with a $P$<0.05. All statistical analyses were conducted using STATA MP, version 17 (College Station, TX).

# RESULTS

A total of 6238 individuals met the established inclusion and exclusion criteria. The mean age of the patients was 54 years (interquartile range, 43–65 years), and 45% were women. Table 1 provides the baseline characteristics of the cohort. The distribution of the number of SMuRFs in the study cohort is shown in Figure 1. It is noteworthy that 23.7% of the study cohort did not have any SMuRFs, whereas 4.3% had all 4 modifiable risk factors. For subsequent analyses, patients who

**Table 1. Baseline Characteristics of the Study Population**

| Characteristic | Patients (n=6238) |
|---|---|
| Demographic characteristics | |
| Age, median (IQR), y* | 54 (43–64) |
| Sex: female, n (%) | 2802 (44.9) |
| Race or ethnicity, n (%) | |
| White | 5296 (84.9) |
| Black | 183 (2.9) |
| Hispanic | 156 (2.5) |
| East Asian | 171 (2.7) |
| Other† | 432 (6.9) |
| Risk factors, n (%) | |
| Hypertension | 2054 (32.9) |
| Dyslipidemia | 3030 (48.6) |
| Diabetes | 733 (11.8) |
| Chronic kidney disease | 147 (2.4) |
| Smokers | 2959 (47.4) |
| Medical therapy, n (%) | |
| Statin | 2193 (35.2) |
| Nonstatin lipid-lowering therapy | 295 (4.7) |

IQR indicates interquartile range.
*At time of lipoprotein (a) test.
†Other includes Indian, Middle Eastern, Native American, other, Pacific Islander, and unknown.

had 4 SMuRFs were combined with those who had 3 SMuRFs. Figure S1 displays the distribution of Lp(a) percentiles in the study cohort. Of the total cohort, 436 (7%) patients had high Lp(a), whereas 3618 (58%) had low Lp(a). Table S1 presents a comparison of baseline characteristics between patients with no SMuRFs and those with a least 1 SMuRF. Patients without SMuRFs were younger, with comparable rates of women and racial or ethnic distribution, and exhibited a more favorable lipid profile compared with individuals with at least 1 SMuRF. Figure 2 displays the rates of high and low Lp(a) according to the number of SMuRFs. The figure shows a gradual increase in the rates of high Lp(a) and a gradual decrease in the rate of low Lp(a) as the number of SMuRFs increases.

Over a median follow-up of 8.8 years (interquartile range, 4.2–12.8 years; range, 0.02–19.2 years), 234 (3.75%) patients experienced an AMI. Among the entire cohort and when separately examining patients with high and low Lp(a), there was an increase in the risk of incident AMI with a higher number of SMuRFs (Figure 3, Figure S2). However, in all subgroups of SMuRFs, the incidence of AMI was considerably higher among patients with high Lp(a) compared with those with low Lp(a), as shown in Figure 3. Notably, as the number of risk factors increased, the absolute difference in the incidence of AMI between patients with high Lp(a) versus those with low Lp(a) became greater. When evaluating the incidence rates of these subgroups, the risk associated with elevated Lp(a) was similar to having 2 additional SMuRFs. Table S2 shows the hazard ratios of the individual SMuRFs for developing incident myocardial infarction (MI). Notably, all SMuRFs were significantly associated with increased risk of AMI with an increasing risk for AMI with higher number of SMuRFs. Similarly, high Lp(a) levels [versus low Lp(a)] were significantly associated with increased risk of AMI (Table S2, Figure S3). After adjusting for age, sex, and the number of SMuRFs in a multivariable Cox model (Table 2), high Lp(a) remained significantly associated with the first occurrence of AMI, with an HR of 2.9 (95% CI, 2.0–4.3), and a $P<0.001$. This was similar to the HR associated with having 2 SMuRFs (HR, 2.97; $P=0.001$). The cumulative incidence function of MI was significantly higher in patients with high Lp(a) than in patients with low Lp(a) after adjusting for other causes of death as competing risk ($P<0.001$).

## DISCUSSION

In this retrospective contemporary cohort study of patients who did not have prior ASCVD, we evaluated the risk of first AMI associated with high Lp(a) relative to SMuRFs. The key findings were that: (1) high Lp(a) was significantly associated with an increased risk of first AMI regardless of the presence or number of SMuRFs, and this association remained highly significant after adjusting for risk factors; and (2) the excess risk imparted by having a high Lp(a) was similar to the risk of having 2 SMuRFs.

The association between Lp(a) and AMI or CAD has been extensively studied through various epidemiologic and genetic investigations in different populations. Indeed, the association between Lp(a) and CAD has been supported by multiple genetic studies, which have provided strong mechanistic evidence for this association.[20,49,50] In addition, epidemiologic studies have demonstrated a robust and independent graded association between Lp(a) and CAD or AMI.[20,21,39,51–53] Although some of these studies have accounted for baseline characteristics and standard risk factors, the risk associated with elevated Lp(a) in relation to other risk factors has not been fully explored, and prior studies have not focused on modifiable risk factors.

Recently, several studies have examined the cardiovascular risk associated with increased Lp(a) relative to various individual risk factors. For example, elevated Lp(a) was found to be linked to an increased risk for MI, stroke, and cardiovascular mortality in patients with diabetes and prediabetes in a stepwise association.[54] Mehta et al[55] studied >12 000 participants in the ARIC (Atherosclerosis Risk in Communities) study and found that elevated Lp(a) and family history of coronary heart

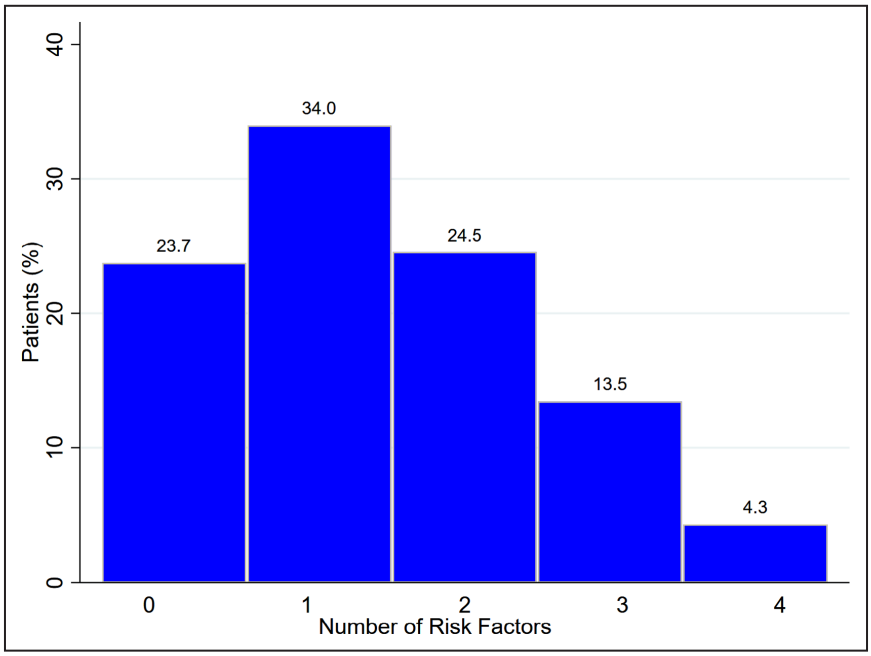


**Figure 1. Distribution of the number of standard modifiable risk factors in the study cohort.**

disease had independent and additive joint associations with the risk of coronary heart disease. In another study, Verbeek et al[56] evaluated the prognostic association between Lp(a) and LDL-C in a primary prevention setting and found that the risk associated with elevated Lp(a) was attenuated among patients with LDL-C levels <100 mg/dL. However, the justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin[57] demonstrated that the association between baseline Lp(a) and first incident cardiovascular event was similar at LDL-C levels above and below the median (110 mg/dL) and even at low levels (54 mg/dL).

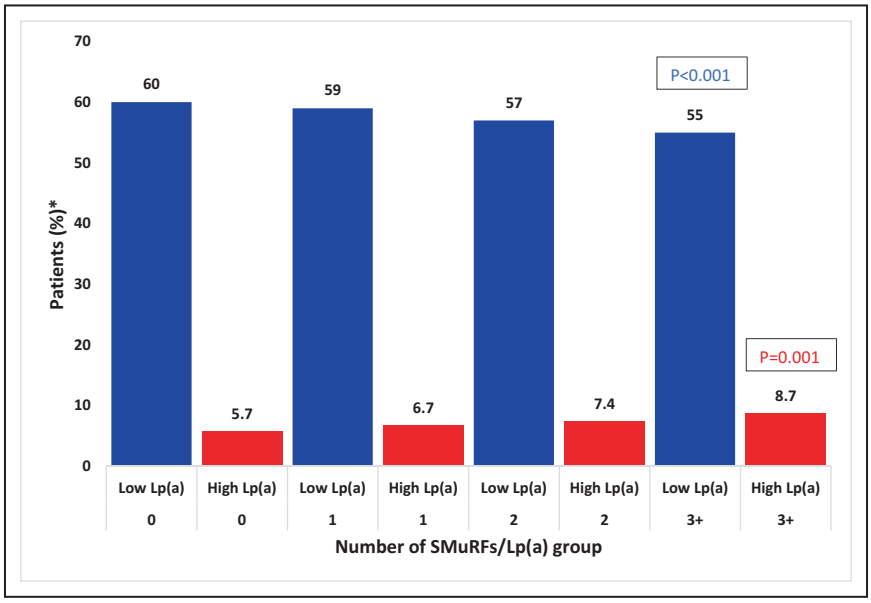


**Figure 2. The rate of high and low lipoprotein (a) [Lp(a)] according to the number of standard modifiable risk factors (SMuRFs).**
*Percentages presented are out of total number of patients in every SMuRF category. High Lp(a) was defined as a value >90th percentile in the cohort, and low Lp(a) as <50th percentile.

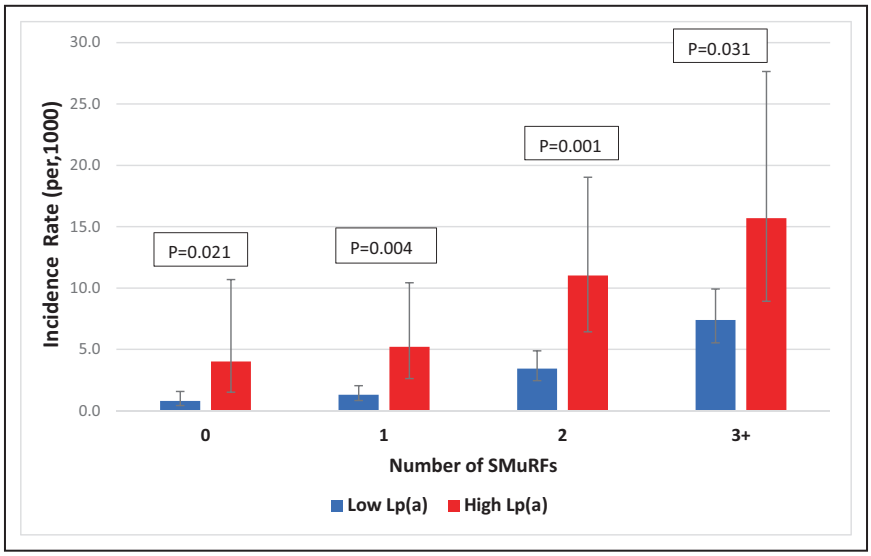


**Figure 3. Incidence of acute myocardial infarction according to the number of standard modifiable risk factors (SMuRFs) stratified by lipoprotein (a) [Lp(a)].**
Incidence rates are presented with 95% CIs.

Trinder et al[58] investigated whether apolipoprotein B could explain the risk of CAD associated with Lp(a) particles, but found that the concentration of apolipoprotein B could only explain the association of LDL-C with CAD, not that of Lp(a).[58] Hedegaard et al[59] conducted a study to contextualize the risk associated with Lp(a) by comparing it with that of familial hypercholesterolemia. According to their findings, the risk associated with Lp(a) becomes clinically significant at a level of 30 mg/dL, and the strength of the association was similar to that of familial hypercholesterolemia at levels which exceeded 70 mg/dL.

Thomas et al[21] reported that Lp(a) is a significant contributor to ASCVD and MI regardless of CRP (C-reactive protein) levels. Furthermore, Lp(a) was found to be an independent prognostic marker among patients with acute coronary syndrome without SMuRFs, potentially explaining their worse outcomes.[28] Previous evidence suggests that inflammation and thrombosis may play a significant role in mediating these adverse outcomes.[22,60,61]

**Table 2. Multivariable Cox Model Adjusted for Age and Sex**

| Parameter | HR (95%CI) | *P* value |
|---|---|---|
| No. of SMuRFs | | |
| 0 | Reference | … |
| 1 | 1.35 (0.70–2.63) | 0.370 |
| 2 | 2.97 (1.59–5.54) | 0.001* |
| ≥3 | 4.65 (2.50–8.66) | <0.001* |
| Low Lp(a) | Reference | …* |
| High Lp(a) | 2.88 (1.97–4.21) | <0.001* |
| Age† | 1.04 (1.03–1.05) | <0.001* |
| Female sex | 0.70 (0.50–0.99) | 0.045* |

HR indicates hazard ratio; Lp(a), lipoprotein (a); and SMuRF, standard modifiable risk factor.
*Significance was considered when $P<0.05$.
†Increase of 1 year.

The current study builds on and extends previous research in several ways. First, it focuses on the role of SMuRFs and Lp(a) among a primary prevention population who did not have prior ASCVD. Second, it offers a simple estimation of risk that can enable clinicians to understand the interplay between Lp(a) and the number of SMuRFs in assessing the risk of MI. For instance, for any given number of risk factors (ie, SMuRF category), having a high Lp(a) was associated with a nearly 3× higher level of risk of incident MI. Moreover, having a high Lp(a) was associated with a similar risk level as having 2 additional modifiable risk factors.

Given the robust risk of Lp(a) in risk assessment observed in this study, our results reinforce the European and Canadian Dyslipidemia guidelines that advocate for wider Lp(a) screening, wherein Lp(a) is measured at least once in every adult to enhance risk stratification and therapeutic decision-making.[4,24,62] Our results support the role of Lp(a) testing even among individuals with minimal or no cardiovascular risk factors, because high Lp(a) levels can be linked to a substantially elevated risk. Additional assessment of other nonstandard risk factors was advised for these patients.[17] Although there are currently no effective therapies for lowering Lp(a), patients who are found to have higher risk should be aggressively managed with respect to their modifiable risk factors, especially LDL-C.[63] Indeed, our results show that even in the presence of high Lp(a), the number of SMuRFs is strongly associated with risk (ie,

4× increase in risk between those with ≥3 risk factors versus those with no SMuRFs). These data suggest that controlling modifiable risk factors likely has an important role on risk reduction.

## Limitations

The current study has certain limitations. First, because of its retrospective design, risk factors were not assessed in a standard manner, and there is possible unmeasured confounding. Additionally, the evaluation of risk factors was conducted around the time of Lp(a) measurement, which was a priori defined as the baseline covariate window.[29] However, relying on a single baseline period may underestimate the prevalence of SMuRFs, as patients may develop additional risk factors over additional follow-up time up until the incidence of AMI. Underestimation, and consequently undertreatment, of SMuRFs is considered 1 of the proposed mechanisms contributing to poorer outcomes observed in SMuRFless patients, as reported in numerous other studies.[7–19,64] Second, our cohort comprised patients who were tested for Lp(a) as part of routine clinical care, which may introduce selection bias. However, we focused on patients without prior ASCVD who were referred for testing, and as such these results remain generalizable to the population of patients in whom Lp(a) is currently tested in the United States. Nevertheless, the generalizability of our findings may be limited in other cohorts and, thus, further investigation is warranted. Moreover, there is a possibility that the risk observed among high-risk patients [those with a high prevalence of SMuRFs or high Lp(a)] was attenuated through the management of these risk factors. Third, the registry used for this study represents a single geographic region of the United States, which could limit the generalizability of the findings, particularly as our patient population was predominantly White race. Fourth, Lp(a) was measured by different techniques in our cohort; however, we standardized the assays using percentiles, as also done by prior studies. Nevertheless, there is a need for additional validation of conversion methods as well as further data comparing the performance of different types of Lp(a) assays. Fifth, for practical and simplicity reasons, our risk factors were assessed in a binary manner, and thus we did not account for the severity of various SMuRFs (eg, LDL level, blood pressure); however, our approach has been used in the vast majority of observational cohorts. Sixth, we have included low high-density lipoprotein as a component of modifiable dyslipidemia, which may be controversial.

# CONCLUSIONS

This retrospective analysis from a large contemporary Lp(a) registry demonstrated that high Lp(a) levels are significantly associated with an increased risk for first AMI, regardless of the presence or number of SMuRFs. The study also revealed that the incremental risk posed by high Lp(a) was similar to that of having 2 additional SMuRFs. These findings could be useful in risk assessment and in guiding currently available preventive therapies.

## ARTICLE INFORMATION

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## Supplemental Material

Data S1
Tables S1–S2
Figures S1–S3

## REFERENCES


1. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, et al. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. *Circulation*. 2021;143:e254–e743. doi: 10.1161/cir.0000000000000950
2. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet (London, England)*. 2018;392:1789–1858. doi: 10.1016/s0140-6736(18)32279-7
3. Grant PJ, Cosentino F. The 2019 ESC guidelines on diabetes, prediabetes, and cardiovascular diseases developed in collaboration with the EASD: new features and the 'ten commandments' of the 2019 guidelines are discussed by professor Peter J. Grant and professor Francesco Cosentino, the task force chairmen. *Eur Heart J*. 2019;40:3215–3217. doi: 10.1093/eurheartj/ehz687
4. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111–188. doi: 10.1093/eurheartj/ehz455
5. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European Society of Cardiology and Other Societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & rehabilitation (EACPR). *Atherosclerosis*. 2016;252:207–274. doi: 10.1016/j.atherosclerosis.2016.05.037
6. Loudon BL, Gollop ND, Carter PR, Uppal H, Chandran S, Potluri R. Impact of cardiovascular risk factors and disease on length of stay and mortality in patients with acute coronary syndromes. *Int J Cardiol*. 2016;220:745–749. doi: 10.1016/j.ijcard.2016.06.188
7. Gonzalez-Pacheco H, Vargas-Barron J, Vallejo M, Pina-Reyna Y, Altamirano-Castillo A, Sanchez-Tapia P, Martinez-Sanchez C. Prevalence of conventional risk factors and lipid profiles in patients with acute coronary syndrome and significant coronary disease. *Ther Clin Risk Manag*. 2014;10:815–823. doi: 10.2147/tcrm.s67945
8. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, Wilson PW. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *JAMA*. 2003;290:891–897. doi: 10.1001/jama.290.7.891
9. Khot UN, Khot MB, Bajzer CT, Sapp SK, Ohman EM, Brener SJ, Ellis SG, Lincoff AM, Topol EJ. Prevalence of conventional risk factors in patients with coronary heart disease. *JAMA*. 2003;290:898–904. doi: 10.1001/jama.290.7.898
10. Plakht Y, Gilutz H, Shiyovich A. Ethnical disparities in temporal trends of acute myocardial infarction (AMI) throughout a decade in Israel. Soroka acute myocardial infarction (SAMI-II) project. *Int J Cardiol*. 2016;214:469–476. doi: 10.1016/j.ijcard.2016.04.009
11. Plakht Y, Gilutz H, Shiyovich A, Zahger D, Weitzman S. Gender and ethnic disparities in outcome following acute myocardial infarction among Bedouins and Jews in southern Israel. *Eur J Pub Health*. 2011;21:74–80. doi: 10.1093/eurpub/ckq012
12. Roe MT, Halabi AR, Mehta RH, Chen AY, Newby LK, Harrington RA, Smith SC Jr, Ohman EM, Gibler WB, Peterson ED. Documented traditional cardiovascular risk factors and mortality in non-ST-segment elevation myocardial infarction. *Am Heart J*. 2007;153:507–514. doi: 10.1016/j.ahj.2006.12.018
13. Canto JG, Kiefe CI, Rogers WJ, Peterson ED, Frederick PD, French WJ, Gibson CM, Pollack CV Jr, Ornato JP, Zalenski RJ, et al. Atherosclerotic risk factors and their association with hospital mortality among patients with first myocardial infarction (from the National Registry of myocardial infarction). *Am J Cardiol*. 2012;110:1256–1261. doi: 10.1016/j.amjcard.2012.06.025
14. Vernon ST, Coffey S, Bhindi R, Soo Hoo SY, Nelson GI, Ward MR, Hansen PS, Asrress KN, Chow CK, Celermajer DS, et al. Increasing proportion of ST elevation myocardial infarction patients with coronary atherosclerosis poorly explained by standard modifiable risk factors. *Eur J Prev Cardiol*. 2017;24:1830. doi: 10.1177/2047487317720287
15. Vernon ST, Coffey S, D'Souza M, Chow CK, Kilian J, Hyun K, Shaw JA, Adams M, Roberts-Thomson P, Brieger D, et al. ST-segment-elevation myocardial infarction (STEMI) patients without standard modifiable cardiovascular risk factors-how common are they, and what are their outcomes? *J Am Heart Assoc*. 2019;8:e013296. doi: 10.1161/jaha.119.013296
16. Figtree GA, Vernon ST, Hadziosmanovic N, Sundström J, Alfredsson J, Arnott C, Delatour V, Leósdóttir M, Hagström E. Mortality in STEMI patients without standard modifiable risk factors: a sex-disaggregated analysis of SWEDEHEART registry data. *Lancet (London, England)*. 2021;397:1085–1094. doi: 10.1016/s0140-6736(21)00272-5
17. Figtree GA, Redfors B, Kozor R, Vernon ST, Grieve SM, Mazhar J, Thiele H, Patel MR, Udelson JE, Selker HP, et al. Clinical outcomes in patients with ST-segment elevation MI and No standard modifiable cardiovascular risk factors. *JACC Cardiovasc Interv*. 2022;15:1167–1175. doi: 10.1016/j.jcin.2022.03.036
18. Shiyovich A, Ovdat T, Klempfner R, Beigel R, Halabi M, Shiran A, Skalsky K, Porter A, Orvin K, Kornowski R, et al. Worse outcomes of ACS patients without versus with traditional cardiovascular risk factors. *J Cardiol*. 2022;79:515–521. doi: 10.1016/j.jjcc.2021.10.019
19. Chunawala ZS, Caughey MC, Bhatt DL, Hendrickson M, Arora S, Bangalore S, Erwin JP, Levisay JP, Rosenberg JR, Ricciardi MJ, et al. Mortality in patients hospitalized with acute myocardial infarction without standard modifiable risk factors: the ARIC study community surveillance. *J Am Heart Assoc*. 2023;12:e027851. doi: 10.1161/jaha.122.027851
20. Bhatia HS, Wilkinson MJ. Lipoprotein(a): evidence for role as a causal risk factor in cardiovascular disease and emerging therapies. *J Clin Med*. 2022;11:11. doi: 10.3390/jcm11206040
21. Thomas PE, Vedel-Krogh S, Kamstrup PR, Nordestgaard BG. Lipoprotein(a) is linked to atherothrombosis and aortic valve stenosis independent of C-reactive protein. *Eur Heart J*. 2023;44:1449–1460. doi: 10.1093/eurheartj/ehad055
22. Berman AN, Blankstein R. Current and future role of lipoprotein(a) in preventive cardiology. *Curr Opin Cardiol*. 2019;34:514–518. doi: 10.1097/hco.0000000000000661

23. Shiyovich A, Berman AN, Besser SA, Biery DW, Huck DM, Weber B, Cannon C, Januzzi JL, Booth JN III, Nasir K, et al. Cardiovascular outcomes in patients with coronary artery disease and elevated lipoprotein(a): implications for the OCEAN(a)-outcomes trial population. *Eur Heart J Open*. 2023;3:oead077. doi: 10.1093/ehjopen/oead077
24. Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, Dweck MR, Koschinsky M, Lambert G, Mach F, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European atherosclerosis society consensus statement. *Eur Heart J*. 2022;43:3925–3946. doi: 10.1093/eurheartj/ehac361
25. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2019;140:e596–e646. doi: 10.1161/cir.0000000000000678
26. Berman AN, Blankstein R. Optimizing dyslipidemia management for the prevention of cardiovascular disease: a focus on risk assessment and therapeutic options. *Curr Cardiol Rep*. 2019;21:110. doi: 10.1007/s11886-019-1175-z
27. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/cir.0000000000000625
28. Wang L, Cong HL, Zhang JX, Hu YC, Li XM, Zhang YY, Yang H, Ren LB, Qi W, Liu CW. Prognostic significance of preprocedural N-terminal pro-B-type natriuretic peptide assessment in diabetic patients with multivessel coronary disease undergoing revascularization. *Front Cardiovasc Med*. 2021;8:721260. doi: 10.3389/fcvm.2021.721260
29. Berman AN, Biery DW, Ginder C, Hulme OL, Marcusa D, Leiva O, Wu WY, Singh A, Divakaran S, Hainer J, et al. Study of lipoprotein(a) and its impact on atherosclerotic cardiovascular disease: design and rationale of the mass general Brigham Lp(a) registry. *Clin Cardiol*. 2020;43:1209–1215. doi: 10.1002/clc.23456
30. Berman AN, Biery DW, Besser SA, Singh A, Shiyovich A, Weber BN, Huck DM, Divakaran S, Hainer J, Kaur G, et al. Lipoprotein(a) and major adverse cardiovascular events in patients with or without baseline atherosclerotic cardiovascular disease. *J Am Coll Cardiol*. 2024;83:873–886. doi: 10.1016/j.jacc.2023.12.031
31. Hibino T, Sakuma N, Hashimoto T, Ohte N, Yoneyama A, Satoh T, Fujinami T. Elevated serum Lp(a) concentration and the rare apo(a) phenotype in a patient with myocardial infarction. *Clin Cardiol*. 1996;19:758–759. doi: 10.1002/clc.4960190917
32. Iyengar PV. Regulation of ubiquitin enzymes in the TGF-β pathway. *Int J Mol Sci*. 2017;18:1–9. doi:10.3390/ijms18040877
33. Regan S, Meigs JB, Grinspoon SK, Triant VA. Determinants of smoking and quitting in HIV-infected individuals. *PLoS One*. 2016;11:e0153103. doi: 10.1371/journal.pone.0153103
34. Koschinsky ML, Marcovina SM. Lipoprotein(a). In: Ballantyne CM, ed *Clinical Lipidology: a Companion to Braunwald's Heart Disease*. Elsevier; 2015.
35. Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. *J Am Coll Cardiol*. 2017;69:692–711. doi: 10.1016/j.jacc.2016.11.042
36. Marcovina SM, Albers JJ. Lipoprotein (a) measurements for clinical application. *J Lipid Res*. 2016;57:526–537. doi: 10.1194/jlr.R061648
37. Langsted A, Kamstrup PR, Nordestgaard BG. High lipoprotein(a) and high risk of mortality. *Eur Heart J*. 2019;40:2760–2770. doi: 10.1093/eurheartj/ehy902
38. Madsen CM, Kamstrup PR, Langsted A, Varbo A, Nordestgaard BG. Lipoprotein(a)-lowering by 50 mg/dL (105 nmol/L) may be needed to reduce cardiovascular disease 20% in secondary prevention. *Arterioscler Thromb Vasc Biol*. 2020;40:255–266. doi: 10.1161/ATVBAHA.119.312951
39. Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City heart study. *Circulation*. 2008;117:176–184. doi: 10.1161/circulationaha.107.715698
40. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. *J Am Coll Cardiol*. 2014;63:470–477. doi: 10.1016/j.jacc.2013.09.038
41. Langsted A, Nordestgaard BG, Kamstrup PR. Elevated lipoprotein(a) and risk of ischemic stroke. *J Am Coll Cardiol*. 2019;74:54–66. doi: 10.1016/j.jacc.2019.03.524
42. Waldeyer C, Makarova N, Zeller T, Schnabel RB, Brunner FJ, Jørgensen T, Linneberg A, Niiranen T, Salomaa V, Jousilahti P, et al. Lipoprotein(a) and the risk of cardiovascular disease in the European population: results from the BiomarCaRE consortium. *Eur Heart J*. 2017;38:2490–2498. doi: 10.1093/eurheartj/ehx166
43. Simony SB, Mortensen MB, Langsted A, Afzal S, Kamstrup PR, Nordestgaard BG. Sex differences of lipoprotein(a) levels and associated risk of morbidity and mortality by age: the Copenhagen general population study. *Atherosclerosis*. 2022;355:76–82. doi: 10.1016/j.atherosclerosis.2022.06.1023
44. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362:2155–2165. doi: 10.1056/NEJMoa0908610
45. Andrade SE, Harrold LR, Tjia J, Cutrona SL, Saczynski JS, Dodd KS, Goldberg RJ, Gurwitz JH. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. *Pharmacoepidemiol Drug Saf*. 2012;21(suppl 1):100–128. doi: 10.1002/pds.2312
46. Birman-Deych E, Waterman AD, Yan Y, Nilasena DS, Radford MJ, Gage BF. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. *Med Care*. 2005;43:480–485. doi: 10.1097/01.mlr.0000160417.39497.a9
47. Cozzolino F, Montedori A, Abraha I, Eusebi P, Grisci C, Heymann AJ, Lombardo G, Mengoni A, Orso M, Ambrosio G. A diagnostic accuracy study validating cardiovascular ICD-9-CM codes in healthcare administrative databases. The Umbria Data-Value Project. *PLoS One*. 2019;14:e0218919. doi: 10.1371/journal.pone.0218919
48. Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying venous thromboembolism using administrative and claims data. *Pharmacoepidemiol Drug Saf*. 2012;21(suppl 1):154–162. doi: 10.1002/pds.2341
49. Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, Parish S, Barlera S, Franzosi MG, Rust S, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med*. 2009;361:2518–2528. doi: 10.1056/NEJMoa0902604
50. Kamstrup PR, Tybjærg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and improved cardiovascular risk prediction. *J Am Coll Cardiol*. 2013;61:1146–1156. doi: 10.1016/j.jacc.2012.12.023
51. Bennet A, Di Angelantonio E, Erqou S, Eiriksdottir G, Sigurdsson G, Woodward M, Rumley A, Lowe GD, Danesh J, Gudnason V. Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data. *Arch Intern Med*. 2008;168:598–608. doi: 10.1001/archinte.168.6.598
52. Paré G, Çaku A, McQueen M, Anand SS, Enas E, Clarke R, Boffa MB, Koschinsky M, Wang X, Yusuf S. Lipoprotein(a) levels and the risk of myocardial infarction among 7 ethnic groups. *Circulation*. 2019;139:1472–1482. doi: 10.1161/circulationaha.118.034311
53. Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, Marcovina SM, Collins R, Thompson SG, Danesh J. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA*. 2009;302:412–423. doi: 10.1001/jama.2009.1063
54. Jin JL, Cao YX, Zhang HW, Sun D, Hua Q, Li YF, Guo YL, Wu NQ, Zhu CG, Gao Y, et al. Lipoprotein(a) and cardiovascular outcomes in patients with coronary artery disease and prediabetes or diabetes. *Diabetes Care*. 2019;42:1312–1318. doi: 10.2337/dc19-0274
55. Mehta A, Virani SS, Ayers CR, Sun W, Hoogeveen RC, Rohatgi A, Berry JD, Joshi PH, Ballantyne CM, Khera A. Lipoprotein(a) and family history predict cardiovascular disease risk. *J Am Coll Cardiol*. 2020;76:781–793. doi: 10.1016/j.jacc.2020.06.040
56. Verbeek R, Hoogeveen RM, Langsted A, Stiekema LCA, Verweij SL, Hovingh GK, Wareham NJ, Khaw KT, Boekholdt SM, Nordestgaard BG, et al. Cardiovascular disease risk associated with elevated lipoprotein(a) attenuates at low low-density lipoprotein cholesterol levels in a primary prevention setting. *Eur Heart J*. 2018;39:2589–2596. doi: 10.1093/eurheartj/ehy334
57. Khera AV, Everett BM, Caulfield MP, Hantash FM, Wohlgemuth J, Ridker PM, Mora S. Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER trial (justification for the use of statins in prevention: an intervention trial evaluating Rosuvastatin). *Circulation*. 2014;129:635–642. doi: 10.1161/circulationaha.113.004406

58. Trinder M, Zekavat SM, Uddin MM, Pampana A, Natarajan P. Apolipoprotein B is an insufficient explanation for the risk of coronary disease associated with lipoprotein(a). *Cardiovasc Res*. 2021;117:1245–1247. doi: 10.1093/cvr/cvab060
59. Hedegaard BS, Bork CS, Kaltoft M, Klausen IC, Schmidt EB, Kamstrup PR, Langsted A, Nordestgaard BG. Equivalent impact of elevated lipoprotein(a) and familial hypercholesterolemia in patients with atherosclerotic cardiovascular disease. *J Am Coll Cardiol*. 2022;80:1998–2010. doi: 10.1016/j.jacc.2022.09.021
60. van der Valk FM, Bekkering S, Kroon J, Yeang C, Van den Bossche J, van Buul JD, Ravandi A, Nederveen AJ, Verberne HJ, Scipione C, et al. Oxidized phospholipids on lipoprotein(a) elicit arterial wall inflammation and an inflammatory monocyte response in humans. *Circulation*. 2016;134:611–624. doi: 10.1161/circulationaha.116.020838
61. Lieb W, Enserro DM, Larson MG, Vasan RS. Residual cardiovascular risk in individuals on lipid-lowering treatment: quantifying absolute and relative risk in the community. *Open Heart*. 2018;5:e000722. doi: 10.1136/openhrt-2017-000722
62. Pearson GJ, Thanassoulis G, Anderson TJ, Barry AR, Couture P, Dayan N, Francis GA, Genest J, Grégoire J, Grover SA, et al. 2021 Canadian cardiovascular society guidelines for the Management of Dyslipidemia for the prevention of cardiovascular disease in adults. *Can J Cardiol*. 2021;37:1129–1150. doi: 10.1016/j.cjca.2021.03.016
63. Bittner VA, Szarek M, Aylward PE, Bhatt DL, Diaz R, Edelberg JM, Fras Z, Goodman SG, Halvorsen S, Hanotin C, et al. Effect of Alirocumab on lipoprotein(a) and cardiovascular risk after acute coronary syndrome. *J Am Coll Cardiol*. 2020;75:133–144. doi: 10.1016/j.jacc.2019.10.057
64. Parwani P, Bhatt DL. In NSTEMI, are patients without SMuRFs real? *Eur J Prev Cardiol*. 2022;29:1081–1083. doi: 10.1093/eurjpc/zwab210