Interrelation of Lipoprotein(a) Concentrations with The Intensity of Recurrent Coronary Strokes in CAD Patients with Assorted LDL-C Levels

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Abstract

Cardiovascular diseases impose a major threat to public health in the developing world. Bangladesh, in the midst of an epidemiological transition from communicable to non-communicable diseases, is witnessing a rising prominence of Lp(a). While higher Lp(a) is widely identified as a substantial threat for coronary artery disease (CAD), it is not regularly assessed in clinical practice. An investigation of higher Lp(a) levels in persons with LDL-C can aid in identifying the risk of cardiovascular disease. People at high risk for CAD may be identified through evaluation for increased Lp(a) when coupled with LDL-C. This study addresses the interrelation between higher levels of Lp(a) and the risk of CAD at a variety of LDL-C levels. The study was conducted at the Bangabandhu Sheikh Mujib Medical College Hospital in Faridpur, Bangladesh which included 100 patients who were classified into low-Lp(a) and high-Lp(a) catagories. These groups have been compared with the frequency of MACE and ACE. One of the key findings demonstrate that ACE and MACE were higher in the high-Lp(a), particularly when LDL-C was 1.4 mmol/L or higher, according to subgroup analysis that further subdivided patients based on LDL-C levels. Nevertheless, the relation ceased to exist if LDL-C were below 1.4 mmol/L. In short, the results establish Lp(a) as a viable noninvasive screening method for predicting CAD and prompt the development of Lp(a)-reducing therapies as an emerging concern.

Keywords
Lipoprotein(a) elevations, CAD, coronary strokes, cardiovascular disease and epidemiological transition.

1. Introduction
CAD exhibits a significant mortality and disability rate, which renders it a prominent global health concern. A considerably high number of cases are reported to suffer from CAD annually, of which more than one-fifth will experience a recurrent stroke within a short period (Strong K, Mathers C, 2007). Although notable progress in the detection and treatment of CAD, patients still encounter MI, stroke, and the necessity for revascularization. The progress made in figuring out modifiable risk factors for CAD has enabled the development of practice protocols and evidence-based guidelines in medical treatment. These advancements have played a significant role in reducing mortality rates associated with CAD. Nevertheless, regardless of these breakthroughs, approximately 40% of all fatalities can be ascribed to CAD. Moreover, throughout the limited duration of clinical trials that assess treatments, only a minority of patients experience positive outcomes, while a greater number of adverse events occur in patients receiving active therapy compared to those that are averted. These findings indicate that the existence of extra risk factors has a role in increasing the risk of CAD. (Dariush Mozaffarian, Emelia J. Benjamin, Alan S. Go, 2014). Lp(a) elevation is a prevalent hereditary dyslipidemia that affects around 20% of the global population. It is considered a

distinct risk factor for CAD (Børge G. Nordestgaard, M. John Chapman, Kausik Ray 2010; Panos Deloukas, Stavroula Kanoni 2013).

Lp(a) is composed of apo(a), which binds to an apoB-100.- LDL-like particle containing oxidised phospholipid (Katsiki N, Al-Rasadi K, 2017). **Figure 1** illustrates the Lp(a), which consists of a solitary apo(a) molecule and the apoB100 polypeptide of 4536 amino acids. These components form a shape resembling a ribbon and bow, encircling the cholesteryl-ester core of the LDL part. Apo(a) consists of 10 classes of kringle modules and a protease domain. The variation in the number of KIV-2 modules contributes to the reported differences in the shape of apo(a) isoforms. The diversity within this group may influence the non-covalent connections among apo(a) and apoB. Previous research has demonstrated that Lp(a) contributes to the development of atherosclerosis, inflammation, and thrombosis, making it a distinct risk factor for CAD (Erqou S, Kaptoge S and Di Angelantonio E, 2009; Tada H, Takamura M, 2019). Lp-PLA2, an enzyme from inflammatory cells, predominantly attaches to LDL in the bloodstream (Stafforini DM, Tjoelker LW, McCormick SP, 1999). Further investigation reveals that OxPL on Lp(a) can increase the expression of inflammatory genes and trigger the secretion of interleukin-8 (Corey A. Scipione, Sera E. Sayegh, 2015) and monocyte chemoattractant protein-1 (Philipp Wiesner, Maria Tafelmeier, 2013). The presence of monocyte chemoattractant protein-1 on Lp(a) can potentially facilitate its penetration into the vascular wall. In addition, apo(a) has lysine-binding sites, which enable it to strongly connect to exposed areas on damaged endothelium. This results in its buildup in sub-intimal gaps, leading to inflammation.

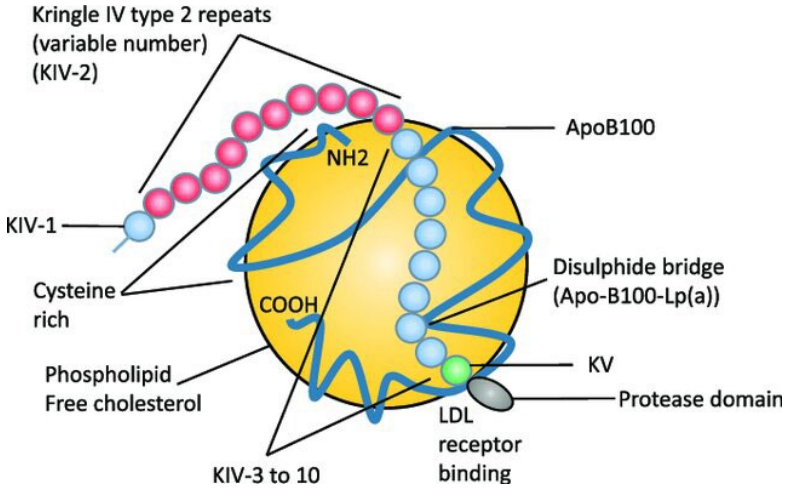

Figure 1. The structure of Lipoprotein(a)

According to the 2019 guidelines from the ESC and EAS, it is recommended that all adults receive at least one examination of Lp(a) levels over their lifespan (Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M and Al., 2020). Nevertheless, the usefulness of Lp(a) in forecasting recurring incidents in patients with CAD who are receiving secondary preventive approaches is still a subject of debate. Research on the involvement of Lp(a) in atherosclerosis and its treatment has been conducted in the Russian Federation for a period of thirty years. Currently, there is a dearth of knowledge about how higher Lp(a) is linked to the existence of IHD, MI, and stroke (Ezhov MV, Safarova MS, Afanasieva OI, 2014; Pokrovsky SN, Afanasieva OI, 2016).

Several studies provide contradictory results about the interrelation between higher Lp(a) and CAD, regardless of LDL-C levels. Several investigations, including those conducted by Ref (O'Donoghue ML, Fazio S, Giugliano RP, Stroes ESG, Kanevsky E, 2019; Szarek M, Bittner VA, Aylward P, Baccara-Dinet M, Bhatt DL, 2020; Hoogeveen RC, 2021) suggest that higher levels of Lp(a) are linked with a greater likelihood of experiencing cardiovascular events, irrespective of LDL-C levels. On the other hand, other research, such as the ones conducted by Ref (Maher VM, Brown BG, 1995; O'Donoghue ML, Morrow DA, Tsimikas S, Sloan S, Ren AF and Al., 2014; Afshar M, Rong J, Zhan Y, Chen HY, Engert JC, 2020), indicate that the interrelation of Lp(a) and CAD becomes more noticeable when LDL-C levels are higher. These studies specifically reveal a connection between the amount of plaque and MACE when there are high levels of LDL-C. However, this connection becomes limited whenever LDL-C levels are very low. The present study intends to strengthen the existing information by investigating the correlation between

elevated Lp(a) levels and CAD in persons with varying LDL-C levels, with a specific emphasis on those with LDL-C less than 1.4 mmol/L. The study intends to elucidate the intricate relation between Lp(a) and CAD, particularly in connection to diverse LDL-C profiles.

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2. Methods

2.1 Study Population

The study included a thorough examination of 100 patients who were diagnosed with ACS, including UA, NSTEMI, and STEMI at the Cardiology department of BSMMCH in Faridpur, Bangladesh. The study was conducted between January 1 and December 31, 2019. Standard drugs were administered to all patients in accordance with national guidelines. A regimen of dual antiplatelet medication was prescribed, comprising of 100 mg of aspirin and either 75 mg of clopidogrel or 180 mg of ticagrelor. This therapy was to be followed for at least 12 months. The recommendation also included lifelong administration of a single antiplatelet treatment, consisting of either 100 mg of aspirin. LLT consisted of administering 10 mg of rosuvastatin to all patients. Additionally, ezetimibe was introduced if the initial LDL-C level was above 3.4 mmol/L. Additional medicines were provided at the judgement of the attending physician for each individual patient.

The exclusion criteria for this study were:

1. Patient discontinuation or unauthorized changes to the medication during the follow-up period.
2. Significant fluctuations in LDL-C levels during the follow-up.
3. Patients with a history of coronary artery bypass grafting.
4. Patients exhibiting severe renal function deficiency.
5. Patients with an approximate survival time of less than 3 years.

Figure 2 depicts the study's flow chart. Following a period of observation, 22.2% encountered MACE, while 12.5% suffered from ACE. The study establishes a consistent and non-linear relationship between Lp(a) and the risk of CAD. Once a specific threshold is surpassed, the risk of CAD experiences a substantial and notable increase. Patients had been classified into two categories based on their Lp(a) levels at the 1-month follow-up: a low-Lp(a) group and a high-Lp(a) group. The participants were then separated into subgroups based on their LDL-C levels at the 1-month follow-up. Subgroup S1 consisted of participants with LDL-C levels higher than or equal to 1.8 mmol/L, subgroup S2 consisted of participants with LDL-C between 1.4 and 1.8 mmol/L, and subgroup S3 consisted of participants with LDL-C less than 1.4 mmol/L. This approach enabled an in-depth investigation of the interactions between Lp(a), LDL-C, and the risk of CAD in multiple groups of patients.

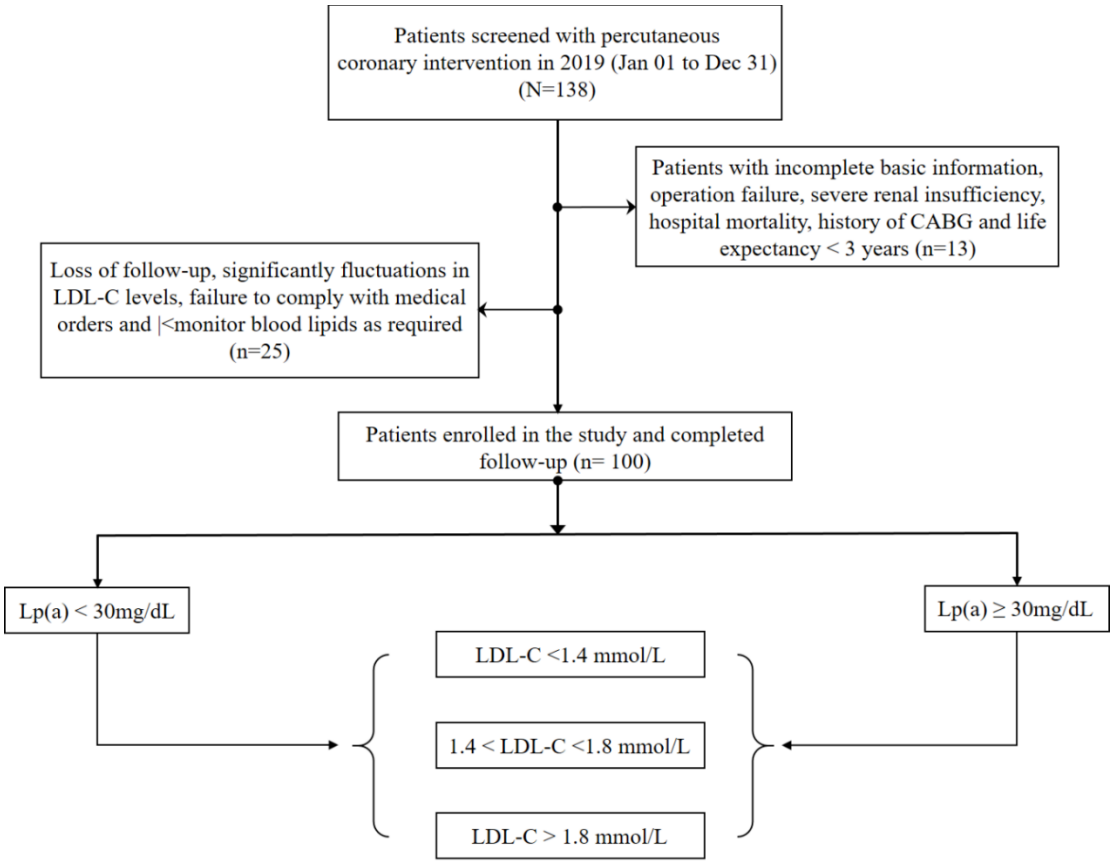

Figure 2. Process of study selection

2.2 Data collection

This study executed a successive sampling approach to choose participants. Each participant willingly and knowingly provided consent in writing. Previous information was acquired, and clinical evaluations were conducted utilizing standard clinical methods. Comprehensive demographic profiles, including age and significant risk factors like diabetes, hypertension, previous CHD, and family history of CHD, were carefully documented. The body height was measured in the standing position without shoes. The study obtained information on the subjects' body height and weight, and measured their waist circumference at the position halfway between the lower edge of the ribs and the highest point of the hipbone, while the subjects were standing and had finished exhaling. Using aseptic procedures, a 5 ml fasting blood sample was collected from patients while they were seated, with little use of a tourniquet. On the day of blood collection, we analyzed the fasting lipid profile, serum Lp(a), and fasting plasma glucose. The procedure of coronary angiography was conducted using percutaneous either femoral or radial methods. Coronary angiograms were acquired for each coronary vessel using at least two projections. Proficient interventional cardiologists at the hospital laboratory performed visual examination of the coronary angiograms.

For a period of 36 months following PCI, patient follow-up was performed utilizing outpatient and inpatient records, as well as telephone communications, to monitor compliance with medications, blood lipid control, and endpoint events. A meticulous record-keeping system was implemented to guarantee a comprehensive assessment of patients' medical condition and commitment to treatment. Routine outpatient follow-up was provided to all patients, with particular emphasis on conducting repeated lipid measurements within the initial month following discharge. During the post-discharge follow-up period, a minimum of two blood lipid measurements were performed on each patient. By employing this methodology, ongoing evaluation of lipid concentrations was possible, guaranteeing efficient control and prompt intervention, if required, to enhance patient results subsequent to PCI.

2.3 Statistical Analysis

The descriptive statistical methods were employed to provide a summary of the data, providing the average values, and the proportions for distinct variables. The categorical variables were represented as total cases and examined using either the Fisher's exact test. The means along with their standard deviations were reported as mean SD and were subjected to analysis using variance analysis. Continuous variables that have a distribution that is not normal were demonstrated as the median and assessed using nonparametric tests. Comparison of event-free survival between groups was conducted using Kaplan-Meier curves. The study utilized Cox proportional hazards models to measure HR and the level of $p < 0.05$ was deemed to have statistical significance. The statistical method employed facilitated a thorough examination of the study data, encompassing an evaluation of both descriptive features and survival results.

3. Results

3.1 Baseline Characteristics

Table 1 provides a concise overview of the fundamental attributes of the individuals involved in the study. The mean age of the participants in the study was 60.0 ± 8.8 years, with 66 male individuals (65.8%). TC, LDL-C, and HDL-C levels were greater in the high-Lp(a) catagory compared to the other one. The high-Lp(a) group exhibited higher creatinine levels, a greater percentage of females, and total coronary occlusion. There was insignificant differences in other attributes among these two categories.

Table 1: Attributes of the study population

Factors	Low - Lp (a) (n = 71)	High - Lp (a) (n = 29)	P
Age (years)	60 ± 8.80	63.10 ± 8.46	0.115
Male (cases, %)	43 (65%)	23 (35%)	0.018
BMI (kg / m²)	24.19 ± 3.00	24 34 ± 3.38	0.878
Systolic pressure (mmHg)	125.43 ± 13.33	129.88 ±15.36	0.116
Diastolic pressure (mmHg)	68.92 ± 10.17	69.03 ± 9.68	0.91
Current smokers	5	3	0.447
Hypertension history	53	16	0.186
Diabetes history	22	14	0.404
Family history	6	2	0.418
Creatinine (μmol / L)	85.99 ± 16.71	90.87 ± 22.01	0.033
Baseline lipids levels			
TC (mmol / L)	4.34 ± 1.19	4.70 ± 1.09	0.001
LDL - C (mmol / L)	2.53 ± 0.98	2.88 ± 0.85	0.003
HDL - C (mmol / L)	1.15 ± 0.28	1.24 ± 0.28	0.001
Lp (a) (mg / dL)	10.0 (70-14.0)	42.0 (28.0-74.0)	< 0.001
Post-discharge treatment			
Statins	71	29	1
Ezetimibe	5	2	0.25
Aspirin	71	29	1
Clopidogrel	56	23	0.987
Ticagrelor	15	6	0.987
Pre-endpoint prescription drugs			
Statins	71	29	1
Ezetimibe	4	2	0.532
Dual antiplatelet therapy	6	4	0.124
Aspirin	6	4	1
Clopidogrel	4	3	0.489
Ticagrelor	2	2	0.489
Single antiplatelet therapy	58	20	0.124
Aspirin	58	21	0.579
Clopidogrel	8	5	0.579
Ticagrelor	0	0	

3.2 Endpoint Action

After an observational period of almost 3 years, 23 instances of MACE and 16 instances of ACE were documented. According to the data presented in **Table 2**, the incidents of both MACE and ACE was notably greater in the high-Lp(a) catagory relative to the lower one. Additional examination of MACE demonstrated that the frequencies of hospitalization associated with UA were elevated in the high-Lp(a) cohort. The combined incidents of cardiac mortality and MI was infrequent, and there seemed no statistically significant variations between these two groups. The results highlight the possible link among higher levels of Lp (a) and experiencing negative cardiovascular events during the observation period.

Table 2: Analysis of the frequency of endpoint events in groups with high and low Lp(a)

Endpoint events	Low-Lp(a) (n=71)	High-Lp(a) (n=29)	P
Major adverse cardiovascular events (MACE)	14	9	0.003
Cardiac death	2	1	0.633
Ischemic stroke	4	3	0.226
Hospitalization related to UA	6	5	0.026
Unplanned coronary revascularization	12	8	0.008
Acute coronary events (ACE)	9	7	0.006

3.3 The comparative CAD Risks Associated with Higher Lp(a) or LDL-C

Table 3 presents a concise overview of the hazard ratios linked to different established risk factors for CAD. The investigation demonstrates a notable correlation between increased concentrations of Lp (a) in the bloodstream and a higher susceptibility to cardiovascular events. Even when considering other established risk factors like high levels of LDL-C, those with higher levels of Lp(a) still exhibited a significantly greater risk of cardiovascular events in comparison to those with lower levels of Lp(a). The findings emphasize the potential significance of Lp(a) as a pivotal determinant in CAD, underscoring the imperative to incorporate it into the assessment and management of CAD.

Table 03: Predictors of CAD

Factors	Hazard Ratio	95% CI	P Value
Age	1.05	1.05-1.07	
Women	0.5	0.49-0.74	
Systolic blood pressure	1.05	1.01-1.02	<0.0001
Current smoking	1.65	1.29-2.12	
Diabetes mellitus	1.95	1.43-2.68	

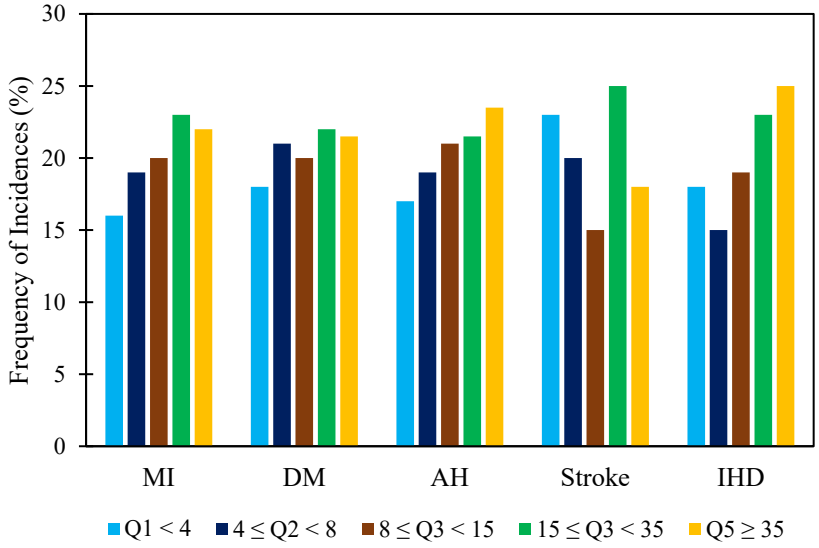

Figure 3. Diseases Frequency with respect to Lp(a)

3.4 Associations with CAD

Figure 3 illustrates the prevalence of CAD, AH, and DM across different quintiles of Lp(a) levels. The research establishes a clear and direct association with the Lp(a) and the incidence of MI, IHD, and AH. The frequencies of MI, IHD, and AH are displayed for both the lowest and highest quintiles. The prevalence rates of MI, IHD, and AH in the lowest quintile were 16.2%, 21.3%, and 21.9%. In comparison, the frequencies in the fifth quintile were 20.9%, 25.3%, and 22.5%. There was no notable correlation seen between Lp(a) and stroke or DM. This suggests a pattern in which higher Lp(a) is linked with more frequent occurrences of MI, IHD, and AH, highlighting the possible contribution of raised Lp(a) to the onset of these cardiovascular diseases.

3.5 CAD Risk Associated with Lp(a) of Different Ethnic Groups

The literature widely recognizes the existence of racial disparities in Lp(a) levels, apo(a) isoforms, and LPA SNPs (Clarke R, Peden JF, Hopewell JC, 2009; Pia R. Kamstrup MD, PhD, Børge G. Nordestgaard MD, 2013). Here kringles are structural domains found inside the Lp(a) molecule, notably in the apo(a) component. **Figure 4** illustrates that persons of African heritage exhibit the highest levels of Lp(a), followed by South Asians, Caucasians, Hispanics, and East Asians in a general sense. The observed variations are most likely a result of the geographical dispersion of the LPA gene from Africa, followed by subsequent alterations in genetic structure. The LPA gene underwent a process of duplication from the plasminogen gene and experienced expansion in the human population over the course of the past 3 million years.

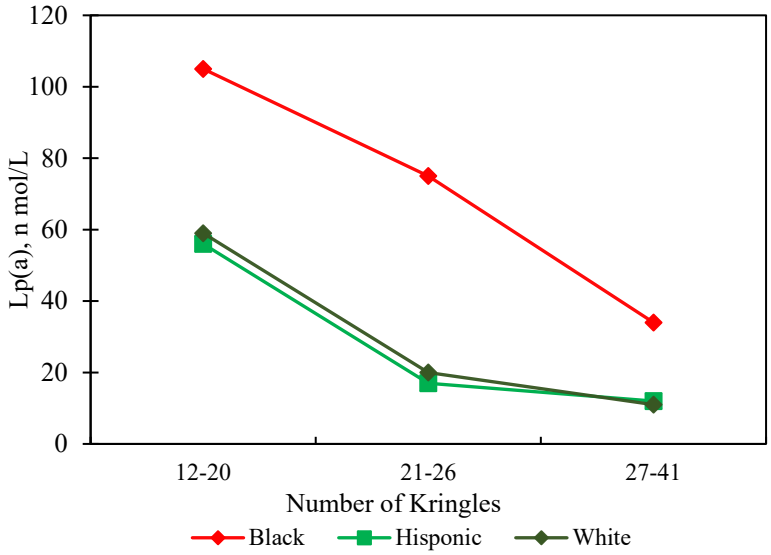

Figure 4. Differences in Lp(a) with respect to ethnic groups

The study has confirmed that higher Lp(a) is an independent risk factor for CAD in all racial groups examined till now (Tsimikas S, Clopton P, Brilakis ES, 2009). In the ARIC study, which lasted for 20 years and included 3,467 black and 9,851 white participants, it was found that levels of Lp(a) were similarly linked to CAD events in both racial communities. This association was observed despite black subjects having a wider range of Lp(a) levels relative to white subjects. Nonetheless, the differing occurrence of higher Lp(a) among different racial groups can lead to variations in the overall clinical presentation of the disease and its occurrence in relation to other risk factors.

3.7 Interrelation of Lp(a) with controlled LDL-C as potential risk factor

In the past, findings from studies on the development of angiography have led to the conclusion that Lp(a) is no longer considered a risk factor while LDL-C is properly managed. Therefore, many medical professionals assumed that the best course of action when faced with high levels of Lp(a) was to focus on reducing increased LDL-C. Nevertheless, current research contradicts this presumption, indicating that increased Lp(a) continues to be a risk factor who attain LDL-C levels less than 70 mg/dl. (Khera AV, Everett BM, Caulfield MP, 2014). Moreover, the principle of decreasing benefits is apparent in LDL-C lowering efficacy studies, where the initial LDL-C levels are frequently below 100 mg/dl, although the actual reduction in risk is minimal. In the IMPROVE-IT (Cannon CP, Blazing MA, Giugliano RP, 2015), after 6 years of follow-up, the risk of MACE was 33.8% in the group that had ezetimibe and achieved a LDL-C level of 54 mg/dl. This was compared to a MACE rate of 34.8% in the group that received simvastatin alone and gained an LDL-C level of 70 mg/dl. Although the outcome is praiseworthy, a 32.7% recurring hard MACE rate with an LDL-C level of 54 mg/dl indicates that targeting LDL-C alone may not be the most effective approach to reducing occurrences, especially when using PCSK9 inhibitors. The most recent findings from the AIM-HIGH (Albers JJ, Slee A, O'Brien KD, 2013), JUPITER (Khera AV, Everett BM, Caulfield MP, 2014), and LIPID (Nestel PJ, Barnes EH, Tonkin AM, 2013) trials demonstrated that a part of the remaining threat is associated with significantly higher Lp(a) with controlled LDL-C. This highlights the significance of recognizing and dealing with increased Lp(a) as a separate threat, even when LDL-C is being managed.

Table 4: Representation of Higher Risk of Events in Patients With Elevated Lp(a) and on Statin Therapy in the AIM-HIGH, LIPID, and JUPITER trials

Study Name	N	Baseline 4th Quartile Lp(a) (mg/dL)	Achieved LDL-C (mg/dL)	Odds Ratio (95% CI)	P-Value
AIM HIGH - Niacin group	1427	->50	65.2	1.90 (1.33 - 2.72) 65.2	0.001
LIPID - Pravastatin group	7863	>73.7	112.5	1.23 (1.09 - 1.40) 112.5	<0.001
JUPITER - Rosuvastatin group	3877	->21	55	1.71 (0.99 - 2.95) 55	0,06
Overall	13167	54.9 (weighted value)	89.1 (weighted value)	1.61 (weighted value)	

4. Promising therapeutic approaches to minimize Lp(a)

Initial studies explored mipomersen, an ASO inhibiting apoB mRNA, as a potential way to Lp(a) and OxPL-apoB in transgenic Lp(a) (Merki E, Graham MJ, Mullick AE, 2008). The method involved a substantial decrease in apoB synthesis, limiting Lp(a) assembly, without affecting apo(a) production. Clinical trials confirmed a 25% reduction in Lp(a) with mipomersen (Santos RD, Raal FJ, Catapano AL, 2015). Subsequently, ASOs specific to apo(a) for human trials demonstrated dose-dependent reductions in mean Lp(a) by over 80%. An advanced ASO, IONIS-APO(a)-LRx, designed for selective hepatocyte uptake, achieved substantial Lp(a) reductions (66% to 92%, up to 99% in some patients) and also reduced OxPL. This suggests that ASOs, particularly IONIS-APO(a)-LRx, hold promise for effectively reducing Lp(a) levels and mitigating associated cardiovascular risks.

5. Conclusion

Elevated Lp(a) levels are linked with repeated CAD, particularly in the presence of higher LDL-C levels. Nevertheless, it should be acknowledged that this correlation might differ in cases where LDL-C are exceptionally low. Patients who have both LDL-C values of 1.4 mmol/L or more and higher Lp(a) levels should be recognized as highly risky group. These patients necessitate extra interventions to lower LDL-C. Therefore, it is recommended that Lp(a) can be used as an alternative noninvasive diagnostic technique to forecast the degree of coronary artery blockages, thus allowing for its use before considering more invasive procedures. The study recommends that assessing Lp(a) levels can be beneficial in determining the risk level and planning personalized treatment, especially for individuals with distinct LDL-C and Lp(a) profiles. Furthermore, the request for future randomized studies emphasizes the necessity for more study to determine whether reducing Lp(a) levels can offer extra advantages in preventing cardiovascular events, particularly in individuals who have reached their LDL-C goals. This highlights the changing nature of cardiovascular risk evaluation and the significance of taking into account several indicators, such as both LDL-C and Lp(a), when providing treatment.

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