Research Article

CORRELATION OF LIPOPROTEIN(a) AND CORONARY ARTERY DISEASES

Healthcare

Keywords: Lipoprotein (a), atherosclerosis, Cardiovascular Arterial Diseases (CAD), lipid profile.

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Abstract

INTRODUCTION: Cardiovascular diseases (CVD) continue to be one of the leading causes of mortality worldwide. While factors such as diabetes, sedentariness, psychostress, genetic predisposition, hypertension, smoking, and hyperlipidemia are well-known in the etiology of atherosclerosis (Ath) of coronary arteries. Recent studies have also identified high concentrations of lipoproteins (a) [Lp(a)] as a risk factor. In fact, high concentrations of Lp(a) above 30mg/dl (reference value-30mg/dl) have been found to be a risk factor for Ath, leading experts to develop medications aimed at reducing Lp(a) concentrations and preventing atherosclerotic manifestations. *The European Atherosclerosis Society* has also released clinical guidelines for testing and treating high concentrations of Lp(a) as part of the global assessment of cardiovascular risk.

THE GOAL OF THE STUDY: The goal of this study is to investigate the concentration of Lp(a) in patients with coronary disease and its connection to the presentation of atherosclerosis of the coronary arteries in patients with CVD compared to a control group of healthy individuals. Through this study, we hope to gain a better understanding of the role of Lp(a) in CVD and its potential as a target for prevention and treatment. By identifying and addressing risk factors like high Lp(a) concentrations, we can work towards reducing the global burden of CVD and improving health outcomes for individuals around the world.

THE AIM OF THE STUDY: The aim of this study is to determine the concentration of lipoprotein(a) in patients with coronary disease, its connectivity and role in the presentation of atherosclerosis of the coronary arteries in patients with CVD compared to the control group of healthy individuals.

MATERIAL AND METHODS: As working material, the blood taken from the vein of patients with coronary disease was used - N0=80, (with an identical average age of 55.70±6.00 years old, of which 35 were female while 45 were male. In the study, there was also a control group: N0=80 healthy volunteers (45 were male and 35 female) with the same age as the patients. Blood for analysis was taken at 8 o'clock in the morning, at room temperature of 19-24°C, every three months in a period of 12 months.

Echocardiography and EKG were also performed on all the patients with Toshiba SSH-140A machine, color Doppler probe 3.7Hz, sectorial type, taking into account as key parameters the thickness of the back wall of the left ventricle and the thickness of-Left ventricular internal diameter end diastole (LVPVd) and interventricular septal end diastole (IVSd>12 mm). Together with the examination of Lp(a) concentrations, the lipid profile was also analyzed. The analyzes were done at the Clinical Laboratory Institute at the University Clinical Center of the Faculty of Medicine – Skopje, North Macedonia.

STATISTICAL PROCESSING OF THE MATERIAL: From the statistical methods, arithmetic mean value, standard deviation X±SD were used. The comparative statistics of the lipid parameters between the analyzed groups were analyzed with students 't' dependent and independent samples according to the Mann-Whitney U-test and Wilcoxon - test. The results of the lipid fractions will be shown tabularly (see table 3) with the statistical program SPSS V26.

RESULTS: The obtained values of lipids (Col.Total, TG, HDL-ch, LDL-ch) and lipoprotein (a) in both groups are presented with mean values and standard deviation X-SD. Due to the fact that in the obtained results of Lp(a) in both sexes, in patients with coronary disease, we did not notice any significant difference, we will present them as common for both groups, with CVD with maximum values of 78.00-16,00 mg/dl while in the control group =15.20-4.30 mg/dl, with a statistically significant difference with $p<0.000$. The same difference was found from the obtained results of lipid concentrations between the two groups with $p<0.0001$ (as presented in the tables below).

CONCLUSION: The results obtained in the paper proved that high concentrations of Lp(a) > 30 mg/dl are risk factors for the occurrence of Ath of the coronary arteries and that these patients are at a 5-8 times higher risk for the development of Ath of coronary arteries, compared to individuals with normal Lp(a) values, therefore the treatment of high concentrations of Lp(a) should be started at the beginning of their appearance. In conclusion, we can suggest that the adequate treatment of high Lp(a) concentrations and the balancing of the lipid profile can apparently affect the prevention of atherosclerotic processes of the coronary arteries, therefore we prefer that in individuals with a history of CAD and those with coronary disease, the examination of Lp(a) and lipid profile should be one of the initial examinations during the management of patients with CAD.

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INTRODUCTION

The first research on Lp(a) was done by Kare Berg with his co-authors (Gösta Dahlen and Martin Frick) in 1963, who verified that high levels of Lp(a) are associated with CVD (Fless GM et al. 1985, Krempler F et al. 1980, Rader DJ et al. 1993). Initially, values of Lp(a)>30, mg/dl were considered to be the risk assessment for myocardial infarction, a value which is still approved in numerous epidemiological studies. Despite all these activities, still for scientists Lp (a) remains very enigmatic especially in terms of its function and metabolism. Therefore, many multicenter studies are needed to accurately draw conclusions on the atherogenicity of Lp(a). High concentrations of Lp(a) in patients with coronary disease, combined with other risk factors (high concentrations of LDL-ch-atherogenic (holesterol, isatherogenic and contributes to the development of atherosclerosis, increasing the risk of heart disease and stroke), high values of triglycerides, low values of HDL-ch and apolipoprotein-B100 significantly increase the risk of CVD. According to its characteristics and content, Lp(a) is still an enigmatic cell in the class of apoprotein(a) (Nordestgaard BG, Chapman MJ, Ray K, et al.). Since the 2010 *European Atherosclerosis Society (EAS)* consensus statement, knowledge about the role of lipoprotein (a) [Lp(a)] in CVD has prompted the development of new drugs that specifically lower Lp(a) levels. In addition to this preference, the guidelines of the *American Cardiology Association* recommend the measurement of Lp(a) to assess the risk of coronary atherosclerosis. Drugs such as statins, Niacin do not show the expected effects on reducing Lp(a) concentrations, but new drugs such as: the inhibitor proprotein convertase subtilisin/kexin type 9 (PCSK9), and the antisense oligonucleotide for apo(a), adenosine-triphosphate-citrate-lyase inhibitor, 2-azetidione, have shown high efficacy in reducing high concentrations of Lp(a) and LDL-ch. Despite medicinal and therapeutic advances in the prevention of coronary atherosclerosis (Ath), the risk from high concentrations of Lp(a) still remains an important and intriguing challenge for experts in this disease (Maranhão RC et al. 2014, M. Bihari Warga et al. 1992, Wilson DP et al. 2019).

MATERIAL AND METHODS

As working material, the blood taken from the vein of patients with coronary disease was used - N0=80, (with an identical average age of 55.70±6.00 years old, of which 35 were female while 45 were In the study, there was also a control group: N^0=80 healthy volunteers (45 were male and 35 female) with the same age as the patients. Blood for analysis was taken at 8 o'clock in the morning, at room temperature of 19-24^{0}C, every three months in a period of 12 months. Echocardiography and EKG were also performed on all the patients with Toshiba SSH-140A machine, color Doppler probe 3.7Hz, sectorial type, taking into account as key parameters the thickness of the back wall of the left ventricle and the thickness of-Left ventricular internal diameter end diastole (LVPVd) and interventricular septal end diastole IVSd>12mm. Together with the examination of Lp(a) concentrations, the lipid profile was also analyzed. The analyses were done at the Clinical Laboratory Institute at the University Clinical Center of the Faculty of Medicine – Skopje, North Macedonia.

STATISTICAL PROCESSING OF THE MATERIAL

From the statistical methods, arithmetic mean value, standard deviation X±SD were used. The comparative statistics of the lipid parameters between the analyzed groups were analyzed with students "t" dependent and independent samples according to the Mann-Whitney U-test and Wilcoxon- this test. The results of the lipid fractions will be shown tabularly and graphically (table 3) with the statistical program SPSS V26.

RESULTS

The obtained values of lipids (Col.Total, TG, HDL-ch, LDL-ch) and lipoprotein (a) in both groups are presented with mean values and standard deviation X±SD. Due to the fact that in the obtained results of Lp(a) in both sexes, in patients with coronary disease, we did not notice any significant difference, we will present them as common for both groups, with CVD with maximum values of 78.00±16,00 mg/dl while in the control group=15.20±4,30 mg/dl, with a statistically significant difference with p<0.000. The same difference was found from the obtained results of lipid concentrations between the two groups with p <0.0001 (presented in the tables below).

Table 1 Distribution of patients and the control group according to gender and average age

Total number-80	**Mean age±DS**
Female-35	55,70± 6,00 years
Male-45	55,70± 6,00 years
Control group-80	54,60± 5,20 years

The obtained values of lipids (Col.Total, TG, HDL-ch, LDL-ch) and Lp(a) in both groups are presented with the mean values and standard deviation X±SD. Because the obtained results from the two groups of patients with CVD (F+M) were without any significant statistical difference, we will present them as common for both groups, with maximum values of 78.00±16.00 mg/dl, while in the control group=15.20±4.30 mg/dl, with a statistically significant difference with p<0.0001. Even from the obtained results of lipid concentrations between the two groups, significant differences were observed with p<0.000.

Table 2 Concentrations of Lp(a) according to the etiology of CAD and the control group

Coronar Artery Disease	**Number of patients**	**Lp(a) mg/dl(F+M)**	**Lp (a) to the control group**
Acut Myocardial Infarct	35	79,00±19,00 mg/dl,	15.20 ± 4.30 mg/dl,
St.post Infarctum Miocardi	20	67,40±10,00 mg/dl,	15.20 ± 4.30 mg/dl,
Angina pectoris	10	75,00± 14,80 mg/dl,	15.20 ± 4.30 mg/dl,
Stented patient	10	63,00± 12,00 mg/dl,	15.20 ± 4.30 mg/dl,
Patients with CABP	5	69,00± 15,00 mg/dl,	15.20 ± 4.30 mg/dl,

The table itself shows that the concentration of Lp(a) in patients with various coronary diseases is significantly higher compared to the values obtained for the control group with a significant statistical difference for p=0.0001.

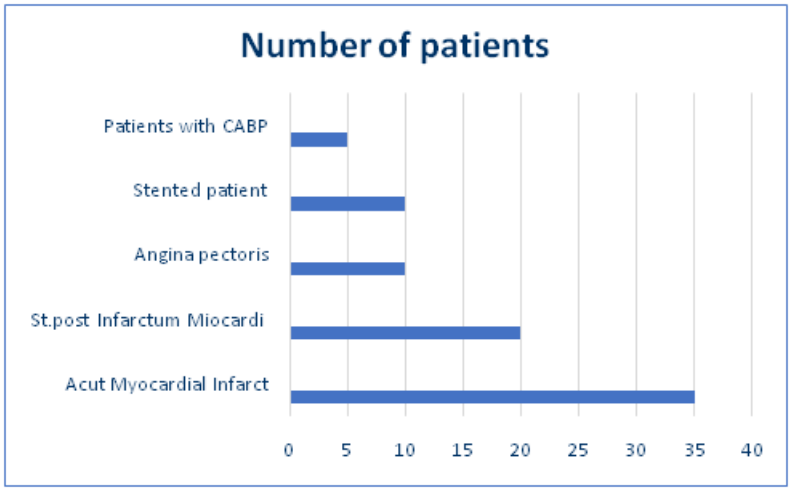

Figure 1. Concentration of Lp(a) in number of patients with various coronary diseases

Table 3 Concentrations of Lp(a), lipid profile (ChT, TG, HDL-ch, LDL-ch) and the control group according to the etiology of CVD and the control group.

	Number	ChT mmol/I	TG mmol/I	HDL-chmmol/I	LDL-ch	Lp(a) mg/dl
Patient with CAD	80	5,80±1,60	2,90± 0,50	0,98 ±0,60	4,20±1,60	78,00±16,00 ↑↑
Control group	80	5,60±1,00	1,20±0,50	1,37 ±0,72	2,70±0,50	15,20 ± 4,30
p		0.8600	0.0001	0.0001	0.0001	0.0001
Patient with CAD	80	5,80±1,60	2,90± 0,50	0,98 ±0,60	4,20±1,60	78,00±16,00 ↑↑

From table number 3, a significant difference can be observed for the analyzed parameters of the lipid profile with the values obtained from patients with CAD with a significant statistical difference for *p*=0.0001, except for total cholesterol, where the difference was not significant for *p*=0.8600, results which are also compatible with the findings of many studies by the authors cited in the text.

DISCUSSION

A large number of clinical studies have verified that increased levels of Lp(a) are an independent risk factor for the development of atherosclerosis of the coronary arteries and CVD, and in particular, the risk increases even more if they are accompanied by an increase in LDL-ch, TG and reduction of HDL-ch. (Danesh J et al. 2000, Luc G et al. 2002, Seman LJ et al. 1999, Eckardstein A et al. 2001). A meta-analysis of 5436 CKD subjects from 27 prospective studies concluded that individuals with Lp(a) concentrations 1/3 above normal values were 70% more likely to develop (CAD) than those individuals with values lower than 1/3.

From this point of view, it is preferable that the modifying risk factors are treated aggressively in these patients. In the concentration of Lp(a) between the sexes there is a difference of ~5-10%, higher in women than in men. The exact mechanism of the influence of Lp(a) on the development of atherosclerosis is still unknown, but the atherogenic potential of Lp(a) is based on the similarity of the structure of Lp(a) to LDL-ch. Many studies on the atherogenic effect of Lp(a) have verified that high values of Lp(a) are a new risk factor for atheromatosis and recurrent restenosis in stented cases, CABP-coronary artery bypass graft and after Percutaneous Coronary Angioplasty (PTCA-Percutaneous Transluminal Coronary Angioplasty; coronary artery balloon angioplasty). Lp(a) is a particle that contains two different elements: the first element is an LDL-like particle that contains a particle of apolipoprotein B-100 (apoB-100), which is insoluble in water, and apolipoprotein (a) [or(a)].

The liver and kidney are the main organs where apo(a) is synthesized and which clear Lp(a) from circulation. The mode of catabolism of Lp(a) remains precisely undiscovered. But kinetic studies in humans have revealed that the catabolism of Lp(a) was slower than that of LDL, regardless of Lp(a) concentration. Recent studies have verified that patients with Lp(a) concentrations ≥ 58.6 mg/dL have progression of heart valve stenosis (Andrea Pasta et al. 2020, Scipione CA et al. 2018, Kraft HG et al. 1989, Rader D et al. 1994, Rader DJ et al. 1995, Florian Kronenberg et al. 2022). High levels of Lp (a) are associated with macrocalcifications of coronary, cerebral and peripheral arteries. With the prevalence of CVD predicted to increase dramatically by 2050 by >300%, this despite affecting ≈1.4 billion people worldwide, the impact of high Lp(a) concentrations on cardiovascular risk remains underestimated. Impaired renal function may increase levels, possibly due to increased hepatic synthesis of Lp(a) caused by loss of protein in the urine, particularly in nephrotic syndrome or peritoneal dialysis or impaired catabolism. The production and concentration of Lp(a) is low during hepatic damage because it is produced in the liver, so it is easy to understand because the level of Lp(a) is low during hepatic damage. Given that the risk associated with particle-based Lp(a) may exceed that of LDL (Van der Valk FM et al. 2016, Garg PK, Guan et al. 2021, Kaiser Y et al. 2022, Bouchareb R et al. 2015), Lp(a)-mediated cell signaling effects rather than Lp(a) accumulation per se may contribute mainly to atherogenicity. With the prevalence of Ath presentation in coronary arteries and their early stenosis, the number of patients with cardiovascular disease is predicted to increase dramatically until the year 2050 by >300%) before the early detection of Lp concentrations (a) and adequate treatment remains an urgent need. Treatment with protein convertase subti-lisin/kexin type 9 (PCSK9) inhibitors, antisense oligonucleotide (ASO), IONIS-APO(a)Rx and AKCEA-APO(a)-LRx (ISIS 681257), a second generation that increase levels of the LDL receptor, preventing its degradation, that affect the reduction of the level of Lp(a) and the reduction of LDL-ch up to 30-80%, remain the most preferred drugs (Ginsberg HN et al. 2014, Watts GF et al. 2018, Reyes-Soffer Get al. 2017, Tsimikas S. 2019). Other agents besides Niacins in reducing high concentrations of Lp(a) are also L-carnitine, Tocopherol, L-lysine and ascorbite (3g/day of each).

CONCLUSION

This study proved that high concentrations of Lp(a) > 30 mg/dl are risk factors for the occurrence of Ath of the coronary arteries and that these patients are at a 5-8 times higher risk for the development of Ath of coronary arteries, compared to individuals with normal Lp(a) values, therefore, the treatment of high concentrations of Lp(a) should be started at the beginning of their appearance.Consequently, we can suggest that the adequate treatment of high Lp(a) concentrations and the balancing of the lipid profile can apparently affect the prevention and prevention of atherosclerotic processes of the coronary arteries. In our opinion, the examination of Lp(a) and lipid profile should be one of the initial examinations during the management of patients with CAD and those who have coronary disease.

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COMPETING INTERESTS

All authors declare that they have no competing interests.

REFERENCES

Andrea Pasta, Anna Laura Cremonini, et al. PCSK9 inhibitors for treating hypercholesterolemia 2020 Feb; 21(3): 353-363. Expert opin Pharmacoter. 2020 Feb; 21(3): 353-363. https://doi.org/10.1080/14656566.2019.1702970 [Google Scholar] [PubMed]

Berg K., Dahlen G., and Frick M. H. Lp(a) lipoprotein and pre-β1 lipoprotein in patients with coronary heart disease. Clin. Genet. 1974. 6: 230-235. https://doi.org/10.1111/j.1399-0004.1974.tb00657.x [Google Scholar] [PubMed]

Berg K. A new serum type system in man–the Lp system. Acta Pathol.Microbiol. Scand. (1963), 59: 369-382. https://doi.org/10.1111/j.1699-0463.1963.tb01808.x [Google Scholar] [PubMed]

Bouchareb R, Mahmut A, Nsaibia MJ et al. Autotaxin derived from lipoprotein(a) and valve interstitial cells promotes inflammation and mineralization of the aortic valve; Circulation, 2015; 132: 677–690. https://doi.org/10.1161/CIRCULATIONAHA.115.016757 [Google Scholar] [PubMed]

Danesh J, Collins R, Peto R. Lipoprotein(a) and Coronary Heart Disease. *Meta-Analysis Of Prospective Studies*. Circulation. 2000; 102: 1082-1085. https://doi.org/10.1161/01.CIR.102.10.1082 [Google Scholar] **[**PubMed**]**

Fless GM, ZumMallen ME, Scanu AM. Isolation of apolipoprotein(a) from lipoprotein(a). J Lipid Res, 1985; 26: 1224-1229. https://doi.org/10.1016/S0022-2275(20)34270-X [Google Scholar] **[**PubMed**]**

Florian Kronenberg, Samia Mora et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. *European Heart Journal*, Volume 43, Issue 39, 14 October 2022, Pages 3925-3946. https://doi.org/10.1093/eurheartj/ehac361 [Google Scholar] [PubMed]

Garg PK, Guan W, Karger AB. Lipoprotein (a) and risk for calcification of the coronary arteries, mitral valve, and thoracic aorta: the multi-ethnic study of atherosclerosis.J Cardiovasc Comput Tomogr. 2021; 15: 154–160. https://doi.org/10.1016/j.jcct.2020.06.002 [Google Scholar] [PubMed]

Ginsberg HN, Stein EA. Effect of alirocumab, a monoclonal proprotein convertase subtilisin/kexin 9 antibody, on lipoprotein(a) concentrations (a pooled analysis of 150 mg every two weeks dosing from phase 2 trials). Am J Cardiol, 2014; 114: 711-715. https://doi.org/10.1016/j.amjcard.2014.05.060 [Google Scholar] [PubMed]

Jennie Olopaade, Pharm D, RPH. Pietrangelo PCSK9 Inhibitors: What September 1, 2021. [Crossref]

Kaiser Y, Daghem M, Tzolos E, et al. Association of Lipoprotein(a) With Atherosclerotic Plaque Progression. J Am Coll Cardiol. 2022 Jan, 79 (3) 223–233. https://doi.org/10.1016/j.jacc.2021.10.044 [Google Scholar] [PubMed]

Kraft, H. G., Menzel, H. J., Hoppichler, F., Vogel, W., & Utermann, G. (1989). Changes of genetic apolipoprotein phenotypes caused by liver transplantation. Implications for apolipoprotein synthesis. *The Journal of clinical investigation*, *83*(1), 137-142. https://doi.org/10.1172/JCI113849 [Google Scholar] [PubMed]

Krempler, F., Kostner, G. M., Bolzano, K., & Sandhofer, F. (1980). Turnover of lipoprotein (a) in man. *The Journal of clinical investigation*, *65*(6), 1483-1490. https://doi.org/10.1172/JCI109813. [Google Scholar] **[**PubMed**]**

Luc G, Bard JM, Arveiler D, et al. Lipoprotein (a) as a predictor of coronary heart disease: the PRIME Study. Atherosclerosis. 2002; 163: 377-384. https://doi.org/10.1016/S0021-9150(02)00026-6 [Google Scholar] [PubMed]

Maranhão RC, Carvalho PO, Strunz CC, Pileggi F. Lipoprotein (a): structure, pathophysiology and clinical implications. Arq Bras Cardiol. 2014 Jul; 103(1): 76-84. https://doi.org/10.5935/abc.20140101 [Google Scholar] **[**PubMed**]**

McLean J.W., Tomlinson J.E. et al. cDNA sequence of human apolipoprotein(a) is homologous to plasminogen. *Nature*. 1987. 330: 132-137. https://doi.org/10.1093/eurheartj/ehq386 [Google Scholar] [PubMed]

M.Bihari Warga, G.Kostner, and A. Czinner. Lp(a) the risc of Coronarz Heart Disease.European Journal of Epidemiolgy 0392-2990, supl.1:1992, pp.33-35. https://doi.org/10.1007/BF00145347 [Google Scholar] **[**PubMed**]**

Nordestgaard BG, Chapman MJ, Ray K, et al. European Atherosclerosis Society Consensus Panel. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J. 2010 Dec; 31(23): 2844-53. https://doi.org/10.1093/eurheartj/ehq386 [Google Scholar] [PubMed]

Nordestgaard BG, Chapman MJ, Ray K et. Al. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J, 2010, 31; 2844-2853. https://doi.org/10.1093/eurheartj/ehq386 [Google Scholar] [PubMed]

Osnabrugge RLMylotte D, Head SJ et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol, 201; 62: 1002–1012. https://doi.org/10.1016/j.jacc.2013.05.015 [Google Scholar] [PubMed]

Rader DJ, Cain W, Zech LA, Usher D, Brewer HB., Jr Variation in lipoprotein(a) concentrations among individuals with the same apolipoprotein (a) isoform is determined by the rate of lipoprotein(a) production. J Clin Invest, 1993; 91: 443-447. https://doi.org/10.1172/JCI116221 [Google Scholar] **[**PubMed**]**

Rader DJ, Cain W, Ikewaki K, et al. The inverse association of plasma lipoprotein(a) concentrations with apolipoprotein(a) isoform size is not due to differences in Lp(a) catabolism but to differences in production rate. J Clin Invest, 1994; 93: 2758-2763. https://doi.org/10.1172/JCI117292 [Google Scholar] [PubMed]

Rader DJ, Mann WA, Cain W, et al. The low density lipoprotein receptor is not required for normal catabolism of Lp(a) in humans. J Clin Invest, 1995; 95: 1403-1408. https://doi.org/10.1172/JCI117794 [Google Scholar] [PubMed]

Reyes-Soffer G, Pavlyha M, Ngai C, et al. Effects of PCSK9 Inhibition with Alirocumab on Lipoprotein Metabolism in Healthy Humans. Circulation, 2017; 135: 352-362. https://doi.org/10.1161/CIRCULATIONAHA.116.025253 [Google Scholar] [PubMed]

Scipione CA, Koschinsky ML, Boffa MB. Lipoprotein(a) in clinical practice: New perspectives from basic and translational science. Crit Rev Clin Lab Sci. 2018 Jan; 55(1): 33-54. https://doi.org/10.1080/10408363.2017.1415866
[Google Scholar] [PubMed]

Seman LJ, DeLuca C, Jenner JL, et al. Lipoprotein(a)-cholesterol and coronary heart disease in the Framingham Heart Study. Clin Chem. 1999; 45: 1039-1046. https://doi.org/10.1093/clinchem/45.7.1039
[Google Scholar] [PubMed]

Tsimikas S, Stroes ESG. The dedicated "Lp(a)clinic": A concept whose time has arrived? *Atherosclerosis* 2020; 300: 1-9. https://doi.org/10.1016/j.atherosclerosis.2020.03.003
[Google Scholar] [PubMed]

Tsimikas S. Potential Causality and Emerging Medical Therapies for Lp(a) and Its Associated Oxidized Phospholipids in Calcific Aortic Valve Stenosis. Circ Res, 2019; 124: 405-415. https://doi.org/10.1161/CIRCRESAHA.118.313864
[Google Scholar] [PubMed]

Van der Valk FM, Bekkering S, et al.Oxidized phospholipids on lipoprotein(a) elicit arterial wall inflammation and an inflammatory monocyteresponse in humans. Circulation 2016; 134: 611, 624. https://doi.org/10.1161/CIRCULATIONAHA.116.020838
[Google Scholar] [PubMed]

von Eckardstein A, Schulte H, Cullen P, Assmann G. Lipoprotein(a) further increases the risk of coronary events in men with high global cardiovascular risk. J Am Coll Cardiol. 2001; 37: 434-439. https://doi.org/10.1016/s0735-1097(00)01126-8
[Google Scholar] [PubMed]

Watts GF, Chan DC, Somaratne R, et al. Controlled study of the effect of proprotein convertase subtilisin-kexin type 9 inhibition with evolocumab on lipoprotein(a) particle kinetics. Eur Heart J, 2018; 39: 2577-2585. https://doi.org/10.1093/eurheartj/ehy122
[Google Scholar] [PubMed]

Wilson DP, Jacobson TA, Jones PH, et al. Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association. J Clin Lipidol. 2019 May-Jun; 13(3): 374-392. https://doi.org/10.1016/j.jacl.2019.04.010
[Google Scholar] [PubMed]