The Journal of Cardiovascular Diseases
J Cardiovasc Dis 2022;18(2):72 - 76

REVIEW ARTICLE
DOI: 10.55958/jcvd.v18i2.89

ASSOCIATION OF LIPOPROTEIN a, A PREDISPOSING RISK FACTOR, FOR IN-STENT RESTENOSIS

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Date of Submission: 15-12-2021; Date of Acceptance: 03-02-2022; Date of Publication: 30-09-2022

ABSTRACT:

INTRODUCTION: *Elevated plasma lipoprotein (a) concentration is considered as a predisposing risk factor for cardiovascular disease and in-stent restenosis. Lipoprotein (a) is a lipoprotein with an LDL-like particle that contains Apo-lipoprotein B100 and is associated with cardiovascular complications. The most prevalent complication associated with percutaneous coronary intervention is in-stent restenosis.In-stent Restenosis affected 40% of all angioplasties in the pre-stent era, then 28% in the (BMS) era. Furthermore, the introduction of (DES) second generation and drug-coated balloons has further reduced restenosis rates to less than 10%. The aim of this review paper is to investigate the clinical association of Lipoprotein (a) concentration in the occurrence of in-stent restenosis. Our paper possesses some limitations Firstly, it does not explain how lipoprotein concentrations are established. Secondly, the mechanism underlying the lipoprotein (a) lowering effect of current therapy.*

KEY WORDS: *Lipoprotein a, in-stent restenosis, predisposing factor, Diabetes mellitus, Cardio-vascular disease.*

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Author's Contribution: KA: Inroducation, literature review, paper drafting. MAA: Review. MA: Study design. HUR: Paper drafting. KS: Literature review.

INTRODUCTION:

Cardiovascular complications are associated with the alteration in lipoprotein (a) concentration. Lipoprotein (a) is a plasma protein, consists of Apo B-100 and Apo-lipoprotein A and is attached through the Disulfide bridge.[1-3] This combination would competitively inhibit plasminogen binding in the thrombolytic system. Moreover, Apo A and Lp (a) both stimulate the proliferation of the smooth vessel walls of the muscles cells, which would raise their probable role in restenosis after coronary artery stenting.[1,3,4] Lp (a) plasma concentrations in humans range from 1 mg/dL to >100 mg/dL, with levels of >25 to 30 mg/dL considered as an increased risk of cardiovascular disease.[2,5] Genetically Lipoprotein (a) plasma concentration is determinedas an autosomal co-dominant characteristics.Lipoprotein concentration remains the same in each individual except for a patient with the acute myocardial infarction (AMI), peripheral vascular disease, venous thrombosis, vein graft stenosis and surgical operations and is not affected by the environmental conditions, age, gender, and diet.[1,6] Plasma Lp (a) concentrations are under genetic control and remain generally consistent throughout life. In the treatment of coronary artery disease, percutaneous coronary intervention (PCI) with stent implantation is commonly employed.[7,8]

High levels of Lipoprotein (a) in the body are considered as the predisposing factor for in-stent restenosis. Recent large population studies and meta-analyses have identified elevated lipoprotein concentration as a causal risk factor for heart disease, calcific aortic valve disease, and stent restenosis.[6,9,10] But according to some research, it has been found that plasma Lp (a) concentration is not a reliable predictor of restenosis following

Table-1. Factors associated with occurrence of in-stent restenosis		
Patient related responsible factors of ISR	**Lesion related responsible factor of ISR**	**Procedure related responsible factors of ISR**
• Age	• Complex lesion	• Stent type
• Gender	• Ostial lesion	• Stent overlap
• Diabetes mellitus	• Small vessels	• Stent under-expansion
• Genetic factor	• Multi-vessel (CAD)	• No. of stents and length

stent implantation. Histological analysis found that the formation of arterial plaque is strongly linked to high plasma Lp (a) concentrations. [6,10,11] As a result, Lipoprotein (a) might be involved in the repair of arterial damage. Horie and their colleagues showed that plasma Lp (a) concentrations dramatically lowered immediately after PCI.

Sometimes due to cardiovascular complications associated with coronary stents implantation, it fails to maintain cardiovascular patency, which cause the restenosis.Restenosis is a process of re-narrowing of the stented section that usually happens 3 to 12 months after the stent is placed. [12,13] It normally manifests as recurrent angina, but in around 10% of patients, it can manifest as acute myocardial infarction. The incidence rate of restenosis is high which is more or less to 50% in patients who undergo balloon angioplasty. [8] In-stent restenosis decreases the luminal diameter of the vessel by 50% in the stent area as it is considered as the "enemy" of interventional cardiologists. In-stent restenosis occurs when the section of an artery with a stent becomes blocked. In certain research analyses lipoprotein (a) was linked to a higher rate of restenosis, but not in others. [2,6,14] Technological advances in the last two decades reduce the occurrence of restenosis; first advancement is the development of bare-metal stents (BMS) then drug-eluting stents (DES), and in the last drug-coated balloons (DCB). The bare-metal stent (BMS) era has given way to the drug-eluting stent (DES) era. Drug-eluting stent being able to diminish in-stent restenosis (ISR) more effectively than a BMS. [5,12] In-stent restenosis (ISR) is estimated to be 30-40% in the BMS era. But in the drug eluting era, the in-stent restenosis rate is less than 10%(3). However, ISR, a significant consequence following successful coronary stenting, remains unsolved. [9,15]

RESPONSIBLE FACTORS FOR ISR:

Due to different clinical, angiographic, and operative factors the exact frequency of in-stent restenosis is not easy to determine. [5,16] But there are some responsible factors associated with the occurrence of ISR, as shown in Table 1.

PLASMA LIPOPROTEIN AND RISK OF RESTENOSIS AFTER PCI PROCEDURE

Previous research has looked into the association between plasma lipoprotein (a) concentration and the chance of inducing restenosis after percutaneous coronary intervention. And these studies discovered that the plasma Lipoprotein (a) level is an independent predisposing factor for in-stent restenosis. [10-12,15] However, other research studies were unableto explain the link between lipoprotein (a) association with the occurrence of in-stent restenosis. PCI with stent implantation can successfully enlarge a stenotic coronary artery lumen; nevertheless, there are various disadvantages to this procedure, one of which is ISR.The stent functions as a stimulator throughout the implantation process, causing local vascular inflammation, platelet activity, and the creation of mural thrombus. [2,10,11,17] This process causes smooth muscle cell proliferation to be stimulated and contributes to the occurrence of in-stent restenosis. According to certain studies, plasma Lipoprotein (a) concentration is more in patients suffering from in-stent restenosis. Access lipoprotein (a) concentration accumulates in artery walls at damage locations and inhibits cell surface plasminogen activation, resulting in plasmin production and TGF-b, a smooth muscle cell proliferation inhibitor, being significantly reduced. [11,18] A limited number of studies explain the association between lipoprotein A and ISR after stenting. Hence it is not possible to explainthe exact cut-off value of restenosis after stent implantation. Due to appropriate evidence from earlier studies, lipoprotein (a) best describes the risk of in-stent restenosis. But depending on the patient disease historythe relationship between elevation in plasma Lp (a) concentration and the possibility of developing ISR may differ.[19, 20]

ASSOCIATION OF LIPOPROTEIN a IN DIABETIC PATIENTS AND RISK OF ISR:

Lipoprotein (a) induced atherosclerosis in diabetic patients. Coronary artery disease plays a role in the onset and progression of stent restenosis (1SR).

However, it may be determined that poor diabetes control can worsen a patient's prognosis following coronary stenting. Its mode of action could be owing to a stimulatory effect of growth hormones causing an increase in neo-intimal hyperplasia. [6,17,21] The key cardiovascular risk variables such as age, sex, hypertension, and smoking in the development of restenosis following coronary artery stenting are still under debate. Some earlier studies explain the link between diabetes and restenosis and some others have not. But a large number of data support the association of lipoprotein (a) in the occurrence of stent restenosis in diabetic patients. After adjusting traditional risk factors, lipid profiles, angiographic factors, medical history, and other biomarkers, the VLDL-C level and UA level considered as thepredictors of in-stent restenosis in diabetic patients[22]. Although there was growing evidence that diabetes mellitus (DM) constituted a substantial key role in the development of ISR. [6,16,23] In comparison to non-diabetic individuals, diabetic patients appeared to have 2–4 times increased chance of developing ISR after PCI. The anatomy of coronary lesions in diabetic patients is more convoluted, with tiny and diffusely damaged arteries. Furthermore, patients with DM are more likely to have hypertriglyceridemia and systemic pro-thrombotic conditions due to platelet aggregation and coagulation system activation. [6,11,23] Overall, this renders diabetes patients a difficult population to treat with the disease.

LIPOPROTEIN (a) AND CARDIOVASCULAR DISEASE:

Numerous investigations have linked Lp (a) levels to cardiovascular disease.The incidence of aortic atherosclerosis as well as coronary artery disease, has considerably linked to Lp (a) serum levels. [4,15,19,20] Furthermore, higher Lp (a) values has been found to be linked with more tissue injury. Motta et al suggested that measuring Lipoprotein (a) values regularly in patients with coronary artery disease could help predict future acute vascular events. After percutaneous trans-luminal coronary angioplasty, bypass graft atherosclerosis and cardiac transplantation-related coronary atherosclerosis [24] lipoprotein (a) should be considered as a marker for restenosis.[8,11-13,20] Lipoprotein (a) screening test is not presently recommended for primary prevention for assessment of cardiovascular disease. According to recent recommendations, but it may be useful in patients with a strong family history of cardiovascular disease.

CORONARY STENT:ASIGNIFICANT MILESTONE IN INTERVENTIONAL CARDIOLOGY

The introduction of coronary stents constituted a significant milestone in interventional cardiology practice. In today's practice, coronary stent implantation is largely considered as the standard in the several types of percutaneous coronary (PC) procedures.[5,23,25] Traditional percutaneous trans-luminal coronary angioplasty (PTCA) was plagued by acute mechanical difficulties such as abrupt artery closure, coronary dissection, and other issues.In addition, because of the high prevalence of restenosis (40–50%), coronary stents implantation is suggested as a method for improving immediate procedural success while lowering angiographic and clinically significant in-stent restenosis.[13] Despite advancements in stent development, implantation procedures, and pharmaceutical therapy, there is still a need for more research in coronary intervention and stent implantation to decrease the chance of restenosis. According to Kim and its colleagues, the overall possibilityof developing in-stent restenosis after implantation of stents remains high. Although the traditional treatment for BMS restenosis is usually the insertion of a DES. But the best treatment for in-stent restenosis is still unknown.[3,19,23,26] Innovative techniques in the digital era, such as drug-coated balloons and novel stent technologies, are expected to be included as technology advances.

CONCLUSION:

Lastly, we conclude that elevation in baseline plasma Lp (a) levels are linked to a higher risk of cardiovascular disease after successful PCI with stent implantation. Furthermore, the concentration of plasma lipoprotein (a) is thought to be an independent risk factor for in-stent restenosis. Finding the optimum therapy strategy to treat in-stent restenosis is critical for future research directions.

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