Review Article

# Lipoprotein(a) : always relevant for Indians

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**Lipoprotein(a) [Lp(a)] comprises of an LDL-like particle consisting of apoB which is covalently bound by a disulfide bond to apolipoprotein(a) (apo[a]). Role of Lp(a) in promoting cardiovascular disease (CVD) is well-proven. Apo(a) predisposes to atherosclerosis through its three prong actions : proinflammatory, proatherogenc and prothrombotic. The "residual risk" following adequate lowering of LDL with statins is predominantly attributable to elevated Lp(a). This particularly explains the high prevalence of atherosclerotic CVD amongst Asian Indians because as many as 40% of Indian population has elevated Lp(a). Niacin and PCSK9 inhibitors are only agents with any appreciable effect on Lp(a) lowering. The newest emerging therapy in lowering Lp(a) is a group of agents called Antisense Oligonucleotides (ASO). It remains to be seen whether lowering genetically elevated Lp(a) can reduce CVD risk.**

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Cardiovascular disease(CVD) includes myocardial infarction (MI) or coronary artery disease (CAD), stroke and peripheral vascular disease and is a major cause of mortality in developed as well as developing countries including India. Deaths due to CVD in India was estimated to have doubled in the 30 years from 1985 to 2015[1]. When it comes to the subject of prevention of cardiovascular disease (CVD), most preventive strategies have targeted the established modifiable risk factors like smoking, dyslipidemias, diabetes, hypertension and obesity. Unfortunately, however, people continue to suffer from these diseases. It seems that inspite of therapeutic advances, some risk factors continue to elude us and these may be responsible for the additional CVD risk. Of all the lipid disorders currently held responsible for CVD risk, elevated lipoprotein(a) (Lp[a]) is usually the most commonly overlooked one. Role of Lp(a) in promoting CVD and calcific aortic valve stenosis(CAVS) has been consistently proven and now presents to us a unique opportunity to modify CVD risk by targeting the same with novel therapeutic modalities.

## Lipoprotein(a): Structure and Metabolism:

Lp(a) along with very low-density lipoprotein(VLDL), intermediate-density lipoprotein(IDL) and low-density lipoprotein(LDL) all contain apolipoprotein B-100 (apoB) and it is now apparent that apoB containing lipoproteins are maximally responsible for CVD risk. Lp(a) consists of an LDL-like particle consisting of apoB which is bound covalently by a disulfide bond to apolipoprotein(a) (apo[a]), the pathognomonic constituent of Lp(a)[2]. The apo(a) gene is located on the telomeric region of chromosome 6 (6q26-27)[3] and was found to have evolved from the plasminogen gene, a fact which might have pathophysiological implications as mentioned later. The plasminogen molecule consists of 5 kringles (KI to KV) and a protease domain. Only 2 out of these, the KIV and KV are present in apo(a) along with an inactive protease domain. Absence of KI to KIII has led to loss of plasmin activity and KIV has expanded into 10 subtypes($KIV_{1-10}$) due to further mutation. A variable number of KIV copies are present ( 1 copy each of KIV1 and $KIV_{3-10}$ and 1 to >40 copies of $KIV_2$).

Another unique feature of apo(a) protein is the extensive variation in size, with >40 different isoforms, and thus, >40 different sizes of Lp(a) particles. Other circulating proteins usually have a single defined mass. Size of the isoform is dictated by the number of $KIV_2$ repeats. Individuals may carry 2 different isoforms with greater contribution to the total Lp(a) level being from the smaller sized isoform. The size of the isoform correlates inversely with plasma Lp(a) levels as the smaller isoform can be produced in larger molar quantities than the larger form in the same amount of time.Apo(a) differs from apoB as it does not contain any lipid domains and instead, is hydrophilic in nature and has a propensity to bind to lysine moieties of the denuded and exposed vascular endothelium. This action is similar to that of plasminogen and hence might lead to a competitive inhibition of fibrinolytic activity in-vivo.

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Apo(a) is synthesized exclusively in the liver but the exact site of assembly of the molecule is not known. During assembly, the apo(a) docks onto an LDL molecule and there is formation of a disulfide bond between the KIV-9 of apo(a) and apoB of LDL. The LDL component was found to have been newly synthesized rather than being derived from a VLDL precursor. The apo(a) component is larger than apoB and is attached near the LDL receptor (LDLR) binding site of the apoB, thereby hindering clearance of the LP(a) molecule through the LDLR. That the LDLR does not play any major role in Lp(a) metabolism is also evident from the fact that statins, which upregulate LDLR, do not lower Lp(a), whereas proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors increase LDLR numbers, yet reduce Lp(a). The mechanisms by which Lp(a) metabolism occurs are still unclear. The kidney, scavenger receptor B1 and plasminogen receptors, and proteolytic cleavage of apo(a) may play a role but conclusive data is lacking[4,5].

## Lp(a ) as a Mediator of Atherosclerosis :

Apo(a) predisposes to atherosclerosis through three mechanisms:proinflammatory, proatherogenic and prothrombotic (Fig 1).The oxidized phospholipid (OxPL) component of apo(a) is proinflammatory in nature. Patients with elevated Lp(a) levels were found to have increased arterial inflammation detected by raised levels of 18-fluorodeoxyglucose in the carotids and the aorta[6]. In addition there is increased production of proinflammatory cytokines from the macrophages in these vessels, along with enhanced ability to penetrate the endothelial layer[7]. Some trials have even showed that elevated levels of OxPL on apoB-containing particles(OxPL-apoB) are similar or superior to Lp(a) in predicting CVD and CAVS[8]. These proinflammatory effects are diminished when a specific antibody is used to inactivate OxPL, thus firmly establishing its role in the pathogenesis of the proinflammatory state. Release of interleukin-8[9] and monocyte chemoattractant protein-1(MCP-1)[10], two inflammatory mediators, is also stimulated by OxPL. In fact the MCP-1 molecule is present on the Lp(a) and facilitates its entry into the vessel wall. Lysine-binding sites are also present on apo(a) which bind to denuded endothelium. Thus, entry of apo(a) into subintimal spaces via these mechanisms and its accumulation also promotes inflammation.

The enhanced binding to endothelial cells(EC)is also due to upregulation of adhesion molecules like intercellular adhesion molecule-1(ICAM-1)[11], vascular cell adhesion molecule-1(VCAM-1), E-selectin, endothelin-1[12,13], and I-309[14]. Enhanced EC binding along with increased proliferation of smooth muscle cells and formation of foam cells are some of the characteristics of Lp(a) that impart the proatherogenic effect. Lp(a) also inhibits plasminogen activation by competitive inhibition of binding to lysine rich vascular endothelium and thereby decreases fibrinolytic activity, which is the major prothrombotic effect. However, it must be kept in mind that except in individuals with very high Lp(a) levels, plasminogen levels are usually much greater than Lp(a) levels and hence the potential role of competitive inhibition of plasminogen activity is questionable.Other proposed prothrombotic mechanisms include decreased tissue plasminogen activator[15], decreased fibrin degradation, increased platelet responsiveness and increased plasminogen activator inhibitor-1[16] (PAI-1) expression.

## How is Lp(a) Different from LDL?

Synthesis of Lp(a) requires attachment of an apo(a) particle to the apoB of an LDL particle. The apo(a) component is larger than apoB and is bound near the LDL receptor (LDLR) binding site of apoB. Thereby it interferes with the clearance of the Lp(a) molecule through the LDLR. Lp(a) thus has a longer plasma half-life than LDL. Lp(a) also carries a greater atherogenic risk than LDL, because not only does it contain all the proatherogenic characteristics of LDL, but also those of apo(a)[17]. Circulating Lp(a) levels are predominantly genetically determined (LPA gene), and there is only minor, if any, influence of diet and environmental factors[18]. Almost 90% of circulating Lp(a) levels are quantitatively related to the LPA gene locus and plasma levels are more-or-less constant throughout a person's lifetime. Thus it is proposed that Lp(a) level should be estimated only once and no subsequent testing is needed. This is in contrast to the changes in levels of LDL which must be regularly monitored and therapies modified accordingly.

Earlier it was assumed that controlling LDL-C levels

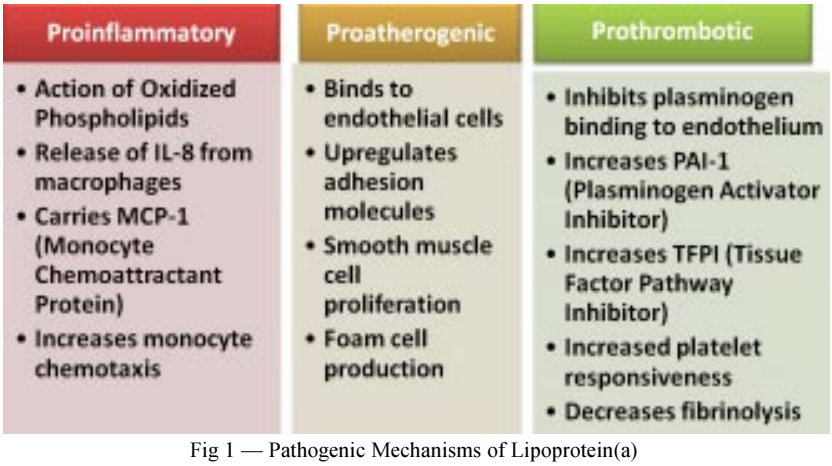



Fig 1 — Pathogenic Mechanisms of Lipoprotein(a)

eliminates the risk due to elevated Lp(a) levels. As a result, on finding elevated Lp(a), clinicians would start treating the LDL-C rather than the Lp(a). Recent trials like the JUPITER trial (Justification for the Use of Statins in Prevention: an Interventional Trial Evaluating Rosuvastatin) have shown that Lp(a) remains a risk factor even in patients in whom an LDL-C level <70 mg/dl has been achieved thereby revealing the flaw in the above-mentioned approach[19]. In the IMPROVE-IT trial (Improved Reductionof Outcomes: Vytorin Efficacy International Trial), a combination of simvastatin and ezetimibe added to CAD patients was able to reduce LDL-C to a mean level of 54mg/dl but the subsequent major adverse cardiovascular event(MACE) rate was still 32.7%[20]. This "residual risk" of CVD in statin treated patients is suggested to be due to elevated Lp(a), which plays a major role independent of the LDL-C action.

## When and in Whom to Measure Lp(a) Levels?

Before instituting lipid-lowering therapy, the aim of the clinician is to classify a patient into either a high risk or a low risk group. In the Bruneck study, it was observed that addition of Lp(a) to established risk scores (like Framingham or Reynolds) helped in reclassifying almost 40% of intermediate risk individuals into either high risk or low risk categories[21]. Although the impact of withholding therapy in a low risk patient is not well established, the potential benefit of starting statins is definitely high in patients newly upgraded to the high risk group. In the 2016 European Society of Cardiology(ESC) and European Atherosclerosis Society(EAS) guidelines, Lp(a) estimation is suggested in selected individuals with high risk, or a family history of premature CVD and also for reclassification in those with borderline risk[22]. As Lp(a) levels do not vary over a lifetime, it is rational to add Lp(a) measurement to the lipid panel when a person's lipids are measured for the first time with no need for further testing irrespective of change in diet or therapy.Traditionally Lp(a) levels < 30 mg/dl were suggested as optimal and associated with negligible CVD risk, but current EAS recommendations delineate Lp(a) levels <50 mg/dl as optimal.

## Existing and Emerging Therapies for Lp(a) Reduction :

Earlier statins were thought to exert no effect on Lp(a), the metabolism of which is independent of LDLR. Now, however, there is data to suggest that statins raise Lp(a) levels by 10-20% although the mechanisms by which it does so is unclear. In a recent study, comparison in patients pre- and post-statin therapy showed an increase in Lp(a) levels by 11% and in OxPL-apoB levels by 24% in the post-statin group[23]. Thus, failure of statin therapy might suggest that the patient has most of his harmful cholesterol in the form of Lp(a) rather than LDL-C.

Unfortunately there are no approved medications which are specifically targeted at lowering Lp(a) levels and there has been a remarkable lack of randomized trials of Lp(a) lowering till now. Niacin and PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors like aliorocumab and evolocumab are the only agents with any recognized efficacy in lowering Lp(a), with estrogen also being used in a limited population. Niacin reduced Lp(a) levels by around 39%in patients with high baseline levels (>50 mg/dl) in the AIM-HIGH study[24] but no reduction in event rate was seen. In the same trial, cholesterol ester transfer protein (CETP) inhibitors like anacetrapib, evacetrapib showed a 20-30% reduction in Lp(a) levels but again without any clinical benefit. The inference that was drawn from these findings was that potential benefit of Lp(a) lowering will not become evident unless >50% reductions in mean levels is achieved.Another existing option is the use of apheresis for reducing Lp(a) and clinical benefit has been observed in some cases[25]. Lp(a) levels >60 mg/dl are used as cutoff for reimbursement of lipoprotein apheresis in Germany and the United Kingdom.

The newest emerging therapy in lowering Lp(a) is a group of agents known as Antisense Oligonucleotides (ASO) (Fig 2). Mipomersen is a prototype ASO targeting apoB mRNA that was shown to lower Lp(a) and OxPL-apoB in trials on transgenic mice[26] and these findings were subsequently confirmed in several randomized trials[27]. ASOs are injected subcutaneously and accumulate in the liver where they bind to the target mRNA to form a double-stranded unit. Ribonuclease H1 cleaves the sense strand to prevent protein synthesis but releases the antisense strand in an intact form which can then attach to additional mRNAs. Mipomersen only inhibited apoB production and thereby Lp(a) synthesis whereas apo(a) continued to be secreted as free molecules into the circulation. Similarly, trials involving ASOs specific to apo(a) have also been initiated and have seen promising results with reduction in apo(a) production by almost 80%[28].

## Clinical Evidence Supporting Lp(a) as a Major Promoter of Cvd And Cavs in the Community — The International Scenario:

Throughout the world, over the last decade, epidemiological studies carried out in individuals without any prior CVD have comprehensively proved that elevated Lp(a) levels are associated with a greater risk of myocardial infarction, stroke and peripheral arterial disease[29-31]. In the Cardiogram Plus 4CD Consortium, studies carried out in coronary artery disease(CAD) patients identified several genetic

loci associated with increased susceptibility for CAD. Among these, the LPA locus was determined to have the strongest association, thus proving the role of LPA gene as one of the strongest monogenetic risk factors for CAD[32]. This, in turn, has paved the way for introducing specific therapies targeting Lp(a) for lowering CVD risk[33].

Similar evidence is also available in support of Lp(a) being the only monogenetic risk factor for aortic valve calcification and CAVS[34]. The ASTRONOMER Trial (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin) studied patients with pre-existing mild-to-moderate aortic stenosis and showed that the individuals with elevated Lp(a) and OxPL-apoB had a faster progression rate and an earlier need for aortic valve replacement[35]. Further, younger patients were found to progress more rapidly and had the highest need for valve replacement, a fact that can be explained if we consider the genetically mediated Lp(a) to be the major determinant. Recently, an enzyme called autotaxin was also found to play an important role in CAVS[36]. Autotaxin helps in breakdown of lysophosphatidylcholine to lysophospatidic acid, an inflammatory mediator, and elevated autotaxin activity was found to be associated with raised levels of Lp(a) and OxPL-apoB. Thus, in summary, we can hypothesize that Lp(a) transfers autotaxin as well as OxPL into the substance of aortic valve leaflets and promotes inflammation and calcification[37].

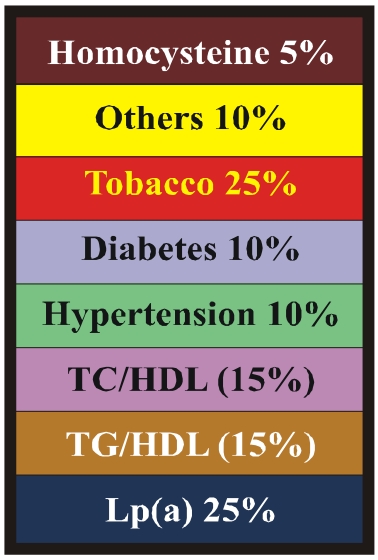



Fig 3 — Contribution of various risk factors for CAD amongst Indian

(1) Antisense oligonucleotide binds to the mRNA.
(2) This double, stranded region can inhibit the production of protein by two mechanisms
- Stopping the ribosome from reading the message
- Leading to the destruction of the mRNA by an enzyme already in the cells called RNAse H.

Fig 2 — Mechanism of Action of Antisense Oligonucleolide

## Current Status of Lp(a) In India :

According to recent studies more than 60% of CAD in Indians is unexplainable by the conventional risk factors[38]. Failure of established preventive strategies in reducing the risk of CVD in the Indian population ushered in renewed efforts to identify newer modifiable risk factors including Lipoprotein(a) and homocysteine etc[39]. The role of Lp(a) in pathogenesis and progression of atherosclerosis and coronary artery disease(CAD) specifically in the Indian population has been established by several recent studies[40,41]. Presence of related risk factors also enhance the association between Lp(a) and CVD[42,43]. A study in North Indian CAD patients found elevated levels of Lp(a) and raised Lp(a)/HDL-C ratio to be valuable predictive markers[44].

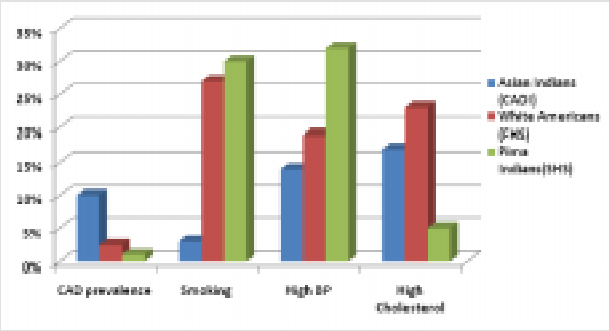
The high rate of CAD in Asian Indians is due to a combination of nature (genetic predisposition) and nurture (life style factors). The “nature" component is predominantly contributed by elevated level of Lp(a) which has a prevalence of more than 40% amongst the Indian population and accounts for 25% of all deaths due to CAD (Fig.3).

## Special Relevance of Lp(a) in Indians All Over the World :

In the Coronary Artery Disease in Asian Indian(CADI) study, the prevalence of CAD in Indians residing in the United States of America(USA) was found to be four-fold higher compared to Caucasian population and six-fold higher than the Chinese Americans of the same age group[46]. This was in spite of the fact that almost half of the Indian population in the study had vegetarian dietary habits, a factor that is considered to be protective against CAD.This phenomenon of high CAD rates appears to hold truefor all inhabitants of the Indian subcontinent and immigrants from these countries to various regions of the world. Studies in countries other than USA also found a higher CAD incidence in Indian immigrants compared to those of other ethnic origins. It appears now ,that Indians as a race, have a higher predisposition to CAD and this is characterized by three important features: extreme prematurity, marked severity and relatively low prevalence of conventional risk factors.

Indians are prone to develop CAD five to ten years earlier than other populations and risk of occurrence of first MI before the age of 40 years is five-to-ten times higher as well. The severity of disease is also greater in Indians as detected by coronary angiography. Extensive multi-vessel disease is seen in a majority of individuals and sometimes even in non-smoking premenopausal women. Surprisingly, the high rates of CAD in Indians was accompanied by a low rate of conventional risk factors (Fig 3). Among the population studied in the CADI study, only 3% were smokers, 3% were obese, and 14% had high blood pressure. The corresponding percentages in White Americans were 27%, 31% and 19%[47]. Studies on Pima Indians in the US also showed similarly low CAD risk despite high prevalence of conventional risk factors[48]. With the help of further research, this disproportionately high incidence and severity has now been attributed to a genetic predisposition due to elevated Lp(a) levels[49].The CADI study found significantly raised Lp(a) levels (>30 mg/dl) in 25% of Indians settled in the US compared to 17% of Whites and

Table 1 — *Prevalence of CAD and its risk factors in Indian immigrants in comparison with other populations in the US*




CADI : Coronary Artery Disease in Indians Study[46]
FHS : Framingham Heart Study[47]
SHS : Strong Heart Study[48]

8% of Hispanics. A strong correlation between Lp(a) levels and severity of CAD in Indians was alsoreported by Shaukat *et al*[50]. Furthermore, as adult levels of Lp(a) are reached early in life, its effects start earlier than other risk factors and this may explain its role in premature-onset CAD in Indians.

In addition to being an independent risk factor, Lp(a) has its effects multiplied by elevated levels of other lipoproteins. The pathological effects of Lp(a) become much more pronounced in Indians due to co-existence of the well-known lipid triad (high triglycerides, high LDL, and low HDL). This unique pattern of dyslipidemia or lipid tetrad (elevated Lp(a) in combination with the lipid triad) is a common finding in Indians and is rarely encountered in other populations. In contrast, in the African Americans, the harmful effects of high Lp(a) is partially neutralized by low LDL, triglyceride and high HDL[51].

## Conclusions :

It is clear that the excess burden of CVD in Indians cannot be explained by the conventional risk factors.Hence, it is unlikely that conventional approaches to prevention and treatment will be sufficient for the Indian population. About one in four Indians has elevated Lp(a) levels and Lp(a) is now considered to be responsible in a major part for the genetic predisposition of Indians to CAD. As already mentioned, Lp(a) is fully expressed in the first few years of life. Thus, identification of risk and prevention of CAD in Indians can begin at an early age. Several potent and efficacious therapies targeting Lp(a) are currently in development and once they are introduced, further data will become available to test the hypothesis that reduction of genetically elevated Lp(a) can reduce CVD risk. In conclusion, it can be said thatLp(a) as a risk factor for CVD will always be relevant throughout the world and more so in the Indian population.

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