

## Lipoprotein (A) in clinical practice

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Lipoprotein (a) is a strong and independent risk factor for atherosclerosis severity and a predictor of the risk of ischaemic heart disease and stroke. Many questions are still unanswered in relation to the clinical relevance of the scientific observations on Lp(a) and its application in the realms of cardiovascular prevention. Lp(a), a lipoprotein subtype, is linked to the Apo(a) gene located on chromosome 6q26-27 independently associated with increased risk of coronary artery disease (CAD). For this review, data sources from Cochrane, Pubmed, MEDLINE from 1960 till 2012 were analysed systematically. At least one-off measurement of plasma Lp(a) was found to be indicated in those with premature coronary disease when no real causative factor was identified. Management seemed promising with PCSK9 I, apheresis, CETPI, dietary choices and ACEi. There was clear evidence that Lp(a) is a definite risk marker for atherosclerotic cardiovascular disease (CVD).

**Keywords:** Lipoprotein (a), Cardiovascular disease, Apolipoprotein B, Myocardial infarction.

### Introduction

Lipoprotein (a) is a strong and independent risk factor for atherosclerosis severity and a predictor of the risk of ischaemic heart disease (IHD) and stroke. Much has been written about its molecular structure and putative function at sub-cellular levels, but there still remain many unanswered questions in relation to the clinical relevance of the scientific observations on Lp(a) and its application in the realm of cardiovascular prevention. This review article attempts to crystallise the available clinical information and the peak-body guidelines to provide clinicians with vital practical knowledge on who needs assessment, when the assessment is needed and how best to manage Lp(a) in a clinical setting. It is important for clinicians to gain insight into how scientific information on this important element in the cholesterol profile relates to practical application.

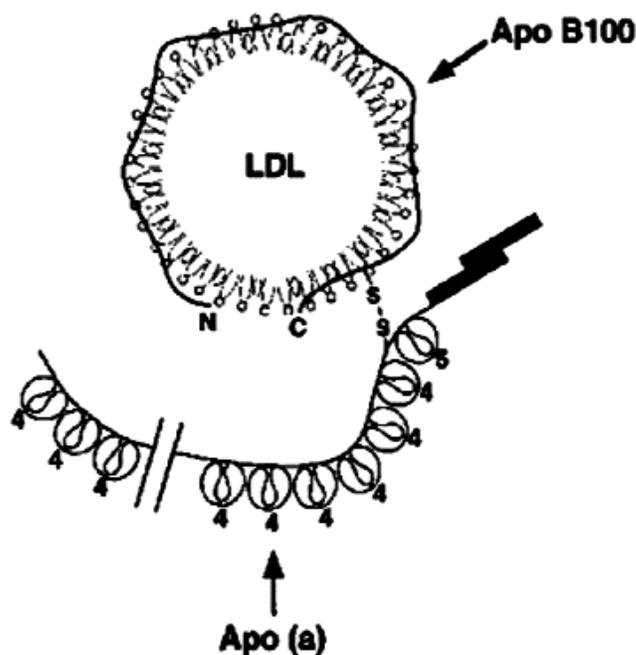
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### Molecular structure of Lp(a)

Lp(a) is a lipoprotein subtype that has been associated with increase risk of coronary artery disease (CAD) and stroke.<sup>1</sup> It is made up of a low-density lipoprotein (LDL)-like particle to which Apo lipoprotein (a) [Apo(a)] is covalently bound by a bisulphide link (Figure). Lp(a) synthesis is linked to the Apo(a) gene located on chromosome 6q26-27 and its plasma levels are for the most part genetically determined and, hence, heritable.<sup>2</sup>

This molecule was first described in 1963 as a genetic variant of  $\beta$ -lipoproteins.<sup>3</sup> The precise physiological function of Lp(a) has not been described conclusively. There is a structural resemblance between Apo(a) and plasminogen.<sup>4</sup> Therefore, it is possible that Lp(a) has functions related to the coagulation cascade and haemostasis, but this has not been verified in vivo. Other possible associations include inflammation, angiogenesis and even wound healing. Very low levels of Lp(a) do not seem to result in any ill effect, however.



Lp(a): Lipoprotein (a). LDL: Low-density lipoprotein.

**Figure:** Molecular structure of Lp(a). An LDL particle is attached to kringle-like apoprotein (a) by a disulphide bridge.<sup>5</sup>

## Pathological mechanisms in CVD

Many studies have indicated that Lp(a) is an independent risk factor for cardiovascular disease (CVD) and stroke.<sup>6</sup> This is due to its strong atherogenic and pro-inflammatory properties.<sup>7</sup>

Its ability to stimulate smooth muscle proliferation appears to contribute to atherosclerotic plaque formation.<sup>8</sup> Due to its structural resemblance to plasminogen and tissue plasminogen activator it has the ability to competitively inhibit fibrinolysis and this property together with its ability to promote thrombogenesis may contribute to its association with myocardial infarction (MI) and ischaemic stroke.<sup>9,10</sup>

High Lp(a) plasma concentrations contribute to enhanced cardiovascular risk in those with other traditional risk factors. Its pro-inflammatory properties may contribute to vulnerable plaque formation and subsequent plaque rupture leading to ischaemic events.<sup>11</sup>

Lp(a) has also been identified as a strong independent risk factor for CVD in many different populations and ethnicities.<sup>12</sup> But the ethnic diversity in its levels and expression is quite distinct and remarkable. African populations and African Americans seem to have higher plasma levels compared to those from other geographical regions.<sup>13,14</sup>

## Association with Coronary Risk

Despite the fact that many publications indicate the heightened risk of atherosclerotic coronary disease and stroke due to elevated Lp(a), there are other studies that indicate little or no association.<sup>15</sup> These conflicting observations have been attributed to methodological and sampling errors that may have confounded the results of some studies. It is clear that there is a certain lack of standardisation in the units and methods used for the measurement of Lp(a). To address this issue the International Standardisation Committee recommends that the previous practice of reporting Lp(a) as a total mass be superseded by the measurement of Lp(a) protein either in terms of Apo(a) or as Apo(a) linked to ApoB100.<sup>16</sup>

## Genetics of Lp(a) and CAD

In the multi-centred case-control study PROCARDIS<sup>17</sup> (Precocious Coronary Artery Disease) involving 3145 cases (2100 candidate genes) and 3352 controls, using single-nucleotide polymorphisms (SNP) (novel gene chip containing 48742 SNPs) also with replication testing for evaluating association, 3 chromosomal regions were associated with CAD, namely 6q26-27, 9p21, 1p13.

LPA locus on 6q26-27 encoding Lp(a) has the strongest association, of which 2 common variants at rS 10455872, rS 3798220 were independently associated with increased risk of CAD. Both variants correlate with Lp(a) level and risk of CAD. One in 6 persons carries a variant LPA allele and risk of CAD is increased by a factor of 1.5. 9p21: 25 SNPs were mapped and were associated with CAD and Type 2 diabetes mellitus (T2DM). 1p13: 6 SNPs localised showed association with CAD and LDL levels.

Interesting enough to suggest 3 distinct genetic patterns in precocious CAD possibly; Lp(a) levels is of importance in this group of patients with precocious CAD and is an independent risk factor. Also noted in this study was a linear-dose relationship of the LPA variants at the LPA locus for both Lp(a) level & the risk of CAD.<sup>17</sup>

## Investigation and Measurement

When the measurement of Lp(a) level would be indicated or relevant in clinical practice and what implications it has in the management of risk prone individuals are questions that yet remain unanswered (Table-1).

Serum levels of Lp(a) are genetically determined with little or no environmental impact.<sup>18</sup> Diet, physical activity and body habitus are not known to affect Lp(a) levels to any significant extent. Therefore, some experts suggest that a single, one-off measurement of Lp(a) suffices in those with premature coronary disease with no real causative factor identified. But it is important to note that renal failure may increase Lp(a) levels.

Lp(a) may also be useful in those individuals in the intermediate risk category according to the commonly used cardiovascular risk calculators to justify the use of aggressive risk mitigation strategies, including pharmacotherapeutics.

## Management

Currently there are few therapeutic means whereby improvement in Lp(a) levels can be achieved. Extended release niacin at a dose of up to 3g per day is able to reduce Lp(a) levels by about 30%.<sup>18</sup> A recent meta-analysis indicated that Atorvastatin has the ability to lower Lp(a) levels by up to 30% at higher doses.<sup>19</sup> Angiotensin Converting Enzyme (ACE) inhibitors are known

**Table-1:** Risk stratification.

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**Desirable:** < 14 mg/dL (< 35 nmol/l)

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Borderline risk: 14-30mg/dL (35-75nmol/l)

High risk: 31-50mg/dL (75-125nmol/l)

Very high risk: >50mg/dL (>125nmol/l)

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to improve elevated Lp(a) levels, particularly in those with proteinuria. The precise mechanism whereby this is achieved relates to reversal of proteinuria that in turn lowers the production of Lp(a) in the liver.<sup>20</sup> Researchers have demonstrated that Fosinopril is able to bring about similar effects also in the non-proteinuric population by increasing Apo(a) fragmentation followed by the excretion into the urine.<sup>20</sup>

The bigger challenge many lipidologists face relates to achieving effective control of the comprehensive lipid profile, including Lp(a) levels, in those with familial hypercholesterolaemia, treatment-resistant hypercholesterolaemia and those that are severely intolerant to available pharmacotherapies. Extracorporeal lipid apheresis is a very effective means whereby plasma lipid and Lp(a) levels can be reduced by up to 80%, and is used selectively in cases resistant to standard therapy. In these individuals the therapeutic goal is to control Lp(a) levels to below 50mg/dL (and even 30mg/dL according to some experts).<sup>18</sup>

Despite being expensive, the apheresis technique is very potent and effective in those selected groups of patients who require special consideration.<sup>21</sup>

The potential future therapeutic options for targeted Lp(a) control include cholesterol-ester transfer protein inhibitors (CETPI), anti-sense oligonucleotides (ASO) and proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK-9I) and L-carnitine.<sup>22,23</sup> The CETP inhibitor Anacetrapib has been shown to reduce Lp(a) plasma levels by up to 50%.<sup>24</sup> The ASO Mipomersen lowers Lp(a) by up to 50% in phase 2 trials with single injections given fortnightly.<sup>25</sup> Maximum reductions occur after 3-6 months of continuous therapy, and slowly return to baseline after cessation of therapy.<sup>25</sup> The PCSK-9I, AMG-145, has similar effects on Lp(a) levels with once monthly injections.<sup>26</sup> Carnitine supplementation therapy in doses of up to 1gm daily leads to 10-15% reduction (Table-2).<sup>23,24</sup>

Lp(a) levels were lower in post-menopausal women taking oestrogen as hormone replacement therapy (HRT) (median 9.4mg/dl vs. 11.6mg/dl,  $p < 0.0001$ ).<sup>27</sup> But the clinical effect or benefits thereof have not been described clearly as yet.<sup>27,28</sup> Some workers have reported that regular consumption of alcohol in moderation could reduce plasma Lp(a) levels, but there is no clear consensus on this observation.<sup>29</sup> An epidemiological study revealed that fish eaters had lower Lp(a) levels than vegetarians, indicating possible Lp(a) lowering effects of fish oils.<sup>30</sup>

In practical terms, most experts recommend measuring Lp(a) routinely in those with premature CVD (age <55

**Table-2:** Influence of drugs and other substances on plasma Lp(a) concentrations.<sup>19</sup>

Substance	% Decrease
Omega-3 Fatty Acids:	5-20
Palm Oil:	10-25
Vegetarian Diet:	10
Nicotinic acid and derivatives:	15-35
Aspirin:	15-20
L-Carnitine:	15-Oct
Lp (a)/LDL-Apheresis:	60-80
ACE-Inhibitors:	10-40
Atorvastatin	Unclear
Hormone replacement therapy	Unclear
Alcohol	Unclear
Fish oil	Unclear

ACE: Angiotensin Converting Enzyme.

years in men and <65 years in women, and in those with a family history of premature CVD.<sup>31</sup> Lowering of LDL cholesterol more aggressively to levels below 1.8 mmol/L in those with serum Lp(a) levels above 30mg/dl, in addition to low-dose aspirin for anti-thrombotic effect, may provide more effective cardiovascular prevention even though hard evidence to support this practice is lacking.<sup>21</sup> The recently released European Society of Cardiology guidelines on cardiovascular prevention indicates that there is no justification for screening the general population for Lp(a) at present, and no evidence that any value should be considered as a target.<sup>31</sup>

## Conclusion

Lp(a) is a definite risk marker for atherosclerotic CVD. Evaluating and therapeutically managing Lp(a) in clinical practice can benefit such patients. Future trials need to be designed to address this issue and define the precise role of Lp(a) in global CVD risk mitigation.

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