

## Current and Emerging Insights and Therapeutics of Lipoprotein (a)

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Per American Heart Association (AHA), cardiovascular disease (CVD) remained number one cause of mortality in 2017 within United States with ~2.9 million deaths and ~17.8 million deaths globally [1]. Given the rising burden of CVD globally and many factors which lead to CVD, it has become crucial to explore and invest in its multi-faceted prevention. Lipoprotein (a) (Lp(a)) is an atherothrombotic molecule which may be overlooked in standard clinical practice when managing lipids and can lead to premature coronary artery disease, stroke [2,3] and aortic valve stenosis. Lp(a) is composed of apolipoprotein B-100, apolipoprotein (a) and low-density lipoprotein (LDL) like particle. Its atherogenic potential is supported by the LDL-like particle while the apo(a) brings about its thrombotic properties by meddling in plasminogen activation [4]. The Lp(a) is inherited and exists in variations > 1000 fold in-range (< 0.1 mg/dL to > 100 mg/dL) within the population with apolipoprotein (a) gene contributing to ~91% of this variation [5].

Several studies have outlined the atherothrombotic potential of Lp(a). In a study with patient's experiencing major adverse cardiovascular events (MACE), including cardiogenic shock, heart failure, cardiovascular death, malignant arrhythmias, and postinfarction angina, a significant difference in survival was observed in low Lp(a) (104.3 hours) versus high Lp(a) (60.6 hours) group; furthermore, the hazards ratio was 4.63 - 4.69 in high Lp(a) group [6]. In an analysis of Odyssey Outcomes in patients with recent acute coronary syndrome, it was concluded that risk of peripheral artery disease (PAD) is related to Lp(a) level, but to assess similar relation of venous thromboembolism (VTE) to Lp(a) would require further study [7]. Consequently, a meta-analysis on Fourier and Odyssey Outcomes showed that PCSK9 inhibitors significantly reduced the risk of VTE and Lp(a) may have played a significant role [8]. High Lp(a) also increases incidence of lower limb deep vein thrombosis (DVT) and pulmonary embolism (PE). A prospective study in patients who had undergone splenectomy because of cirrhotic portal hypertension had their Lp(a) analyzed on post-operative days 1, 3, 5, 7 and 14. In the group that suffered from portal/splenic vein thrombosis (PSVT) compared to non-sufferers, Lp(a) was significantly elevated in the earlier group on post-op day 3-5, pointing to the use of post-op Lp(a) levels as a prediction tool for PSVT [9].

### Current therapies affecting Lp(a)

The current on-market therapies for hypercholesterolemia which lower Lp(a) include PCSK9 inhibitors, niacin, lomitapide and lipid apheresis. These therapies are being primarily used and targeted for hypercholesterolemia while the Lp(a) lowering is a "side benefit" of its use. In a pooled analysis of Odyssey trials, alirocumab lowered Lp(a) from baseline by ~26% and upon adjustment for LDL-C changes, there was a significant association between Lp(a) reduction and MACE in patients who had baseline Lp(a)  $\geq$  50 mg/dL [10]. Furthermore, findings on Lp(a) from Fourier study on evolocumab concluded that patients with higher baseline levels of Lp(a), > 37 nmol/L, experienced greatest coronary benefit due to greater absolute reduction of Lp(a) [11]. A mendelian randomization analysis illustrated that lowering the Lp(a) by 101.5 mg/dL lowered the risk of coronary heart disease (CHD) by the same amount as when LDL-C was lowered by 38.67 mg/dL [12].

Lipoprotein apheresis therapy is typically reserved for patients with severe hypercholesterolemia and can also substantially lower Lp(a). In a study of patients with refractory angina and Lp(a) > 50 mg/dL, three months of lipoprotein apheresis on weekly basis was con-

ducted which led to significant reduction of Lp(a) of 100.2 mg/dL [13]. Furthermore, this reduction significantly improved several thrombotic and fibrinolytic parameters [13]. Lomitapide is given as an adjunct therapy for hypercholesterolemia in patients with homozygous familial hypercholesterolemia (HoFH); therefore, more studies are needed on its efficacy on Lp(a). Niacin has been shown to lower Lp(a) by as much as 30%. Consequently, a study in which PCSK9 inhibitor therapy was added on top of niacin showed Lp(a) reduction of ~15% [14]. The current therapies have shown some effectiveness on Lp(a) levels as a “side benefit”, but targeted and less invasive therapies are needed to show the CVD benefits.

### Developing therapies and future considerations

Newer developing therapies tailored to Lp(a) such as antisense antinucleotide IONIS-APO(a)LRx and AKCEA-APO(a)LRx have shown promising Phase I and II results. In both antisense antinucleotide therapies, these phases showed dose-dependent reduction of Lp(a) of 50% - 85% [15,16]. In a study of pro-inflammatory markers using AKCEA-APO(a)LRx in patients with cardiovascular disease (CVD) and elevated Lp(a), it was found that AKCEA-APO(a)LRx lowered Lp(a) by 47%, reduced pro-inflammatory gene expression in monocytes, and in *ex-vivo* demonstrated 17% reduction in transendothelial migration [17]. Further studies need to be done in the CVD patients on antisense antinucleotide therapy to understand its potential for CVD risk reduction.

Given the current COVID-19 pandemic and SARS-CoV-2's ability to induce lethal cytokine storm within patients, it has become imperative to study hypercoagulable factors which may lead to stroke, myocardial infarction, heart failure, cardiogenic shock, etc. The LPA gene, coding for Lp(a), has interleukin-6 (IL-6) response element and according to a hypothesis, this may cause acute increase in Lp(a) ultimately leading to COVID-19 related cardiovascular complications [18]--outlining the need for Lp(a) therapy in COVID-19 cases with baseline or acutely high Lp(a).

Overall, development of Lp(a) targeted therapies should be considered a high priority for prevention of atherothrombotic diseases. Current data shows that lowering Lp(a) in those with baseline Lp(a) >37 mg/dL should be considered in addition to their cholesterol lowering therapy to maximize CVD and thrombosis prevention.

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