Editorial

Reduction of cardiovascular risk in subjects with high lipoprotein (a) levels

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Lipoprotein (a) [Lp (a)] is a plasma lipoprotein consisting of a cholesterol rich LDL particle with one molecule of apolipoprotein *B100* and one protein apolipoprotein (a) [apo(a)].

The two molecules are most likely assembled in the hepatocyte cellular membrane and are connected biochemically by a disulfide bridge through cysteine residues within apo(a) (Cys 4057) and apoB100 (Cys 4326).

Lp(a) closely resembles a low-density lipoprotein (LDL) particle but is found across the continuum of lipoprotein particles including very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) (1-3).

The lipoprotein (a) is directly synthesized by the liver, which releases different isoforms in blood circulation. The heterogeneity of the lipoprotein is genetically determined by the size of apo B100, which in turn is controlled by several alleles of the apo (a) gene (4).

Apo(a) synthesis is dependent on ApoB synthesis (explaining elevated levels of Lp(a) in individuals with familiar hypercholesterolemia), but possibly form a different pool of ApoB 100 than that associated with LDL particle assembly (5).

Within apo (a) is a unique region highly structurally homologous to plasminogen but devoid of protease activity.

By antagonizing plasminogen binding, Lp(a) may play a role in hemostasis and wound healing at sites of arterial injury, attenuating fibrinolysis, promoting thrombosis, coagulation and delivering cholesterol.

Apoprotein(a) is genetically very heterogeneous due to variation in molecular weight secondary to differences in the number of Kringle repeats (6,7).

Apo (a) contains multiple copies of plasminogen-like Kringle IV (KIV) sequences, followed by sequences closely resembling plasminogen Kringle V and an inactive protease domain (8,9).

Lp(a) concentration have a more than 1000-fold inter-individual range that is to a large extent genetically determined up to 70% of the concentrations are explained by a highly polymorphic copy number variation within the LPA gene region that was already described than 25 years ago (10,11).

Recently a genome-wide association study has identified a genetic variant in the LPA gene locus which encodes apolipoprotein (a), determining plasma levels of lipoprotein (a). Although LPA variants have been associated with CHD and aortic valve stenosis (12), four single nucleotide polymorphism (SNPs) in the LPA gene had been associated with plasma Lp(a) levels: rs 10455872, rs 3798220, rs 41272114 and rs 143431368.

The rs 3798220 and rs 10455872 single nucleotide polymorphisms (SNPs), which were most strongly associated with Lp(a) levels, were most strongly associated with coronary disease risk (13).

Epidemiological evidence associate elevated Lp(a)

concentration with increased cardiovascular risk and predict adverse outcome in atherosclerotic disease. Lp(a) is also associated with peripheral arterial disease, venous thromboembolism, cerebral vascular disease, abdominal aorta aneurism, aortic valve stenosis and calcification (14,15). The mechanism by which an increased level of Lp(a) increases the risk of coronary disease is less well understood; it may involve LDL lipoprotein cholesterol, the inhibition of conversion of plasminogen to plasmin, the inhibition of the expression of tissue factor or the carriage of pro-inflammatory oxidized phospholipids.

The consistent observation of a strong correlation between the circulating levels of Lp(a) and oxidized/phospholipid/apolipoprotein B complex which were together directly associated with CVD outcomes suggested to them that Lp(a) transported the pro-inflammatory burden of oxidized phospholipids. In prospective cohort studies, these findings were attributed to the possible increased efflux from plaques of oxidized lipoprotein complex. Moreover it has been demonstrated that lipoprotein complex were associated with angiographic coronary artery disease (16).

In fact elevated Lp(a) level is believed to promote atherosclerosis via Lp(a)-derived cholesterol entrapment in the intima, inflammatory cell recruitment and/or via the binding of pro-inflammatory-oxidised LDL (17-22).

Elevated Lp(a) level promote also thrombosis via the inhibition of fibrinolysis with enhancement of clot stabilization as well as via enhancement coagulation via the inhibition of tissue factor pathway inhibitor.

The relationship between Lp(a) and endothelial dysfunction and pro-inflammatory properties of Lp (a) may be considered as additional explanations.

Experimental studies have shown that Lp(a) may contribute to foam cell formation (23).

The possibility that Lp(a) may become functionally altered in patients with coronary artery disease has been put forward by Tsironis on the basis of mass and specific activity of Lp(a) as mediator of platelet activating factor acetyl-hydrolase activity, an enzyme that hydrolyses oxidized phospholipids (24,25).

The current pharmaceutical armamentarium to lower Lp(a) levels is limited to niacin, L-Carnitine, PCSSK inhibitors and oestrogen.

Nicotinic acid (NA) based treatment (e.g., Tredaptive) was previously felt to be modest effective at lowering LP(a) (26).

The major effect of NA is the partial inhibition of lipolysis from the adipose tissue, resulting in a decreased flux of free fatty acid to the liver, reducing the VLDL production rate.

NA reduces Lp(A) by up to 40% and has been identified as the drug that lowering Lp(a). However several studies have demonstrated that NA treatment is associated with hyperglycaemia and insulin resistance (27).

L-Carnitine plays an important role in fatty acid metabolism and Acetyl-L-carnitine in hepatic their subsequent transport into mitochondrial matrix, where they undergo beta-oxidation for cellular energy production (28-31). L-carnitine treatment decrease Lp(a) levels by about 20%.

Data assessing the impact of statins on LP (a) are limited and highly variable and overall, statins are ineffective at significantly LP (a) (32-34).

In a study by Yeang and colleagues, Lp(a) and Ox Pl-apoB were measured pre- and post-statin therapy the mean patient-level Lp(a) increased by 11% and Ox Pl-apoB increased by 24% (35).

Protein apheresis is a selective lipid lowering extra-corporal treatment by which excess atherogenic apo B-100 containing lipoproteins, including Lp(a) and LDL are removed from blood or plasma (36). Currently, it remains the most effective means of lowering Lp (a) levels (37).

Lipoprotein apheresis is able to produce rapid, prolonged and significant dose-dependent reduction in LDL-cholesterol, apoB100 and other atherogenic apoB (38).

Other Lp(a) treatment are sex hormones therapy, thyroid hormone and inhibitors of interleukine-6 receptor. Sex hormones have an influence on Lp(a) levels. While systemic estrogen alone or in combination with progestin decreases Lp(a), transdermal hormone replacement therapy and the raloxifene selective oestrogen receptor modulator do not effect Lp(a) levels. Tibolone, a synthetic steroid with weak oestrogenic, progestagenic and androgenic properties, has been shown to decrease Lp(a) levels in post-menopausal women.

Tibolone treatment can reduce Lp(a) concentration by 25% (39,40). The mechanism through which sex hormones influence Lp(a) levels is is most likely the down regulation of apo(a) gene expression.

Other novel mechanisms to influence Lp(a) concentrations may involve the inhibitors of interleukin-6 receptor signalling with the Il-6 receptor antibody tocilizumab (41).

The thyroid hormone analogue eprotirome was found to decrease Lp(a) by about 40% (42).

Recent evidence showing that monoclonal antibodies that block proprotein convertase subtilisin/Kexin type 9

(PCSK-9) Evolocumab and Arirocumab, both administered though subcutaneous injections twice per month reduce not only LDL-C, apoB-100, but also Lp(a) concentrations in patient with familiarly hypercholesterolemia (43,44). Inhibitors of the cholesteryl ester transfer protein (CETP) are a new class of lipid-modifying drugs. Anacetrapib has been shown to decrease Lp(a) concentration by about 40% (45). CEPT plays a relevant role in reverse cholesterol transport in humans and its deficiency has been associated with decreased coronary artery diseases (44). Among the promising therapeutic approach the antisense oligonucleotide (ASO) represent a promise in specific targeting of disease-associated genes in dyslipidemia. The most advanced antisense lipid-lowering agent in development is Mipomersen, an apoB-100 synthetises inhibitor. Mipomersen has been shown to significantly decrease Lp(a) concentrations by about 30% (46).

Others ASOs drug reduce Lp(a) up to 80% but are still in phase 1–2 studies (47).

Many studies have shown high levels of Lp(a) (>50 mg/dL) or genotype rs10455872 variant are associated with potential mechanisms that raises cardiovascular risk and grows the atherosclerotic plaque. Perrot *et al.*, in the Epic Norfolk prospective population study evaluated the Cardiovascular Health Score (CHS) in Lp(a) levels or genotype (48).

The Cardiovascular Health Score was calculated on these seven-health metrics with an ideal, intermediate or poor status. The seven components of CHS are body mass index, healthy diet score, physical activity, smoking behaviour, blood pressure, diabetes mellitus and total cholesterol.

This study shows that to reduce cardiovascular disease risk associated with high lipoprotein (a) levels or genotype should be added on top of lifestyle management and on top of other agents that target risk factor for CVD such as LDL cholesterol, blood pressure, diabetes.

Lifestyle programmes have a beneficial effect on cardiovascular risk management and on recurrent cardiovascular events. An improvement of physical activity levels, dietary habits, and smoking cessation showed promising results. In the present era of increasing number of overweight and physically inactive patients, this study confirms the importance of risk factor control through lifestyle modification as a supplement to more intensified drug treatment.

Additional research can take into account adherence to management strategies as well as investigate the effects of multiple interventions. Moreover the lifestyle management strategy require little to no equipment, no expensive medication and can be performed at home or at the convenience of patients.

Further research can examine whether these low-cost strategies are cost-effectiveness compared to other CVD management strategies and demonstrate whether tailored therapies do improve health outcomes and patients adherence.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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