Increased cardiovascular risk associated with hyperlipoproteinemia (a) and the challenges of current and future therapeutic possibilities

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ABSTRACT

Population, genetic, and clinical studies demonstrated a causative and continuous, from other plasma lipoproteins independent relationship between elevated plasma lipoprotein (a) [Lp(a)] concentration and the development of cardiovascular disease (CVD), mainly those related to atherosclerotic CVD, and calcific aortic stenosis. Currently, a strong international consensus is still lacking regarding the single value which would be commonly used to define hyperlipoproteinemia (a). Its prevalence in the general population is estimated to be in the range of 10%–35% in accordance with the most commonly used threshold levels (>30 or >50 mg/dL). Since elevated Lp(a) can be of special importance in patients with some genetic disorders, as well as in individuals with otherwise controlled major risk factors, the identification and establishment of the proper therapeutic interventions that would lower Lp(a) levels and lead to CVD risk reduction could be very important. The majority of the classical lipid-lowering agents (statins, ezetimibe, and fibrates), as well as nutraceuticals (CoQ10 and garlic), appear to have no significant effect on its plasma levels, whereas for the drugs with the demonstrated Lp(a)-lowering effects (aspirin, niacin, and estrogens), their clinical efficacy in reducing cardiovascular (CV) events has not been unequivocally proven yet. Both Lp(a) apheresis and proprotein convertase subtilisin/kexin type 9 inhibitors can reduce the plasma Lp(a) by approximately 20%–30% on average, in parallel with much larger reduction of low-density lipoprotein cholesterol (up to 70%), what puts us in a difficulty to conclude about the true contribution of lowered Lp(a) to the reduction of CV events. The most recent advancement in the field is the introduction of the novel apolipoprotein (a) [apo(a)] antisense oligonucleotide therapy targeting apo(a), which has already proven itself as being very effective in decreasing plasma Lp(a) (by even >90%), but should be further tested in clinical trials. The aim of this review was to present some of the most important accessible scientific data, as well as dilemmas related to the currently and potentially in the near future more widely available therapeutic options for the management of hyperlipoproteinemia (a). *(Anatol J Cardiol 2020; 23: 60-9)*
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Introduction

Lp(a) structure and metabolism

Lipoprotein (a) [Lp(a)] is a plasma lipoprotein consisting of a low-density lipoprotein (LDL) particle, which is cholesterol rich, one molecule of apolipoprotein B-100 (apoB), and an additional high molecular weight glycoprotein, apolipoprotein (a) [apo(a)], covalently bound to apoB with a single disulfide bond (1). Knowing at least some basics of Lp(a) metabolism, starting from its apoprotein synthesis, plasma modifications of the molecule, as well as its catabolism, is important not only for better understanding of its (patho-)physiological role but also to become familiar with the present and future therapeutic options (2).

Apo(a) is structurally homologous with plasminogen, synthesized exclusively by the liver, and encoded by the *LPA* gene. It is hydrophilic and does not contain lipid domains or transport lipid. Genetic polymorphism studies of this gene indicate that Lp(a) is causally implicated in the development of CVD (3, 4). The true basis of the existence of size polymorphism of apo(a) isoforms, which is important not only for Lp(a) plasma levels (less repeats means higher plasma levels) but also for the function of the entire molecule and the cardiovascular risk it carries, is created by the variable number of the so-called kringle IV type 2 repeats (from 2 to >40) within this gene.

The site of the assembly of the Lp(a) molecule, which consists of two steps, first docking of the apo(a) onto the LDL and then linking of its apoB with the kringle IV type 9 of the apo(a), is not exactly known, but it most likely occurs either at the hepatocyte surface or in plasma. In addition, the site and mechanisms of Lp(a) catabolism are not yet fully understood. There is no spe-

cific receptor for Lp(a) or apo(a) described, and basic studies on cell cultures, as well as genetic, animal, and human clinical studies, suggest only a moderate role of LDL receptor (LDLR) in its plasma clearance. It could be that some other catabolic paths can play a role, such as clearance via the kidney, scavenger receptor B1, and plasminogen receptors, as well as proteolytic degradation of apo(a) (1, 2).

Lp(a) and cardiovascular risk

It appears that the predominant physiological role of Lp(a) is to bind and transport proinflammatory oxidized phospholipids in plasma. Lp(a) possesses additional characteristics, which can cause several detrimental effects on human health. It was demonstrated that the molecule is involved in almost all stages of atherothrombosis, from the beginning of the atherosclerotic plaque formation to the thrombosis, which follows its rupture. Lp(a) can induce the expression of inflammatory mediators, modulate platelet aggregation, increase foam cell formation, reduce fibrinolytic activity, and was found to be also involved in vascular remodeling and plaque calcification. All described above can explain the increased risk of atherosclerosis and CVD conferred by hyperlipoproteinemia (a) (1, 2, 5, 6).

Circulating Lp(a) levels are almost entirely (>90%) genetically determined and independent of age and gender. Plasma Lp(a) concentration can be found elevated in kidney disease, hypothyroidism, pregnancy, postmenopause, during growth hormone therapy, familial hypercholesterolemia (FH), and familial defective apoB. Elevated plasma concentration of Lp(a) is strongly associated with an increased risk of cardiovascular mortality and morbidity, mainly from coronary artery disease, ischemic stroke, and calcific aortic valve stenosis (4, 7, 8). Evidence from large genetic and observational studies, as well as systematic reviews of prospective studies, showed a modest, but statistically significant relationship both in primary prevention (within the general population) and in secondary prevention populations (average hazard ratios of approximately 1.2–2.0) (7, 9-13).

From the therapeutic point of view, it is important that the aforementioned almost absolute genetic determination of Lp(a) plasma values is also the main reason of why its increased plasma levels contribute significantly to the residual CVD risk in subjects with other risk factors under control. However, in this context, it is worth to mention the findings of the recently published analyzes from the EPIC Norfolk and Copenhagen City Heart studies (14). It was reported that patients with the highest Lp(a) levels demonstrated a greater risk of CV events at all LDL-C [corrected for a proportion of cholesterol being carried by Lp(a)] levels >2.5 mmol/L, but not in individuals with lower levels of LDL-C (15).

When to measure Lp(a) and the elevated risk threshold values

It is important to note that Lp(a) determination for screening or diagnostic purposes needs to be performed only once, since due to its almost entire genetic determination there are no significant fluctuations over time. The most recent, 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the Management of Dyslipidemias recommend that measurement of Lp(a) should be systematically performed in individuals with high CVD risk or a strong family history of premature atherothrombotic disease. In addition, Lp(a) measurement should be considered in patients with intermediate-to-high risk for CVD (16). Lp(a) testing would be reasonable in adults with first-degree relatives with premature atherosclerotic cardiovascular disease (ASCVD) (<55 years old in men and <65 years old in women) or a personal history of premature ASCVD, as well as in primary severe hypercholesterolemia (LDL-C >190 mg/dL) or suspected FH, and in patients with recurrent or progressive ASCVD despite optimal lipid lowering according to the guidelines developed by the United States-based scientific societies (National Lipid Association (NLA) and American College of Cardiology [(ACC)/American Heart Association (AHA)] (17, 18).

Since the measurement of Lp(a) levels is not included in the standard lipid profile, it is not easy to ascertain the potential number of all subjects with hyperlipoproteinemia (a) who would potentially benefit from treatment. For everyday practice, as well as in clinical studies, the most commonly used lower threshold value to define hyperlipoproteinemia (a) is an Lp(a) level of >30 mg/dL. According to this threshold, large studies in different populations reported its prevalence in the general population in the range of 10%–35% (19). BiomarCaRE project (20), performed on a European population, confirmed Lp(a) as a marker of increased CV risk at the level of >50 mg/dL, which is also in line with the cutoff levels recommended by the ESC/EAS, as well as the ACC/AHA guidelines. The same study also showed a North–South gradient of Lp(a) levels across Europe, with lower levels in the Northern European cohorts. It is worth to mention that the 90th percentile of the values within the study cohorts, both in primary (Copenhagen Heart Study) and in secondary prevention (Long-Term Intervention with Pravastatin in Ischemic Disease), was found at approximately 70 mg/dL.

The reliability of the currently available laboratory measurements

One of the Lp(a)-related issues being recently quite extensively discussed in the literature is related to the validity and reliability of the currently available assays for the measurement of the plasma Lp(a) concentration (21). Plasma Lp(a) levels are generally reported as mass concentrations (mg/dL), which include the protein content of apoB and apo(a), their associated lipids (cholesterol, cholesteryl esters, phospholipids, and triglycerides), as well as carbohydrates attached to apo(a). Lp(a) is mostly measured with immunochemical methods relying on the detection of the apo(a) where the problem arises related to the size polymorphism of this protein. Mass assays may contain significant bias due to a potential of significant heterogeneity of particle sizes to underestimate the levels of small and overestimate large Lp(a)

isoforms. In addition, there are some other important methodical issues in place, so as the fact that Lp(a) particles independently of its size polymorphisms vary in molar mass and hydrated density, as well as that Lp(a) forms mixed aggregates with LDL that are not always fully dissociable (22). This is the reason why the NLA recommended that Lp(a) measurements should be performed using an immunochemical assay that is calibrated against the World Health Organization/International Federation of Clinical Chemistry and Laboratory Medicine secondary reference reagent (23). Anyhow, in the future, more comparison studies of different assays and full standardization of the assays are needed, despite the currently available assays can be considered fairly accurate for differentiating low- from high-risk patients (2).

How much reduction of plasma Lp(a) is needed for the effective decrease of adverse cardiovascular outcomes?

The role of Lp(a) as a potential new therapeutic target evokes substantial and extensively increasing interest on its research (24, 25). From this perspective, it is important to cite the results of the recently published trials using proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (evolocumab and alirocumab, see discussion below), which confirmed that with already a modest Lp(a) reduction of up to 30%, the significant reduction of CV outcomes can also be achieved (26, 27). However, Mendelian randomization analyzes suggested that larger relative reductions would be needed in plasma Lp(a) than in LDL-C for the comparable clinical effects. For each 10 mg/dL reduction of the plasma Lp(a), a 5.8% decreased CV risk was shown, which gives us the basis to calculate that for the substantial and significant effect to reduce the coronary artery disease, the absolute decrease of

Lp(a) by 60–70 mg/dL would be needed (28). As this projected reduction is truly very large, it is important to recall that it may be modified in the overall setting of additional cardiovascular risk factors, where the clarification is needed on whether Lp(a) continues to be or not an important risk factor also in patients with low LDL-C levels (15). It is more than obvious that for the firmer conclusions on all these unanswered questions, further clinical trials would be needed. Emerging therapies targeting the apo(a) component of the molecule have the potential to revolutionize the management of individuals with elevated Lp(a). Prospectively, exciting findings are expected from the additional clinical studies using antisense therapy targeting the synthesis of apo(a), which was already shown to have the potential to lower Lp(a) by >90% of its initial values (29, 30).

Elevated Lp(a) Management–Current Treatment Approaches

The magnitude of Lp(a) lowering effects as well as the most probable mechanisms using currently approved and emerging, both primarily lipid lowering treatments and other Lp(a) lowering effective approaches are summarized in Table 1.

Classical lipid-lowering therapies
Statins

Statins continue to play the widely accepted key role of the comprehensive pharmacotherapy in primary and secondary CVD prevention owing to their substantial potency to decrease both LDL-C and cardiovascular risk. It was suggested that by achieving the target levels of LDL-C <1.8 mmol/L (70 mg/dL), the atherogenic potential of Lp(a) could also be overruled. Such an

Table 1. Currently approved and emerging, both primarily lipid-lowering treatments and other Lp(a)-lowering effective approaches

Treatment	Plasma Lp(a) change	Potential mechanism(s) of Lp(a) lowering
Statins	↓ 5% to ↑ 20%	Partial removal via LDLR, induction of apo(a) mRNA
Ezetimibe	↓ 10%	Partial removal via LDLR, decreased Lp(a) synthesis
Niacin	↓ 23%	Decreased apo(a) production rate
Fibrates	N to ↓ 25%	Inhibition of apo(a) transcription
CETP inhibitors (anacetrapib)	↓ 35%	Decreased apo(a) production rate
Lp(a) apheresis	↓ >60% (per procedure)/↓ 30% (long term)	Physical removal of Lp(a) particles
Anti-PCSK9 antibodies	↓ 30%	Removal via LDLR
Anti-PCSK9 siRNA (inclisiran)	↓ 25%	Decreased production of apoB
Mipomersen	↓ 25–40%	Apo(a) production rate and catabolism
IONIS-APO(a)$_{Rx}$/IONIS-APO(a)-L$_{Rx}$	↓>80%/↓ >90%	Inhibition of apo(a) synthesis
Aspirin	↓ 18–56%	Suppression of apo(a) mRNA and apo(a) production
Hormone replacement therapies (estrogens, tibolone, tamoxifen)	↓ 25%	Inhibition of apo(a) synthesis

Lp(a) - lipoprotein (a); apo(a) - apolipoprotein (a); apoB - apolipoprotein B-100; LDLR - LDL receptor; CETP - cholesteryl ester transfer protein; PCSK9 - proprotein convertase subtilisin/kexin type 9; siRNA - small molecule inhibiting RNA; APO(a)$_{Rx}$ - antisense oligonucleotide that inhibits apo(a) synthesis in the liver; APO(a)-L$_{Rx}$ - APO(a)$_{Rx}$ conjugated with N-acetyl-galactosamine; CV - cardiovascular

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5 key messages related to lipoprotein (a)

- Lipoprotein (a) [Lp(a)] is a proatherogenic, prothrombotic, proinflammatory, and prooxidative particle.
- Circulating Lp(a) levels are genetically determined, so one measurement is sufficient for risk assessment.
- Lp(a) should be measured in individuals with high cardiovascular risk, severe primary hypercholesterolemia, premature atherosclerosis, or a strong family history of premature atherothrombotic disease.
- Currently available treatment options to lower plasma Lp(a) are far from being optimal.
- Novel targeted therapies, e.g., antisense oligonucleotide treatment, to inhibit Lp(a) synthesis are being evaluated in ongoing trials.

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assumption was proven wrong, since it was demonstrated that high plasma Lp(a) stays as an independent major risk factor for CVD even in patients who achieve the recommended LDL-C and leads to increased atherosclerosis burden and residual risk (31-33).

Statin therapy in general does not reduce plasma Lp(a); on the contrary, many studies showed that most of them actually increase its levels, by even up to 25%. The main reason behind could be the fact that LDLR does not play a significant role in Lp(a) clearance, and in addition, based on cell culture studies, it was shown that treatment with statins can result in an increase expression of LPA mRNA and consequently the apo(a) (31, 34, 35).

Recently, it was suggested that in an individual patient, the Lp(a) effect of a statin can differ in accordance with the isoforms of apo(a) size polymorphism, the Lp(a)'s major genetic regulator (35, 36). In subjects who initiated statin therapy, it was observed that statins significantly increased Lp(a) levels in carriers of a small size apo(a), whereas no significant changes were observed among non-carriers, i.e., in patients having a high molecular weight phenotype (37). However, this interesting finding should be interpreted cautiously and need to be confirmed in larger studies, since mechanisms underlying the selective increase in Lp(a) in carriers of a small apo(a) are unclear. One possible hypothesis could even be that perhaps an overall increased awareness of patients initiating statin therapy regarding healthy lifestyle may contribute, while it was shown that the reduced intake of saturated fat could be associated with an increase, whereas its increase with the decrease of Lp(a) level (38-40).

It remains to be recommended, even in patients with elevated Lp(a), that statins should be used in their highest needed or tolerable doses. The rationale behind is to achieve as great as possible reduction of the overall CVD risk through the statin effect on the LDL-C-related portion of it, since at the end, the efficacy of statins in reducing CVD appears similar among subjects with high or low Lp(a) concentrations (32).

Ezetimibe

Ezetimibe can moderately reduce plasma LDL-C, and in very high-risk patients, this effect has been associated with an improvement of cardiovascular prognosis (41). It was hypothesized that this drug would also have an impact on plasma Lp(a), and a beneficial effect of ezetimibe on plasma Lp(a) levels was indeed reported owing to the similarity in the lipid composition between Lp(a) and LDL particles (42-44). Recently published larger meta-analysis of otherwise inconsistent results of 10 randomized placebo-controlled trials showed that this is probably not the case (45). Subgroup analysis did not show any significant change of plasma Lp(a) either in trials evaluating the impact of monotherapy with ezetimibe versus placebo or in trials assessing the impact of adding ezetimibe to a statin versus statin therapy alone (45).

Niacin

Treatment with niacin was proven effective to decrease plasma Lp(a) levels (46). Large meta-analysis demonstrated a 22.9% reduction of Lp(a) with an extended-release niacin (ERN), which was not shown to be dose-related (47). The ERN-induced reduction of Lp(a) levels was shown proportional to the apo(a) isoform size and is due to a significant decrease of apo(a) production rate, either through the direct inhibition of transcription of the apo(a) gene or to the increased retention of apo(a) at the hepatocyte surface (48, 49). Currently, the use of this drug in clinical practice is significantly limited since unfortunately, later trials showed that niacin co-administered with statins in patients with CVD does not improve cardiovascular outcomes and is also associated with an increased risk of adverse events, so the expected potential net beneficial clinical effect can be rather poor (50, 51).

Fibrates

In a meta-analysis, fibrates were shown to have a significantly greater effect in reducing plasma Lp(a) concentration than statins, despite studies showing mixed results – they were effective in some, whereas not in other studies (52, 53).

PCSK9 inhibition

In addition to their prominent substantial effect on plasma LDL-C reduction and associated prevention of major ASCVD events, both currently available anti-PCSK9 antibodies (evolocumab and alirocumab) also significantly decrease Lp(a) plasma concentrations (by up to nearly 30%) (54, 55). Their effects were shown to be greater in patients with higher baseline Lp(a) levels. The mechanism by which PCSK9 inhibitors decrease plasma Lp(a) has not been clearly elucidated. In this context, it is interesting to draw parallels between the findings related to the Lp(a) effects for both PCSK9 inhibitors and statins. Despite

both groups of drugs reduce LDL-C through the upregulation of LDLR, their effect on Lp(a) is different. It could be that while Lp(a) may perhaps have lower affinity for the LDLR than for the LDL particle itself, a reduced level of competition between Lp(a) and LDL as the levels of the latter are reduced might increase the potential for receptor-mediated clearance of Lp(a) (54, 56). It has also been suggested that PCSK9 inhibitor used as a monotherapy lowers the plasma Lp(a) by decreasing the production of Lp(a) particles, whereas PCSK9 inhibition in combination with statins also lowers the plasma Lp(a) pool size by accelerating the catabolism of Lp(a) particles (57).

It was reported that in patients with higher than median Lp(a), greater absolute reduction of different major adverse cardiac event (MACE) can be achieved from CV outcome trials using anti-PCSK9 antibodies (FOURIER and ODYSSEY Outcomes) (26, 27). The same was confirmed in patients with a recent acute coronary syndrome (ACS) treated with alirocumab, which suggested that Lp(a) could be a therapeutic target in selected patients after recent ACS (27). On the other hand, in post-hoc analysis of data pooled from 10 phase 3 alirocumab trials in patients with CVD and/or risk factors and hypercholesterolemia despite statin/other lipid-lowering therapies, the authors could not demonstrate a significant association between Lp(a) reductions and MACE, which would be independent of the LDL-C decrease (55). Recently, it was suggested that in PCSK9 inhibitor-treated patients with hyperlipoproteinemia (a), only modest lowering of Lp(a) – being indeed associated with the significant LDL-C decrease – could be associated with the persistence of the arterial wall inflammation (58).

In addition to anti-PCSK9 monoclonal antibodies, small molecules are also in development which inhibit PCSK9 RNA (siRNA). These agents, through the silencing of the PCSK9 gene, primarily lower LDL-C and apoB. With their use, some promising initial results were already shown, not only in relation to their LDL-C lowering effect but also in their ability to decrease plasma Lp(a). In ORION-1, a phase 2, multicenter, double-blind, placebo-controlled trial, treatment with inclisiran, a long-acting, synthetic siRNA directed against PCSK9, aside of up to 52.6% reduction in LDL-C, resulted in a 25.6% reduction in Lp(a), comparable with evolocumab and alirocumab effects (59).

In summary, conclusive evidence is still lacking as to whether the treatment with PCSK9 inhibition against background statin therapy can actually additionally reduce ASCVD risk due to the lowering of Lp(a), or the beneficial result is simply due to the lowering of LDL-C to levels much lower than achieved by the high-intensity statin treatment as monotherapy (60). As it was already mentioned, the true additional effect to reduce the risk of MACE by targeting Lp(a) may require extensive Lp(a) reductions, larger than those which can be attained with PCSK9 inhibitors, and it can potentially come true either with more potent therapies and/or only in patients with very high initial Lp(a)/LDL-C levels (27). Ongoing trials will undoubtedly provide at least some answers to these questions.

Lp(a) apheresis

Lipoprotein apheresis (LA) can effectively decrease Lp(a) concentrations in patients with severe progressive ASCVD and very high Lp(a) levels. LA involves the physical removal of lipoproteins from the blood, lowers levels of Lp(a) significantly by >60% per treatment, or to an average of approximately 30% on long-term. In principle, this treatment is employed in patients with very high hypercholesterolemia who cannot achieve acceptable plasma lipoprotein levels despite appropriate lifestyle changes and the most intensive possible pharmacologic lipid-lowering interventions applied (61, 62).

Some trials and data from registries show that regular apheresis effectively reduces CV events (63). The results of 5 years of prospective follow-up confirmed that Lp(a) apheresis has a lasting effect on the prevention of CV events in patients with hyperlipoproteinemia (a), reducing the mean annual cardiovascular event rate by up to 80% (64, 65). However, it should be noted that LA removes Lp(a) and LDL simultaneously, which makes it hard to distinguish the beneficial effects of lowering either one or the other molecule of the two.

LA is an invasive, in most cases until recently, also a lifelong therapeutic method by which venous puncture problems may arise, hypotensive episodes may occur, and there is a risk of bleeding due to the use of anticoagulation needed during LA sessions. The method is expensive and impractical for most patients, and its feasibility depends mainly on the healthcare reimbursement system (66). LA still plays a significant role in the management of patients with homozygous FH, as well as in the management of some patients with other severe drug-resistant dyslipidemias and established CVD.

Other less used lipid-lowering therapies

Anacetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, induced up to 35% reduction of plasma Lp(a) concentration, and it appears that Lp(a) lowering could be due to a reduction in the apo(a) production rate (67). Anyway, these drugs are currently not being used in clinical practice, since the effects of these agents in the most important clinical studies on CVD risk were shown to be harmful, neutral, or only slightly positive.

Mipomersen, an antisense oligonucleotide (ASO) targeting the synthesis of apoB [but not the apo(a)], being currently approved for the treatment of homozygous hypercholesterolemia, demonstrated the effect of 25%–40% reduction of plasma Lp(a) (68). The main limitation with this drug to be used for the treatment of hyperlipoproteinemia (a) stays with its safety issues, since several potential adverse effects which frequently lead to a discontinuation of the treatment (e.g., injection-site reactions, hepatic steatosis, and elevated liver enzymes) were reported (69).

Eprotirome, a thyroid hormone analogue, demonstrated even a greater mean reduction of Lp(a) levels of up to 43% in otherwise statin-treated patients (70). Anyhow, longer trials are required to confirm such a beneficial Lp(a)-lowering effect of eprotirome, as

well as its safety with regard to potential long-term adverse thyromimetic effects.

Additional choices
Aspirin

This traditional drug has also been found with a favorable effect in hyperlipoproteinemia (a), and this option appears quite useful since the drug is already almost universally prescribed to patients at high- or very high cardiovascular risk and those who already manifest ASCVD. Reports from two small trials in patients with CAD and/or stroke demonstrated that aspirin in a dose of 81 or 150 mg can reduce Lp(a) plasma concentrations by 18%–56%, with a greater effect shown in patients with higher Lp(a) levels at baseline (71-73). It appears that with the suppression of apo(a) mRNA, the apo(a) production from hepatocytes is also inhibited from in vitro studies on human hepatocytes to explain the potential molecular mechanism of aspirin-induced Lp(a) reduction (74). As it is the case with many other Lp(a)-lowering therapies, such an effect of aspirin will also need to be evaluated in prospective, randomized controlled trials.

Hormone replacement therapies

The favorable effect of estrogen and/or hormone replacement therapy (HRT) on hyperlipoproteinemia (a) is supported with an extensive clinical evidence. Meta-analysis of >100 trials evaluating the different CV protective effects of HRT in postmenopausal women demonstrated a mean Lp(a) level reduction of 25% (75). Such a finding among those taking HRT was confirmed by 19% lower Lp(a) accompanied by an attenuation of the predictive value of Lp(a) levels on CVD risk (76). Despite the Heart and Estrogen/progestin Replacement Study failed to reduce the overall rate of coronary heart disease (CHD) events and was also associated with an increase in the rate of thromboembolic events (77), it was shown that HRT exerted a more favorable effect in women with higher initial Lp(a) levels, and that the subset of women on HRT who achieved substantial reductions in Lp(a) also had a significant reduction in the risk for CHD events (78).

In addition, some other estrogen-related agents, such as tibolone and tamoxifen, were being evaluated for their effect on Lp(a) (79, 80). According to systematic reviews and meta-analyzes, treatment with tibolone can lead to a significant 25.3% mean reduction in Lp(a) levels in postmenopausal women (79). While also with treatment with tamoxifen, a selective estrogen receptor modulator (otherwise widely used in the treatment of breast cancer), a significant reduction in Lp(a) levels was demonstrated (80). However, to make a somehow stronger recommendation on the use of these agents, the impact of the observed Lp(a) reductions on CVD risk remains to be explored in additional trials.

Since the current evidence does not support the use of postmenopausal HRT with the aim of either primary or secondary prevention of CVD, the favorable effect of the use of estrogen/HRT in the treatment of hyperlipoproteinemia (a) is restricted only to women who have an indication for taking it due to a gynecological reason (77, 81).

Nutraceuticals

It was already mentioned above that the increase of saturated fat intake may decrease Lp(a) concentration and, similarly, can be with ethanol (especially red wine) intake, where of course limits are necessary. Coffee and tea intake may decrease Lp(a) level, but further investigation is crucial before they can be considered potent Lp(a)-lowering agents. Meta-analysis on the plasma Lp(a) effect of garlic did not find a relevant change obtained by its consumption; in the subgroup of trials lasting for >12 weeks, a significant increase in plasma Lp(a) concentrations was reported (82). Among food-supplementing strategies, only L-carnitine and coenzyme Q10 were found as potentially promising alternatives in achieving lower Lp(a) levels, whereas despite potential CV benefits, current research fails to justify the use of higher doses of vitamin C, soy isoflavones, and/or ω-3-fatty acids for this purpose (83).

Emerging Treatment Possibilities with RNA-Targeted Therapies

Apo(a) is synthesized in the liver, so the therapies directed on the hepatocytes are also likely to be most efficacious in Lp(a) lowering. As already mentioned, mipomersen, an ASO which markedly inhibits mRNA of apoB, does not affect the production of apo(a), but could lower Lp(a) by influencing the Lp(a) assembly. The ASO by which we can inhibit apo(a) synthesis in the liver is currently the only available approach for specific Lp(a) lowering (84, 85). Being injected subcutaneously, they enter the circulation and bind to plasma proteins, while after entering the liver, they accumulate in the hepatocytes. ASOs bind intracellularly to their target mRNA, mainly in the nucleus, but possibly also in the cytoplasm if mRNA is present there. When a double-stranded complex is formed, ribonuclease H1 cleaves the sense strand to prevent protein synthesis, but the antisense strand (i.e., ASO) can bind to additional mRNA targets. In case of ASO to apo(a), the hepatocytes can continue to synthesize LDL particles and export them; therefore, steatosis (as with mipomersen) should not occur, but both apo(a) alleles will be inhibited, Lp(a) assembly prevented, and plasma Lp(a) levels reduced.

Early phase clinical trials using IONIS-APO(a)$_{Rx}$ showed very substantial, dose-dependent Lp(a) reduction (up to 80%) and at the same time confirmed that the treatment is well tolerated. In addition, a significant reduction was noted in proinflammatory OxPL and in the inflammatory effects of monocytes, which are cells that initiate and accelerate ASCVD (86).

By the development of the advanced, hepatospecific N-acetyl-galactosamine-conjugated molecule (IONIS-APO(a)-L$_{Rx}$), which was genuinely designed to be more highly and selectively taken up by hepatocytes, the drug is approximately 30

times more potent. The results of the IONIS-APO(a)-L$_{Rx}$ phase 2 trial were presented recently. The highest dosages reduced Lp(a) by >90%, and the Lp(a) levels of <50 mg/dL were achieved in almost all patients. Tolerability and safety were confirmed, whereby only injection-site reactions were the most common side effects. It is important to note that in fact, 12% of injections with IONIS-APO(a)$_{Rx}$ were associated with injection-site reactions, whereas IONIS-APO(a)-L$_{Rx}$ was associated with no injection-site reactions. Thus, these new agents targeting the synthesis of apo(a) may potentially assist clinicians effectively to diminish Lp(a)-mediated cardiovascular risk (87). In addition, all described raises hope that the planned phase 3 trial will reproduce these findings and also show a significant reduction of cardiovascular events.

Conclusion

Many pre- and clinical studies confirmed the important role of elevated plasma Lp(a) in increasing the risk of ASCVD, which is independent of the LDL-C effects. This makes hyperlipoproteinemia (a) an optimal therapeutic target in ASCVD prevention. It is well known that an early detection and intervention, preferably before the onset of ASCVD, offers the best opportunity to reduce the time-dependent risk associated with this important risk factor. However, clinical evidence on Lp(a) reduction as a true and beneficial effect in preventing ASCVD events is limited. The currently available treatment options to lower plasma Lp(a) are far from being optimal, either because of too moderate effect to assure the clinical benefit, lack of outcome trials, or safety issues. At the same time, some new therapeutic interventions and novel targeted therapies are being evaluated in ongoing trials. It appears that we can bet the most on the new-coming treatment with ASO therapies targeting apo(a), which in early phase clinical trials have already demonstrated promising results, both regarding efficacy and safety. More extensive and longer clinical studies will confirm those and trust that our optimism will be paid off by the rather quick introduction of these new, potentially much more effective treatments into everyday clinical practice.

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