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Pharmacological methods to lower lipoprotein(a) levels

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ABSTRACT

Lipoprotein(a) exhibits proatherogenic properties, thus promoting the development of atherosclerotic cardiovascular disease. Lp(a) levels are genetically determined and relatively constant at the turn of a patient's life. Even a single measurement could be an important screening test to distinguish a group of patients with increased cardiovascular risk. Despite the lack of specific therapies, drugs with potential effects on reducing Lp(a) levels include ezetimibe, PCSK-9 inhibitors, fibrates, inclisiran, olparisan, aspirin, tocilizumab or mipomersen.

Although ezetimibe has shown a moderate effect on lowering Lp(a) in monotherapy, its combination with statins does not provide a significant additional benefit in reducing Lp(a). PCSK-9 inhibitors contribute to a significant reduction in cardiovascular risk in patients in whom maximum-dose statin therapy fails to achieve lipoprotein targets. Patients with baseline higher Lp(a) levels receive greater benefit from PCSK9 inhibitor therapy. The use of aspirin to reduce Lp(a) levels could be most significant in rs3798220 carriers, but the European Atherosclerosis Society does not support the advisability of such a drug. Studies involving tocilizumab are promising, but data on non-RA groups are lacking. Mipomersen, on the other hand, has shown significant lipoprotein(a)-lowering effects, but is only used to treat familial hypercholesterolemia due to the risk of side effects.

The aim of this systematic review was to discuss lipoprotein(a)'s potential as an independent cardiovascular risk factor and summarize pharmacological approaches available to lower its levels according to currently available knowledge based on the main findings of randomized clinical studies, review studies and meta-analyses.

Keywords: atherosclerotic cardiovascular disease, lipoprotein(a), olparisan, tocilizumab, mipomersen

Introduction

Lipoprotein(a), also known as Lp(a), by its structure resembles low-density lipoprotein (LDL), which plays a key role in the transport of cholesterol in the blood [1]. In addition, it is characterized by the presence of apolipoprotein(a) (apo(a)), bound to apoB-100 via a single disulfide bridge. Lp(a) is produced by hepatocytes, and values of reported plasma Lp(a) concentrations range from < 1 mg to > 1000 mg/dL. Data analysis by Maranhão et al. showed that Lp(a) levels as low as 20–30 mg/dL are associated with a twofold increased risk of developing coronary artery disease (CAD) [2]. A review of 2022 data shows that plasma Lp(a) concentrations especially above 50 mg/dL, are associated with an increased risk of cardiovascular disease, including myocardial infarction, stroke, aortic stenosis, heart failure, peripheral artery disease and mortality from any cause. Homology of Lp(a) with plasminogen may lead to interference with the fibrinolytic cascade, which is an atherogenic mechanism of action of this lipoprotein. Another possible mechanism of action is the interaction of Lp(a) with blood vessel wall cells, including smooth muscle and endothelial cells, and deposition in arterial walls [3].

Elevated Lp(a) levels are identified as an independent genetic cardiovascular risk factor. It is estimated that individuals with elevated Lp(a) levels have a 2–4-fold increased risk of ASCVD (atherosclerotic cardiovascular disease) [4]. A comprehensive meta-analysis

indicates that one in five people worldwide has elevated Lp(a). This global perspective is crucial to understanding the overall impact of Lp(a) on the development of cardiovascular complications in different populations. The Bruneck Study [5] and EPIC-Norfolk cohort [6] showed that measuring Lp(a) levels is an independent factor that improves patient reclassification in the SCORE (Systematic COronary Risk Evaluation), ACC/AHA (American College of Cardiology/American Heart Association), Framingham, Reynolds Risk Score algorithms) for ischaemic heart disease and myocardial infarction.

The aim of this systematic review was to discuss lipoprotein(a)'s potential as an independent cardiovascular risk factor and summarize pharmacological approaches available to lower its levels according to currently available knowledge based on the main findings of randomized clinical studies, review studies and meta-analyses.

Material and methods

To mitigate the risk of bias, a comprehensive review of the published literature was undertaken, adhering to the PRISMA guidelines for the reporting of systematic reviews in healthcare interventions [7]. A database search including PubMed and Google Scholar databases, covering the period from January 2000 through December 2023 was conducted by four independent investigators (N.W., J.O-W., A.D. and K.Ż.), none of whom were involved in any of the retrieved studies. Additionally, materials from the Scientific Sessions of the European Atherosclerosis Society (https://eas-society.org) were reviewed. The following keywords were applied: 'atherosclerotic cardiovascular disease' and 'lipoprotein(a)'. References of retrieved studies were searched manually for additional studies and reviews. No language restrictions were applied. Data were abstracted on prespecified forms. Only clinical studies that detailed the mechanism of action, measurement, and pharmacological strategies for reducing lipoprotein(a) levels, and were available in full text, were deemed suitable for inclusion. The criteria for inclusion in the systematic review required clear reporting on the study's design, characteristics of the participants, the regimen and duration of therapy, and its impact on lipoprotein(a) levels. Data regarding these aspects of the included studies were meticulously extracted. Reviews and meta-analysis were also considered sources of citations of relevant studies and interpretation of their results. After a systematic search 20,034 citations were identified:

2,134 from PubMed and 17,900 from Google Scholar. Citations that were duplicates, multiple, or reviews lacking relevant information were excluded. Eventually, 50 papers discussing lipoprotein(a)'s potential as an independent cardiovascular risk factor, and pharmacological approaches to lower its levels were considered eligible for inclusion in the systematic review.

Recommendations for measuring lipoprotein(a) levels

According to recent European guidelines and a growing body of evidence, lipoprotein(a) levels should be measured in adults a minimum of once at the turn of life [8]. A single measurement may be sufficient, due to the high heritability of Lp(a). Finding an Lp(a) concentration above the 99th percentile is a significant indicator of lifetime ASCVD risk [9].

Lp(a) concentrations can increase until adulthood, therefore repeated measurements are not necessary in adulthood (with few exceptions i.e. acute infections, liver disease, kidney disease), as they do not change the final predicted risk score. In children, risk factors i.e. ischaemic stroke or family history of premature ASCVD may prompt multiple Lp(a) measurements due to the high heritability of this indicator [10]. In the COMPARE study of 450 newborns, low levels of Lp(a) were shown to be present early in life, and levels of Lp(a) in cord blood correlated strongly with its level in venous blood [11]. Further research into neonatal diagnosis and birth (i.e., umbilical or venous) Lp(a) levels could be an important newborn screening test to identify those at higher risk for cardiovascular disease.

Currently, the methodology for determining Lp(a) is a problem. Due to the variability in the size and molecular structure of Lp(a), current methods depend to varying degrees on the Lp(a) isoform. It is therefore still necessary to standardize analytical methods and their results [12]. The 43-variant LPA-GRS genetic risk scale for lipoprotein(a), explains about 60% of the variability in directly measured plasma Lp(a) levels. This study has demonstrated efficacy in predicting CVD (cardiovascular disease) risk and provides a solid basis for clear guidelines in the future [13].

Factors affecting Lp(a) levels

Research is still ongoing to develop effective therapies to lower Lp(a) levels. Currently, there are no approved specific therapies targeting the reduction of elevated plasma Lp(a) levels, although there are clinical data suggesting a benefit from such a reduction.

Ezetimibe

Ezetimibe, as an inhibitor of cholesterol absorption in the small intestine, acts by blocking the Niemann-Pick C1-Like1 (NPC1L1) transporter. The mechanism by which ezetimibe reduces lipoprotein(a) levels remains unclear. A correlation has been suggested between an increase in Lp(a) and increased levels of acute phase reactants in hypercholesterolemic subjects [14].

A comprehensive meta-analysis showed a small clinical but statistically significant benefit of ezetimibe in monotherapy. It noted that ezetimibe at a dose of 10 mg per day for 12 weeks resulted in a 7.06% reduction in Lp(a) compared to placebo [15]. A concurrently published meta-analysis, which included data from 10 randomized placebo-controlled clinical trials, found no significant effect of ezetimibe on the change in plasma Lp(a) levels either with ezetimibe therapy alone or in combination with statins [16]. This is because Lp(a) levels are mainly regulated by differences in biosynthesis, and ezetimibe has no effect on this process. Although ezetimibe has anti-inflammatory effects that could theoretically affect Lp(a) production, the results of the study did not support this hypothesis. Furthermore, ezetimibe improves clinical outcomes in terms of cardiovascular prevention, but the reduction in Lp(a) levels does not contribute to this therapeutic effect [16].

PCSK9 inhibitors

Evolocumab and alirocumab are monoclonal antibodies with high specificity against PCSK9 (proprotein convertase subtilisin/kexin 9) protein. In a study by Gerald F Watts et al. it was shown that evolocumab can show duality in the elimination of Lp(a): in monotherapy by reducing lipoprotein synthesis, while in combination with atorvastatin as a result of its increased elimination [17].

Numerous publications have shown that both evolocumab and alirocumab reduce serum vascular risk in patients who fail to achieve target LDL levels despite statin use [18, 19]. Evolocumab is effective in lowering Lp(a) levels, and patients with baseline high levels of Lp(a) receive the greatest benefit from therapy, as demonstrated in the FOURIER trial [20]. During 48 days of therapy, a mean reduction in Lp(a) of 26.9% was achieved. A clinically relevant aspect was the reduction in the risk of death, which proved to be 16% higher for the group with baseline Lp(a) levels above the median compared to the group with Lp(a) levels below the median [20].

The results of the ODYSSEY OUTCOMES study confirmed that the reduction of Lp(a) under alirocumab therapy was correlated with its baseline concentration.

Patients with baseline Lp(a) levels < 6.7mg/dL showed no significant change under treatment, while those with baseline high Lp(a) levels (> 59.6mg/dL) had a reduction of 20.1mg/dL, which was associated with a 39% reduction in cardiovascular risk [21].

A recent meta-analysis including 13 randomized clinical trials involving 2408 participants, confirmed a significant reduction in Lp(a) levels with PCSK9 inhibitors [22]. The average reduction in Lp(a) across all studies was 20.1%. In addition, there was an increase in Lp(a) reduction from 17.6% to 22.8% with increasing treatment duration from 12 to 24 weeks [22].

Fibrates

Fibrates, effective in the treatment of mixed dyslipidaemia, have shown potential effects on lowering lipoprotein(a) levels, which may be attributed to their ability to induce lipoprotein lipolysis, increase hepatic fatty acid uptake and inhibit triglyceride synthesis. The mechanism involves the activation of PPAR-α receptors, and further, the farnesoid X receptor, which inhibits apolipoprotein A transcription and thus decreases Lp(a) expression [23].

In the DIACOR (Diabetes and Combined Lipid Therapy Regimen) study, a potential effect of combination therapy (simvastatin 20 mg and fenofibrate 160 mg) on lowering lipoprotein(a) levels by 0.5 mg/dL was observed, while an increase in Lp(a) by an average of 0.6 mg/dL in the simvastatin group and 0.2 mg/dL in the fenofibrate group was observed during monotherapy [24]. These results suggest that the combination of statins and fibrates may be beneficial for patients with type 2 diabetes and mixed dyslipidaemia, especially those with high triglyceride levels. In contrast, Davidson et al. in their study did not confirm this hypothesis, reporting an 11.3% increase in Lp(a) levels in the group receiving atorvastatin (40 mg) and fenofibrate (10 mg) [25]. Similar results were obtained by Rizos et al. who observed a clinically insignificant decrease in Lp(a) from a mean Lp(a) level of 0.21 g/L to 0.18 g/L (a 14% decrease) after 16 weeks of pharmacotherapy with ciprofibrate at a dose of 100 mg daily [26].

Finally, an extensive meta-analysis that considered the aforementioned studies showed that the addition of fibrates to statins helps to increase their effectiveness in reducing Lp(a) levels [27]. The combination therapy showed a 1.6 mg/dL greater decrease in Lp(a) compared to statin use alone. However, when fibrate monotherapy was compared with combination therapy, the difference was no longer statistically significant, indicating that the addition of statins to fibrate therapy

did not provide an additional significant benefit in lowering Lp(a) levels compared with fibrates alone. These results suggest that although the combination of fibrates with statins is more effective than therapy with statins alone, it is not necessarily superior to the effectiveness of therapy with fibrates alone in lowering Lp(a) levels. Interestingly, the decrease in Lp(a) levels was particularly pronounced in patients with higher initial levels of this lipoprotein [27].

Inclisiran

Inclisiran is an innovative drug in the siRNA (small interfering RNA) class that inhibits the production of PCSK9 protein in liver cells [28]. The effect of this action is to degrade LDL receptors and lower the LDL fraction of cholesterol in the blood. In addition, inclisiran, acting intracellularly, accelerates the catabolism of lipoproteins including apoB, thereby lowering blood Lp(a) levels. The mechanism of action of inclisiran allows for its subcutaneous injections every 6 months, an advantage over traditional hypolipidemic therapy, which requires more frequent dosing [28].

The efficacy and long-term LDL and Lp(a) lowering effects of incisiran have been evaluated in the phase III ORION-9 [29], ORION-10 and ORION-11 clinical trials [30]. The results of the randomized ORION-9 trial [29] showed that inclisiran used at a dose of 300 mg effectively lowered LDL levels by 39.7%, achieving a significant advantage over the placebo group, where an 8.2% increase was observed. In addition, on the 540th day of the study, a 13.5% reduction in Lp(a) levels was achieved, compared with a 3.7% increase in the placebo group [29]. The ORION-10 and ORION-11 studies, published in subsequent years, involving 1561 patients with a history of atherosclerotic cardiovascular disease (ORION-10) and 1617 patients at high cardiovascular risk (ORION-11), respectively, confirmed these results [30]. The use of inclisiran reduced Lp(a) by 21.9%, while the placebo group showed a 3.7% increase in it (ORION-10). In the ORION-11 study, the percentage difference in Lp(a) levels between the two groups was 18.6% in favor of the group receiving inclisiran. The ORION-4 research study, coordinated by the University of Oxford, is currently underway to determine the efficacy of inclisiran in the secondary prevention of cardiovascular incidents [31].

Olparisan

Olpasiran is a novel drug consisting of a synthetic siRNA and an antisense oligonucleotide (GalNAc complex), offering new perspectives in reducing lipoprotein

(a) levels. The mechanism is to reduce the level of Lp(a) by inhibiting the translation of the messenger RNA of the lipoprotein(a) gene, which prevents its translation to apo(a) [32].

In a study involving 286 patients with known cardiovascular disease and elevated Lp(a) levels, participants received olpasiran at various doses: 20 mg every 4 weeks, 40 mg every 4 weeks, 60 mg every 4 weeks, 20 mg every 2 weeks, 20 mg every week or placebo for 6 to 12 months [33]. Although a reduction in Lp(a) levels was observed in each group, the most beneficial dose was 20 mg olpasiran given weekly, which led to an average 80% reduction in Lp(a) levels compared to 6% in the placebo group. The safety of the various doses of the drug was monitored through regular follow-up visits and laboratory tests, including platelet counts, as well as renal and liver function tests. The most common adverse reaction was mild injection site reactions [33]. In patients taking the 20-mg dose, 98% achieved an Lp(a) level of 50 mg/dL (125 nmol/L) or less, which is the target according to European [34] and US [35] guidelines. In addition, there was a significant reduction in the levels of oxidized phospholipids on both apolipoprotein B and apolipoprotein A in this group, which may indicate an anti-inflammatory effect of olparisan.

In the OCEAN-DOSE study, patients were assigned to four groups depending on the dose of olpasiran (10 mg every 12 weeks, 75 mg every 12 weeks, 225 mg every 12 weeks or 225 mg every 24 weeks) or to a placebo group [36]. The results showed that in the placebo group, Lp(a) levels increased by an average of 3.6%, while olpasiran therapy significantly and substantially reduced Lp(a) levels in a dose-dependent manner, reaching mean percentage changes of −70.5% for the 10 mg dose, −97.4% for 75 mg, −101.1% for 225 mg administered every 12 weeks, and −100.5% for 225 mg administered every 24 weeks This study provides the basis for a phase III study on a larger group of patients [36].

Aspirin

Aspirin is the most commonly prescribed antiplatelet drug [37]. The role of aspirin in the secondary prevention of cardiovascular disease is well known, and the drug is widely used because of the benefits of therapy in terms of absolute reduction of major cardiovascular events.

Current research is focused on demonstrating the role of acetylsalicylic acid (ASA) in regulating Lp(a) levels and its use in primary prevention of CVD. A study by Akaike et al. and Ranga et al. observed the effect of aspirin on the decrease of apo(a) synthesis in hepatocytes

through regulation of apo(a) gene transcriptional activity with suppression of apo(a) mRNA expression [38]. Due to the small group sizes in the aforementioned studies, additional, more advanced clinical trials on a larger group of patients are indicated to further evaluate the effects of aspirin.

In 2009, the Women's Health Study (WHS) project conducted the first randomized trial on a group of 28345 women to evaluate the association of aspirin use at a dose of 100 mg every other day for 10 years with Lp(a) levels [39]. The study included mostly Caucasian patients who carried the secondary allele of the rs3798220 polymorphism in the LPA gene, which was associated with elevated plasma Lp(a) levels and increased cardiovascular risk. Aspirin reduced the risk of cardiovascular disease by more than 2-fold among carriers of the LPA SNP rs3789220, while the risk reduction was moderate in non-carriers. Conducting the study on a group of young women at low risk of cardiovascular events and with a single variant of the LPA gene was a limitation of the study [40].

Another ASPREE project evaluated the effect of taking 100 mg aspirin versus placebo in 19,114 healthy participants aged > 70 years without any cardiovascular events before randomization [41]. The results showed that significant benefits of aspirin were achieved in rs3798220 carriers. The use of genotype-based Lp(a) assessment was one of the limitations of this study, as only 3.2% of the > 12,000 patients carried the high-risk Lp(a) genetic variant rs3798220-C, while elevated Lp(a) levels are estimated to occur in about 20% of the population [42]. Due to the small number of studies and uncertain information, the consensus of the European Atherosclerosis Society does not unequivocally support targeting aspirin use based on Lp(a) levels [8].

Tocilizumab

Tocilizumab (TCZ) is a recombinant humanized monoclonal antibody that targets the IL-6 receptor [43]. Although Lp(a) levels are significantly determined by genetic predisposition, more recent studies also show a correlation between its levels and inflammation.

Studies by Muller et al. [44] and Berthold et al. [45] provide evidence that IL-6 receptor blockade by tocilizumab has a beneficial effect on plasma Lp(a) levels. Long-term treatment with tocilizumab reduces Lp(a) levels by about 30–40%. The main limitation of the presented study is that it was conducted on a group of RA patients with indications for tocilizumab. Although the results of the study are promising and there is indirect evidence of an association between IL-6 and Lp(a)

in the general population as well, a clinical trial involving patients with elevated Lp(a) levels who do not suffer from RA seems necessary in the future. Such a study could unequivocally prove that the metabolic effect of TCZ does not depend on the presence of rheumatologic disease [46].

Mipomersen

Mipomersen is a hypolipidemic drug indicated for the treatment of homozygous familial hypercholesterolemia. It is an antisense oligonucleotide inhibitor of apolipoprotein B-100. Mipomersen is transported to the liver after subcutaneous administration, then binds to apoB-100 mRNA, causing its selective degradation and inhibition of protein translation. This results in reduced production of LDL, VLDL and Lp(a) [47].

In a study by Nandakumar et al. patients received an injectable placebo for 3 weeks, followed by mipomersen injections for 7 weeks [48]. They observed a significant reduction in plasma Lp(a) levels after the drug compared to the placebo group and a concomitant increase in the fractional catalytic ratio (FCR) of apo(a). The efficacy of mipomersen is described as promising, but its use comes with some limitations. First of all, it is a drug indicated for use only in patients with familial hypercholesterolemia. A pooled analysis of four randomized phase III trials at 26 clinical centres in six countries by Santos et al. found that mipomersen consistently reduced plasma Lp(a) concentrations by an average of 26.4% compared with placebo [49]. In addition, in a meta-analysis conducted by Foggaci et al, it was shown that it can cause adverse reactions at the injection site and lead to flu-like symptoms and liver dysfunction, i.e., an increase in liver enzymes or liver steatosis, which can lead to discontinuation of treatment [50].

Conclusions

International guidelines have begun to recognize elevated Lp(a) levels as an independent cardiovascular risk factor. Lipoprotein(a) concentration is an important indicator, the measurement of which could be a screening test as an identifiable independent genetic factor for cardiovascular risk. Currently, there are no approved specific therapies aimed at lowering elevated plasma Lp(a) levels. Hypolipidemic drugs have shown potential toward lowering elevated plasma Lp(a) levels (Table 1). Anti-inflammatory therapies such as aspirin and tocilizumab and the use of antisense oligonucleotides have also shown promising results (Table 1).

Table 1. Comparison of the mechanism of action and average decrease in Lp(a) levels for the drugs presented in the article

Drug	Action mechanism	Average Lp(a) decrease
Ezetimibe	Cholesterol absorption inhibitor blocks the NPC1L1 transporter. Mechanism of Lp(a) reduction unclear [14]	7.06% (in monotherapy) [15]
PCSK9 inhibitors (Evolocumab, Alirocumab)	Monoclonal antibodies against PCSK9. Reduce lipoprotein synthesis and increase lipoprotein elimination [17]	20.1% [22]
Fibrates	They activate PPAR-α receptors, induce lipolysis of lipoproteins and downregulate apolipoprotein A expression, thereby reducing Lp(a) [23]	Variable; 0.5 mg/dl in combination therapy [24]; 14% for ciprofibrate [26]
Inclisiran	PCSK9 siRNA inhibitor in liver cells, lowers LDL and Lp(a) by accelerating lipoprotein catabolism [28]	Up to 21.9% [30]
Olpasiran	As an siRNA complex and antisense oligonucleotide, it reduces Lp(a) levels by regulating the transcriptional activity of the apo(a) gene [32]	Up to 80% [33]
Aspirin	Regulation of apo(a) gene transcriptional activity with suppression of apo(a) mRNA expression [38]	No specific data provided
Tocilizumab	Monoclonal antibody against the IL-6 receptor, reduces Lp(a) levels by reducing inflammation [43, 44]	About 30–40% [46]
Mipomersen	Oligonucleotide antisense to apoB-100, inhibits translation of apoB-100 [47]	26.4% [49]

Article information

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