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Review

LIPOPROTEIN(A) – GAINING CLINICAL IMPORTANCE AS A CARDIOVASCULAR RISK FACTOR. CURRENT STATE OF MEDICAL KNOWLEDGE.

Maria Rybicka*[1], Anna Seroka[2], Michał Obrębski[1], Justyna Chwiejczak[3], Aleksander Górny[4], Jan Kościan[5], Julita Młynarska[6], Karolina Szczerkowska[7], Anna Wójcik[8], Maria Mitkowska[9]

[1] *University Clinical Centre of the Medical University of Warsaw, ul. Banacha 1a, 02-097 Warsaw, Poland.*

[2] *The National Institute of Medicine of the Ministry of Interior and Administration, ul. Wołoska 137, 02-507 Warsaw, Poland.*

[3] *Memorial Bielański Hospital, ul. Cegłowska 80, 01-809 Warsaw, Poland.*

[4] *Praga Hospital of Lord's Transfiguration, al. „Solidarności" 67, 03-401 Warsaw, Poland.*

[5] *Independent Public Hospital them. prof. W. Orlowski Medical Centre of Postgraduate Education, ul. Czerniakowska 231, 00-416 Warsaw, Poland.*

[6] *Saint Anna Hospital of Trauma Surgery, ul. Barska 16/20, 02-315, Warsaw, Poland.*

[7] *Military Institute of Medicine - National Research Institute, ul. Szaserów 128, 04-141 Warsaw, Poland.*

[8] *Warsaw Southern Hospital, ul. rtm. Pileckiego 99, 02-781, Warsaw, Poland.*

[9] *HCP Medical Centre, ul. 28 czerwca 1956 r. 194, 61-001, Poznań, Poland.*

* Correspondence, e-mail: rybickamaria97@gmail.com

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ABSTRACT

Cardiovascular disease has been a major cause of human mortality worldwide for many decades. One of the risk factors for atherosclerosis that is gaining clinical importance is serum lipoprotein(a) (Lp(a)) concentration. The purpose of this publication is to present current knowledge regarding Lp(a) and currently available investigational drugs that reduce serum Lp(a). We also present current recommendations for interventions aimed at reducing the cardiovascular risk associated with high serum Lp(a) concentration. Lipoprotein(a) is a variant of low-density lipoprotein (LDL) containing an additional glycopeptide chain called apolipoprotein(a) (apo(a)) covalently linked to apolipoprotein B-100 (apoB-100). Increased serum Lp(a) is a well-established independent risk factor for atherosclerosis and aortic stenosis. Unlike LDL-cholesterol (LDL-C) concentration, serum Lp(a) does not decrease significantly as a result of recommended lifestyle changes nor as a result of the use of major hypocholesterolemic drug classes. Approximately 20% of people worldwide have high serum Lp(a). Current recommendation is to perform a screen for serum Lp(a) at least once in one's lifetime in general population. Effective lowering of serum Lp(a) falls into the category of urgent unmet medical needs. In the absence of effective drugs to reduce serum Lp(a) in individuals with elevated Lp(a), intensified control of other cardiovascular risk factors and in extreme cases therapeutic apheresis are strongly recommended.

KEYWORDS: Lipoprotein(a), cardiovascular disease, cardiovascular risk factors, atherosclerosis.

1. Introduction

Lipoprotein(a) was first described by the Norwegian researcher Kåre Berg in 1963 [1]. Lipoprotein(a) is a variant of the atherogenic fraction of LDL built from a lipid core of similar composition to LDL and two protein elements: apolipoprotein B-100 (apoB-100) and a specific large glycoprotein called apolipoprotein(a). The protein elements are in a molar ratio of 1:1, and are covalently linked to each other by disulfide bonds [2-4]. The structure of apo(a) has been shown to be similar to that of plasminogen. Both apo(a) and plasminogen have repeating loop-like regions in their structure referred to as "kringle domains". A "kringle" domain is a triple protein loop stabilized by three internal disulfide bonds [5].

Serum Lp(a) concentration is strongly linked to genetic factors and dependent on variants of the *LPA* gene encoding apo(a) located on chromosome 6q22-27 [6]. The molecular weight of apo(a) isoforms is

characterized by high inter-individual variability dependent on the number of kringle IV type 2 (KIV_2) domain repeats ranging from 3 to more than 40 times, which is determined by the number of tandem repeats of the genomic sequence in the *LPA* gene [7].

The molecular weight of apo(a) ranges from ≈250 to 800 kDa. There is a strong inverse relationship between the size of apo(a) isoforms and serum Lp(a) concentration. This implies that small apo(a) isoforms (≤22 total KIV_2 repeats) are correlated with high Lp(a) serum concentration (median ≈ 45 mg/dL) and large apo(a) isoforms (>22 KIV_2 repeats) are correlated with low serum concentrations of this lipoprotein (median 8-10 mg/dL) [8]. Lipoprotein(a) concentration varies by up to 3 orders of magnitude in human population. Africans have on average 2 to 3 times higher serum Lp(a) concentration compared with Europeans and most Asian populations. Serum Lp(a) concentration, being a strongly genetically determined trait, is not susceptible to lifestyle modifications [9].

In approximately 90% serum Lp(a) concentration is genetically determined and constant, with exception for certain inflammatory conditions. In the remaining 10%, Lp(a) blood concentration depends on other factors, including age, gender, ethnicity and comorbidities (e.g., familial hypercholesterolemia, liver disease, and kidney disease). Serum Lp(a) concentration can also rise in response to treatment with interleukin-6 (Il-6) [10]. Lipoprotein(a) is not formed from other lipoproteins, such as VLDL (very-low-density lipoprotein) or LDL [11]. In humans, apo(a) is synthesized in the liver [12], following which it is attached to Lp(a) particles on the surface of hepatocytes [13].

2. Materials and methods

The aim of this study was to update the information on Lp(a), especially on recommended methods for measuring its serum concentration, the scientific societies guidelines on stratification of cardiovascular risk on the basis of its serum concentration and the available and potential methods for reducing Lp(a) serum concentration if required. We performed a literature search on Lp(a) using PubMed and Google Scholar medical databases from year 1963 until the end of May 2024, using the following key words: “lipoprotein(a)”, “cardiovascular disease”, “cardiovascular risk factors”, “atherosclerosis”. Time span in which each database was searched was one week. We also describe current recommendations by the European Society of Cardiology (ESC) (https://www.escardio.org, latest access: 31.05.2024) and the European Atherosclerosis Society (EAS) (https://eas-society.org, latest access: 31.05.2024) regarding Lp(a).

3. Pathophysiological role

The physiological function of Lp(a) is still not clear [14, 15]. High serum concentrations of Lp(a) promote the development of atherosclerosis, inflammation and thrombosis because of various mechanisms described below.

3.1. Atherogenicity and proinflammatory action

Lipoprotein(a), due to its structure, in which apoB-100 is bound to apo(a) by disulfide bonds, has reduced affinity for LDL receptors in the liver. Thus, its intracellular uptake is reduced. In contrast, Lp(a) binds to macrophages through endocytosis by VLDL receptors and enters these cells causing their transformation into foam cells and subsequent cholesterol deposition in the atherosclerotic plaques, followed by smooth muscle proliferation [16-19]. This is supported by observation that Lp(a) is ubiquitous in the atherosclerotic plaques in coronary arteries and detected at higher levels in the atherosclerotic lesions of patients with unstable compared to stable coronary artery disease [20]. Lipoprotein(a) also binds to endothelium and extracellular matrix components: fibrin, fibronectin, proteoglycans, tretranectin, and beta2-glycoprotein [21], thereby potentially interfering with normal endothelial function [22].

Lipoprotein(a) was recognized as the major carrier of oxidized phospholipids (OxPL) in plasma [23]. Oxidized phospholipids incorporated into Lp(a) cause monocyte penetration into the arterial wall [24] and inflammation through a pathway mediated by Toll-like receptor 2 [25], thereby inducing inflammation in the arterial wall [26. 27]. So, the atherogenicity of Lp(a) may be connected with the proinflammatory action of OxPL. Also, cytokines induced by Lp(a) promote inflammation. Macrophages induced by apo(a) release interleukin-8, monocyte chemotactic protein, and tumor necrosis factor-α [28].

3.2. Thrombogenicity

Despite apo(a) structural similarity to plasminogen, apo(a) does not have the enzymatic activity of the latter. The high homology between these two molecules causes apo(a) to be misidentified as plasminogen, resulting in interference with the production of its active form, and consequently inhibiting fibrinolysis and promoting thrombogenesis [29].

Lipoprotein(a) is also positively correlated with platelet aggregation independent of lipoprotein-associated phospholipase A2 (Lp-PLA2), which may be partly responsible for the atherothrombotic effect of Lp(a) [30]. Surprisingly, studies on many individuals have shown that neither high Lp(a) serum concentration nor genetic variants associated with high Lp(a) serum concentration are associated with the risk of venous thrombosis and venous thromboembolic disease [31, 32].

3.3. Aortic valve stenosis/ calcific aortic valve disease

The epidemiological and genetic evidence that high Lp(a) levels are linked with the development of aortic valve stenosis (AVS) is quite strong [33]. Both Lp(a) and apo(a) have been found in end-stage AVS [34]. Lipoprotein(a) may promote the onset and development of AVS by causing aortic valve endothelial dysfunction, accumulating in the valve and delivering its OxPL content along with autotaxin (ATX), an enzyme that is secreted by various types of cells. Lysophosphatidylcholine (LPC) carried by OxPL and Lp(a) is converted to lysophosphatidic acid (LysoPA) by ATX and becomes a ligand for LPAR. This triggers a nuclear factor-κB cascade leading to increased transcripts of interleukin 6, bone morphogenetic protein 2, and runt-related transcription factor 2. This progresses to the actual calcification of the valves through production of alkaline phosphatase and calcium depositions. So, this mechanism promotes not only inflammation but also the osteogenic

transformation of valvular interstitial cells causing calcium deposition [35].

4. Blood measurements

In 2022, the European Atherosclerosis Society (EAS) updated its consensus on Lp(a), recommending measurement of Lp(a) serum concentration at least once in all adults. Such an approach might help to determine those at high cardiovascular risk [9].

Several decades of research efforts have failed to develop a reliable method to measure Lp(a) in human serum. One reason for this outcome is the structure of apo(a), more specifically the composition of apo(a) includes "rim" kringle IV (KIV) domains, which with multiple repeats of up to over 40 times determine the formation of different apo(a) isoforms. It is the kringle IV (KIV) repeats that are the primary source of Lp(a) measurement problems. This apparent difficulty in measuring may account for the original misconception that there was no obvious relationship between serum Lp(a) concentration and cardiovascular risk [36].

Measurement of Lp(a) in human plasma or serum samples can be done by using several methods, including radial immunodiffusion (RID), electroimmunoassay, radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), immunoturbidimetry, nephelometry, dissociation-enhanced lanthanide fluorescent immunoassay (DELFIA), particle concentration fluorescence immunoassay (PCFIA), and electrophoretic and immunofixation electrophoresis.

Each of these methods have its strengths and limitations, however a common feature of all of them is their inability to measure the variability/heterogeneity in Lp(a) size [37] .

Currently, serum Lp(a) concentration is measured either in mass units (mg/dL) or in molar units (nmol/dL), which itself causes problems in clinical practice. Measurements in molar units should be preferred. Polyclonal antibodies are widely used in routine clinical testing. They are highly likely to recognize the repeated motifs of KIV apo(a). However, this method is subject to the error that Lp(a) serum concentration with apo(a) having a large number of KIV repeats may be overestimated, and with apo(a) having a small number of KIV repeats may be underestimated [36]. Measurements cannot be accurately converted from mg/dL to nmol/L and vice versa. A common conversion is to multiply the mass concentration of Lp(a) by 2.0-2.5 to obtain a very rough estimate of the molar concentration of Lp(a), but the variability is considerable and this method cannot be recommended for clinical use. It is worth emphasizing that the “mass” value for Lp(a) refers to the whole lipoprotein particle, not any one of its component parts and the complete chemical composition of Lp(a) is never determined in the clinical laboratory. Therefore, no single conversion factor can be accurate to convert mass units to molecular units [38].

In summary, extensive studies have been performed to better standardize serum Lp(a) measurements, and test manufacturers should follow any progress in this area. Although serum Lp(a) assays are suboptimal at this time, many of them can be used for patient risk stratification and treatment efficacy assessment [37].

5. Evidence of link to cardiovascular disease

Approximately 20% of people worldwide have high serum Lp(a) concentration [39]. Lipoprotein(a) is an independent risk factor for atherosclerotic coronary heart disease, atherosclerotic cerebrovascular disease, atherosclerosis in other vascular beds and aortic stenosis [9]. The association between high serum Lp(a) concentration and cardiovascular disease is present even at low LDL-C concentration [40]. Compared with subjects with mean serum Lp(a) concentration of 7 mg/dL those with Lp(a) concentration of 30, 50, 75, 100 and 150 mg/dL had a 1.22-, 1.40-, 1.65-, 1.95-, and 2.72-fold increase in the risk of atherosclerotic coronary artery disease, respectively [9].

Table 1. Relationship between serum Lp(a) concentration and risk of coronary heart disease [9,41].

Cardiovascular risk	Serum Lp(a) concentration
Low	<30 mg/dL (<75 nmol/L)
Medium = „grey zone”	30–50 mg/dL (75–125 nmol/L)
High	>50 mg/dL (>125 nmol/L)
Very high (extreme)	>180 mg/dL (>430 nmol/L)

5.1. Coronary syndromes

The feature of Lp(a) that promotes the development of ischemic heart disease is its high molar concentration rather than its apo(a) size [42]. In the general population, a serum Lp(a) concentration exceeding 125 nmol/L (equivalent to 50 mg/dL) is associated with an approximately 20% increased risk of symptomatic coronary artery disease. Moreover, an additional 3.5-fold increase in serum Lp(a) concentration results in further 16% increase in this risk [43]. Cohort studies indicate an increased need for coronary revascularization in individuals with increased Lp(a) serum concentration [44].

The association between high serum Lp(a) concentration and increased risk of myocardial infarction has been well documented [45]. In addition, studies show that high serum Lp(a) concentrations can persist even 6 months after myocardial infarction, suggesting the repeated measurements during post-infarction period are justified to predict potential another acute ischemic coronary episode [46].

5.2. Ischemic stroke

Increased serum Lp(a) concentration is considered an independent risk factor for ischemic stroke associated with large artery atherosclerosis, especially in younger individuals [47, 48]. In a systematic review including six studies, the relative risk for ischemic stroke related to high Lp(a) was 2.14 (95% CI 1.85-2.97) [49]. The association between Lp(a) and cerebrovascular disease may be stronger in men than in women [47, 50]. In contrast, no association of Lp(a) serum concentration with the occurrence of stroke due to embolic material of cardiac origin or lacunar strokes has been demonstrated [51].

5.3. Aortic stenosis

A correlation has been described between the presence of genetic variants within the *LPA* gene locus, as expressed by values of serum Lp(a) concentration, and the process of aortic valve calcification leading to one of the most common valvular defects: aortic stenosis. Analysis of the results of a cohort study showed a significant association between the presence of a single nucleotide polymorphism (SNP) in the *LPA* gene (rs10455872) and the occurrence of aortic valve calcification ($p<0.05$ for all studied cohorts: white European, African-American and Hispanic-American) [52]. The findings suggest that reducing serum Lp(a) concentration may slow down valve calcification and thus delay the progression of aortic stenosis [53].

Table 2 shows the quantitative impact of increased serum Lp(a) concentration on various cardiovascular diseases based on large prospective population-based studies.

Table 2. The effect of increased serum Lp(a) concentration on the risk of cardiovascular events based on prospective clinical studies [54].

Types of cardiovascular events	Fold increase in risk between individuals with the highest and lowest serum Lp(a) concentration	Association supported by the Mendel's randomization method*
Coronary artery stenosis	5	Yes
Myocardial infarction	3 to 4	Yes
Aortic stenosis	3	Yes
Carotid artery stenosis	1.7	Yes
Ischemic stroke	1.6	Yes
Femoral artery stenosis	1.6	Yes
Deaths from cardiovascular causes	1.5	Yes
Deaths from all causes	1.2	Yes

*Mendel's randomization method involves testing the effect of genetic variants found in a population on the occurrence of a specific effect.

5.4. Type II diabetes

Evidence from studies in the Icelandic population suggests an increased risk of developing type II diabetes in individuals with very low serum Lp(a) concentration [42]. Other prospective studies suggest that multiple repeats of the type 2 kringle IV domain contribute more significantly to an elevated risk for T2D compared with low Lp(a) concentration alone [55].

6. Recommendations of scientific societies regarding Lp(a)

Currently, the widely accepted main goal of intervention in lipid disorders is to reduce serum LDL-C concentration (Table 3). Secondary targets for hypolipemic therapy are non-high-density lipoprotein cholesterol (non=HDL-C) and serum apoB-100 concentration (Table 3) [56].

Table 3. Target serum concentrations of LDL cholesterol (LDL-C), non-HDL cholesterol (non-HDL-C) and apoB-100 in different cardiovascular risk groups according to ESC/EAS 2019 [56].

Cardiovascular risk	Target concentration LDL-C	Target concentration non-HDL-C	Target concentration apoB-100
Low	<115 mg/dL (<3,0 mmol/L)	Not specified	Not specified
Medium	<100 mg/dL (<2,6 mmol/L)	<130 mg/dL (<3,4 mmol/L)	<100 mg/dL
High	<70 mg/dL (<1,8 mmol/L) and>=50% reduction	<100 mg/dL (<2,6 mmol/L)	<80 mg/dL
Very high	<55 mg/dL (<1,4 mmol/L) and>= 50% reduction	<85 mg/dL (<2,2 mmol/L)	<65 mg/dL

The updated 2022 EAS Lp(a) consensus report includes a risk stratification of ischemic heart disease according to serum Lp(a) concentration (Table 1) [9, 41].

According to the consensus, serum Lp(a) concentration should be measured at least once in life in adults. Acute infections or kidney disease are exceptions, for which multiple measurements may be necessary. In children, determination of serum Lp(a) concentration is recommended in the case of premature atherosclerotic cardiovascular disease in a parent. In addition, cascade testing (testing of a patient's relatives to identify their risk for abnormalities) is recommended for those with a family history of high Lp(a) concentration, familial hypercholesterolemia, and their own or a family history of atherosclerotic cardiovascular disease [9, 40].

The consensus also includes recommendations for the management of patients with known high Lp(a) concentration, which include intensifying control and modification of other cardiovascular risk factors, such as glucose serum concentration, blood pressure and serum LDL-C concentration. Therapeutic apheresis of Lp(a) should be used in patients with very high Lp(a) serum concentration who have clinical complications from atherosclerotic cardiovascular disease despite optimal treatment of other cardiovascular risk factors. Once the specific medications are developed and approved, it is reasonable to assume that a high serum Lp(a) concentration will be the indication for initiating adequate pharmacotherapy. It remained to be determined how much serum Lp(a) concentration should be lowered to achieve a clinically meaningful benefit [9].

Decisions regarding the management of the so-called “gray zone” risk should be made after taking into account the presence of other cardiovascular risk factors and depend on other clinical conditions, such as chronic kidney disease, liver transplant status or pregnancy [9].

Table 4. Recommendations from the 2022 consensus of the European Society for Atherosclerosis Research on management after high serum Lp(a) concentration [9, 41].

• In the absence of specific therapies to reduce Lp(a) serum concentration to date, intensive management of all risk factors is recommended in persons with high levels of this lipoprotein, taking into account their absolute global cardiovascular risk and the additional risk associated with Lp(a).
• Among patients with high Lp(a) serum concentration, all cardiovascular risk factors should be comprehensively addressed according to the recommendations.
• Lipoprotein apheresis can be considered in patients with very high Lp(a) serum concentration and progressive cardiovascular disease despite optimal management of risk factors.
• PCSK 9 inhibitors reduce serum Lp(a) concentrations by about 25-30%. The use of PCSK 9 inhibitors to reduce isolated high serum Lp(a) concentration may not be sufficiently effective and is therefore not recommended.
• Niacin is not recommended for Lp(a) serum concentration lowering.

7. Effects of hypolipemic drugs on serum Lp(a) concentration

Table 5. Effects of hypolipemic drugs and therapeutic apheresis on serum Lp(a) concentration [58, 59].

Lipid-Lowering Drugs	Impact on Lp(a) Serum Concentration
Statins	Possible increase; 8-20%
Fibric acid derivatives	Minimal, possible increase in setting of HTG
Bempedoic acid	No effect
Bile acid sequestrants	No effect
Ezetimibe	Possible reduction; 0-7%
Inclisiran	Reduction; 15-26%
Mipomersen*	Reduction; 25%
CETP inhibitors	Reduction; 25%
PCSK9 inhibitors / inclisiran	Reduction; 20-30%
Nicotinic acid derivatives	Reduction; 30%
ASO based drugs (pelacarsen)	Reduction; 70-90%
(siRNA) based drugs (olpasiran)	Reduction; 70-98%
Apheresis	
Lipoprotein apheresis	Reduction; 20-30%
Lipoprotein (a) apheresis	Reduction; 70-80%

ASO – antisense oligonucleotides; CETP – cholesteryl ester transfer protein; HTG – hypertriglyceridemia; PCSK9 – proprotein convertase subtilisin/kexin type 9; siRNA – small interfering RNA, *EMA (European Medicines Agency) refused mipomersen marketing authorization in 2012 considering that its risks outweigh its benefits [60]. Mipomersen originally authorized by FDA (Food and Drug Administration) in 2013 was associated with adverse effects including hepatotoxicity and injection site reactions, which led to discontinuation in a majority of patients, and FDA approval was withdrawn in 2019 [61].

8. Frequently used hypolipemic drugs with inconclusive effect on serum Lp(a) concentration

8.1. Statins

Statins are the primary hypocholesterolemic drugs effectively reducing LDL-C serum concentration with proven beneficial effects in cardiovascular disease and its mortality. Statins through a mevalonic acid-like moiety competitively inhibit ß-hydroxy ß-methylglutaryl coenzyme A (HMG-CoA) reductase. By reducing the conversion of HMG-CoA to mevalonate, statins inhibit an early and rate-limiting step in cholesterol biosynthesis, which results in increased expression of the LDL receptor gene. Some studies suggested that statins also can enhance the removal of LDL precursors (VLDL and IDL) and decrease hepatic VLDL production [62].

While statins are well-established in lowering LDL-C serum concentration, their effect on Lp(a) remains unclear [59, 63]. There is evidence indicating that statins have no clinically important effect on serum Lp(a) concentration compared to placebo. The results of the recent meta-analysis from 2022 including 39 randomized trials conducted on 24,448 participants, divided into a group treated with statins and a placebo group, are that none of the types of statins changed Lp(a) significantly compared to placebo (very low- to high-certainty evidence), as well as none of the different intensities of statin therapy resulted in significant effect on Lp(a) concentration (low- to moderate-certainty evidence) [63]. Other studies including meta-analysis study from 2020 including 7 randomized clinical trials conducted on 5256 patients have shown that statins can increase serum Lp(a) concentration (the mean percent change from baseline ranged from 8.5% to 19.6% in the statin groups and -0.4% to -2.3% in the placebo groups), although to the level that appears not clinically significant [59]. Even if statins cause a small increase in serum Lp(a) concentration, the confirmed cardiovascular benefits of these drugs on serum LDL-C concentration outweigh their common use.

8.2. Ezetimibe

Ezetimibe is a hypocholesterolemic drug often used in combination with statins to complement the mechanism of action of the latter group and improve efficacy in achieving target serum LDL-C concentration [64]. Ezetimibe inhibits luminal cholesterol uptake by jejunal enterocytes, by inhibiting Niemann-Pick C1–like 1 transport protein, and reduces cholesterol absorption by 54%, precipitating a compensatory increase in cholesterol synthesis that can be inhibited with a cholesterol synthesis inhibitors (e.g., statins). As a consequence there is a reduction in the incorporation of cholesterol into chylomicrons; and the delivery of cholesterol to the liver by chylomicron remnants is diminished [62].

The results of studies of the effect of ezetimibe on serum Lp(a) concentration are not consistent. The results of one meta-analysis involving 10 clinical studies conducted on 5188 participants suggest that treatment with ezetimibe does not reduce serum Lp(a) concentration [65], either in a monotherapy or in combination with statins. The results of another meta-analysis involving 7 clinical trials with 2337 patients indicate a slight reduction in serum Lp(a) concentration

by -7.06% (95% CI - 11.95 to - 2.18; p = 0.005) in patients with primary hypercholesterolemia during ezetimibe monotherapy (10 mg/day) [66].

8.3. Fibric acid derivatives

Fibric acid derivatives, or fibrates, are the drugs that mainly lower serum triglyceride concentration and increase HDL-C serum concentration. Their role in reducing cardiovascular risk has been the subject of research and over the years was not definitively established [56]. The mechanisms by which fibrates lower lipoprotein levels, or raise HDL-C levels, remain unclear. Many of the effects of fibrates on lipid serum concentration are mediated by their interaction with peroxisome proliferator-activated receptors (PPARs) - gene transcription factor. Fibrates bind to PPARα and reduce triglycerides through PPARα-mediated stimulation of fatty acid oxidation, increased lipoprotein lipase (LPL) synthesis, and reduced expression of apo C-III. Fibrate-mediated increases in HDL are due to PPARα stimulation of apo A-I and apo A-II expression, which increases HDL-C levels [62].

Most data indicate that fibrates have no significant effect on serum Lp(a) concentration [67]. However, in patients with significant hypertriglyceridemia, the use of fibrates may be associated with an increase in this lipoprotein serum concentration [68].

9. Hypocholesterolemic drugs with beneficial effects on serum Lp(a) concentration

9.1. PCSK9 inhibitors

PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors could be used in monotherapy as well as in combination therapy of hypercholesterolemia to improve efficacy in achieving target serum LDL-C concentrations. Importantly, PCSK9 inhibitors are the only group of drugs that has been proven so far to simultaneously reduce serum Lp(a) concentration and cardiovascular risk [9]. Currently approved for use both in Europe and in the USA are two fully humanized anti-PCSK9 monoclonal antibodies: alirocumab and evolocumab [69]. When the LDL receptor-LDL-PCSK9 complex is formed it is removed from the cell membrane by endocytosis and removed by the lysosomes. Antibodies (Ab) to PCSK9 block its ability to bind the LDLR-LDL complex, thus preventing degradation of LDLR [62]. The mechanism by which PCSK9 inhibitors lower serum Lp(a) concentration is unclear, but may involve increased LDL receptor clearance, decreased apo(a) production, or decreased Lp(a) formation due to decreased apoB-100 availability [70].

In the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial, which was conducted on a group of 27,564 participants, evolocumab significantly reduced serum Lp(a) concentration by 26.9% (6.2%-46.7%) (initial median = 37 nmol/L) after 48 weeks of use. In doing so, the percent change in serum Lp(a) and LDL-C concentration in the evolocumab group was positively correlated to a moderate degree (r=0.37; 95% CI, 0.36-0.39; P<0.001). In the evolocumab group, there was a 23% reduction in the risk of death from coronary heart disease, myocardial infarction or urgent revascularization (HR 0.77; 95% CI, 0.67-0.88) in patients with initial serum Lp(a) concentration above the median (median = 37 nmol/L) and a significantly smaller 7% reduction in the risk of these events (HR 0.93; 95% CI, 0.80-1.08; p=0.07) in those with Lp(a) concentration equal or below the median [71].

In the ODDYSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab) trial, conducted on the group of 18,924 participants, alirocumab reduced serum Lp(a) concentration by 5.0 mg/dL (initial median = 21.2 mg/dL) after 12 months of use and reduced the risk of MACE (Major Adverse Cardiac Events: Cardiovascular Death, Nonfatal Myocardial Infarction, Nonfatal Stroke and Urgent Coronary Revascularization (HR: 0.85; 95% CI, 0.78 to 0.93)). A 1-mg/dL reduction in Lp(a) with alirocumab was associated with a HR for MACE of 0.994 (95% CI: 0.990 to 0.999; p = 0.0081) [72].

In summary, additional analyses of the FOURIER trial [71] and the ODYSSEY Outcomes trial [73] showed that additional reduction of Lp(a) concentration by PCSK9 inhibitors contributes to cardiovascular risk reduction in patients with higher serum Lp(a) concentration. Similar observations were reported in the analysis of pooled data from 10 controlled phase 3 alirocumab trials involving patients with serum Lp(a) concentration ≥50 mg/dL [73].

9.2. Inclisiran

Inclisiran has been shown to reduce serum LDL-C concentration by approximately 50% [74]. Inclisiran is a small interfering RNA-based (siRNA) therapeutic binding to the messenger RNA (mRNA) precursor of PCSK9, and therefore causing the inhibition of the PCSK9 gene expression [62].

In the ORION-10 and ORION-11 trials conducted on 1561 and 1617 participants, respectively, inclisiran reduced serum Lp(a) concentration by 25.6% (initial median 57 nmol/L) and 18.6% (initial median 42 nmol/L) after 510 days of use, respectively (p values were not established for Lp(a) comparisons with placebo groups), while the reduction in serum LDL-C concentration was about 50% in both trials. Thus, inclisiran causes a similar reduction in Lp(a) and LDL-C serum concentration as monoclonal antibodies against PCSK9 [74].

Clinical evaluation of inclisiran in cardiovascular risk reduction is ongoing [75]. Recent pooled analysis of ORION-9, -10 and -11 included 3655 high-risk patients with elevated LDL-C offers early insights into the potential CV benefits of inclisiran and suggests that this approach may provide CV benefits. Inclisiran significantly reduced composite MACE [OR (95% CI): 0.74 (0.58–0.94)], but not fatal and non-fatal MIs [OR (95% CI): 0.80 (0.50–1.27)] or fatal and non-fatal stroke [OR (95% CI): 0.86 (0.41–1.81)] [76].

10. Investigational drugs that selectively reduce serum Lp(a) concentrations

Drugs that by genetic interference block the formation of apo(a), and thus significantly reduce the serum concentration of Lp(a), are at the advanced stages of development programs. They belong to the group of

antisense oligonucleotides (drugs with the suffix -rsen) and to the group of small interfering mRNAs (siRNAs) (drugs with the suffix -siran).

10.1. Pelacarsen

Pelacarsen (also named TQJ230, IONIS-APO(a)-L_{Rx} and AKCEA-APO(a)-L_{Rx}) is a pre-marketing investigational antisense oligonucleotide that inhibits the Lp(a) synthesis. Pelacarsen is conjugated to N-acetylgalactosamine (GalNAc), which enables rapid selective uptake by the asialoglycoprotein (ASGP) receptor, mainly expressed on hepatic cells [77]. After entering the cell, pelacarsen binds to the mRNA in nucleus by Watson and Crick base pairing, activates ribonuclease H (RNAse-H), what leads to mRNA degradation and consequently blocks the production of the apo(a) protein [58].

The reduction of Lp(a) serum concentration (the placebo-corrected percent change) was investigated in randomized, double-blind study performed in 29 healthy Japanese subjects treated with single ascending doses (SAD) of pelacarsen 20, 40 and 80 mg subcutaneously or multiple doses (MD) of pelacarsen 80 mg monthly for 4 doses. The results were: in the SAD cohorts, at Day 30 -55.4% (p=0.0008), -58.9% (p=0.0003) and -73.7% (p<0.0001) for the 20 mg, 40 mg, and 80 mg pelacarsen-treated groups, respectively, and in the MD cohort, at Days 29, 85, 113, 176 and 204, -84.0% (p=0.0003), -106.2% (p<0.0001), -70.0 (p<0.0001), -80.0% (p=0.0104) and -55.8% (p=0.0707), respectively [78].

Studies are ongoing to determine the effect of pelacarsen on cardiovascular risk in patients with known cardiovascular disease and elevated serum Lp(a) concentration ≥70 mg/dL (Phase 3 HORIZON study conducted on the group of 8,325 participants - scheduled for completion in 2025) [79]. Additionally, a multicenter trial, initiated by Novartis Pharmaceuticals, has been started with the goal to evaluate the efficacy and safety of pelacarsen administrated subcutaneously monthly, compared to placebo, in slowing the progression of calcific aortic valve stenosis (involving 502 participants - scheduled for completion in 2029) [80].

10.2. Olpasiran

Olpasiran (also named AMG860) is a pre-marketing investigational siRNA, which is a polynucleotide incorporated into the cytoplasmic RNA-induced gene expression silencing complex (RISC), resulting in mRNA degradation [81].

The reduction of Lp(a) serum concentration was investigated in randomized, double-blind study performed in 281 patients with established atherosclerotic cardiovascular disease. At 36 weeks, the lipoprotein(a) concentration had increased by a mean of 3.6% in the placebo group, whereas olpasiran therapy had significantly and substantially reduced the Lp(a) concentration in a dose-dependent manner, resulting in placebo-adjusted mean percent changes of -70.5% with the 10 mg dose, -97.4% with the 75 mg dose, -101.1% with the 225 mg dose administered every 12 weeks, and -100.5% with the 225 mg dose administered every 24 weeks (P<0.001 for all comparisons with baseline) [81].

The results of the first study on the cardiovascular effects of olpasiran are expected in 2026 (the phase 3 OCEAN(a) study). The primary objective of this study planned to enroll 7297 participants is to compare the effect of treatment with olpasiran to placebo on the risk for coronary heart disease death (CHD death), myocardial infarction, or urgent coronary revascularization in participants with atherosclerotic cardiovascular disease (ASCVD) and elevated Lp(a) serum concentration [82].

11. Other drugs reducing serum Lp(a) concentration

11.1. Acetylosalicylic acid (aspirin)

Aspirin thanks to its antiplatelet and anti-inflammatory activity has been a long-standing therapy targeted to the prevention of CVD and causing important reductions in morbidity and mortality. Low-dose aspirin (75-100 mg orally daily) is recommended for secondary prevention of ASCVD and might be considered for primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk according to 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease and 2021 European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice [83, 84].

The present studies demonstrated that therapeutically relevant concentrations of aspirin can effectively reduce the production of apo(a) by cultured normal human hepatocytes by suppressing the apo(a) mRNA expression and gene transcription [85]. In a propensity-matched cohort study, conducted on 2183 participants, aspirin use was associated with a 46% reduced risk for coronary heart disease events in individuals with lipoprotein(a) >50 mg/dL (hazard ratio, 0.54 [95% CI, 0.32–0.94]; *P*=0.03) [86]. It is hypothesized that individuals with elevated Lp(a) benefit more from low-dose aspirin therapy than the general population for primary prevention of ASCVD [87].

11.2. Tocilizumab

Tocilizumab is a humanized monoclonal antibody with the ability to selectively bind to the the interleukin-6 receptor [88]. Even though Lp(a) serum concentration is genetically determined, several studies have shown a correlation between its concentration and inflammation [89].

Systemic inflammatory conditions, such as rheumatoid arthritis (RA), systemic lupus erythematosus, and chronic renal failure are associated with high serum Lp(a) concentration. In RA patients high serum Lp(a) concentration is reduced by 30-40% by IL-6 receptor (IL-6R) blockade by tocilizumab, suggesting a potential role for IL-6 in regulating serum Lp(a) concentration [10, 90]. Data obtained suggest that IL-6 blockade might be a promising future therapeutic approach to treat elevated serum Lp(a) concentrations and to reduce CVD risk, but the limitations are that they are based on a surrogate end parameter, i.e. only on the analysis of the drug's effect on Lp(a) concentration, and are limited to the group of RA patients in whom tocilizumab is used according to the registration [90].

12. Non-pharmacological treatment - apheresis

Apheresis is a medical procedure that can be used to extracorporeally selectively remove lipoproteins, including LDL and Lp(a), from the blood [91]. Various techniques can be used for lipoprotein apheresis, including precipitation, adsorption, filtration or immunoadsorption [92]. Procedures to cleanse the blood of excess lipids are used for patients with severe homozygous or heterozygous familial hypercholesterolemia accompanied by elevated LDL cholesterol levels and presence of high cardiovascular disease risk and/or diabetes [91]. Nowadays, this form of treatment in dyslipidemias is limited due to its short-term therapeutic effects requiring regular treatments to maintain the benefit; other disadvantages of this method are high costs and invasiveness [9, 70].

According to current medical knowledge, therapeutic apheresis of Lp(a) should be considered in patients with high serum Lp(a) concentration and progressive atherosclerotic cardiovascular disease [9]. Worldwide, apheresis is used infrequently and for limited indications, except for its frequent use in Germany, where more than 47,500 sessions of lipoprotein apheresis have been documented in GLAR (The German Lipoprotein Apheresis Registry) [93]. In the United States, apheresis has Food and Drug Administration (FDA) approval for use in patients with significantly elevated Lp(a) concentration (>60 mg/dL or >150 nmol/L) regardless of LDL-C concentration [60]. In Poland, the center that offers the reduction of Lp(a) concentration by lipoprotein apheresis is the University Clinical Center in Gdańsk [95].

13. Conclusions

Approximately 20% of people worldwide have high serum Lp(a) concentration. According to current recommendations, everyone should have their serum Lp(a) concentration measured at least once in their lifetime [9, 41].

Lipoprotein(a) is likely a causal independent risk factor for atherosclerotic cardiovascular disease. The risk of cardiovascular events increases linearly with Lp(a) concentrations; the risk increases are clinically relevant as Lp(a) concentrations exceed 50 mg/dL (125 nmol/L) and especially when they exceed 180 mg/dL (430 nmol/L) [9, 41].

No clinical trials have adequately tested the hypothesis that Lp(a) reduction reduces the incidence of cardiovascular events so far. In patients with high Lp(a) (>50 mg/dL or >125 nmol/L) more intensive management of all cardiovascular risk factors is recommended [9, 41].

An effective pharmacotherapy that reduces serum Lp(a) concentration remains to be established, although breakthrough in this area is imminent. It is heralded by the demonstration that PCSK9 inhibitors reduce cardiovascular risk in a manner dependent on baseline and reduced serum Lp(a) concentration during therapy. Drugs that specifically reduce serum concentration of this lipoprotein (e.g., pelacarsen and olpasiran) are undergoing advanced clinical trials to document their clinical significance. Lp(a) apheresis is an effective but costly and invasive method of lowering Lp(a) serum concentration.

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