

LIPOPROTEIN(A)

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ABSTRACT

Lipoprotein(a) is an apo B-containing lipoprotein which has a unique plasminogen-like apolipoprotein(a) attached to apo B-100. The levels of lipoprotein(a) are under strong genetic regulation and vary by several hundred-fold in the general population. Although the exact function of lipoprotein(a) is still a mystery, recent studies have shown that lipoprotein(a) has a causal role in atherosclerosis and its level has been shown to be a risk factor for atherosclerotic cardiovascular disease (ASCVD) and calcific aortic valvular disease. Measurement of lipoprotein(a) level and comparison between different assays are challenging due to differences in reporting units and the absence of a reference method. Various guidelines recommend measurement of lipoprotein(a) levels in order to define cardiovascular risk. Lifestyle modifications have a minimal effect in reducing lipoprotein(a) levels. Currently available lipid-lowering therapies also result in only modest reductions in lipoprotein(a) levels. At present, there is no approved pharmacological treatment option for lowering lipoprotein(a) levels. More potent lipoprotein(a)-lowering medications are under active investigation to prove that lowering lipoprotein(a) level reduces ASCVD events. Lipoprotein(a), therefore, remains a viable and attractive therapeutic target in ASCVD risk reduction.

HISTORY

Lipoprotein(a) was first described by Kare Berg in 1963 (1) and later purified and characterized by

Ehnholm and colleagues as part of human lipoproteins (2). Subsequent studies linked lipoprotein(a) to coronary artery disease (CAD) (3,4) and the threshold of 30 mg/dL was introduced (5). In 1987, amino acid sequences of apolipoprotein(a) [apo(a)], a major protein of lipoprotein(a), were identified and the *LPA* gene, encoding apo(a), was cloned (6,7). The sequence showed homology to plasminogen, a fibrinolytic proenzyme, but the protease domain was inactive (6). Apo(a) size polymorphism and its underlying molecular genetics were discovered and the inverse correlation between apo(a) isoform and lipoprotein(a) levels were demonstrated (8). Early observational and prospective studies showed higher levels of lipoprotein(a) in patients with CAD and myocardial infarction (MI) (4,5,9-12), but others did not (13,14). Lipoprotein(a) was later identified as a main carrier of oxidized phospholipids in the plasma (15). Results from large population-based studies along with Mendelian randomization studies in the past 2 decades have shown that lipoprotein(a) is a causal risk factor for atherosclerotic cardiovascular disease (ASCVD), especially MI and atherosclerotic stenosis (16-19). A surprise finding in 2013 also identified lipoprotein(a) as a key player in calcific aortic valvular disease (CAVD) (20). Currently, lipoprotein(a) is an active therapeutic target and results from ongoing phase 3 clinical studies will soon clarify the lipoprotein(a) hypothesis in ASCVD and CAVD.

STRUCTURE AND ASSEMBLY

Lipoprotein(a) is an apoB-containing lipoprotein resembling low-density lipoprotein (LDL), but apolipoprotein B-100 is covalently linked to a unique glycoprotein, called apolipoprotein(a) or apo(a). Apo(a), encoded by the *LPA* gene, is structurally similar to plasminogen, an important protein involved in fibrinolysis. *In vitro*, apo(a) has been shown to inhibit fibrinolysis (21)

Apo(a) is present only in a subset of primates, including humans, Old World monkeys, and

orangutans, but not in New World monkeys or other primates. The exception is the occurrence of an apo(a)-like protein in the hedgehog (22). A characteristic feature of apo(a) is the presence of loop-like structure stabilized by 3 internal disulfide bonds, called “kringles”. These kringle domains are triple-loop structures found in other coagulation factors, including plasminogen. While plasminogen has 5 kringle domains (KI, KII, KIII, KIV and KV) and one protease domain at the end, apo(a) has only KIV, KV and an inactive protease domain (Figure 1).

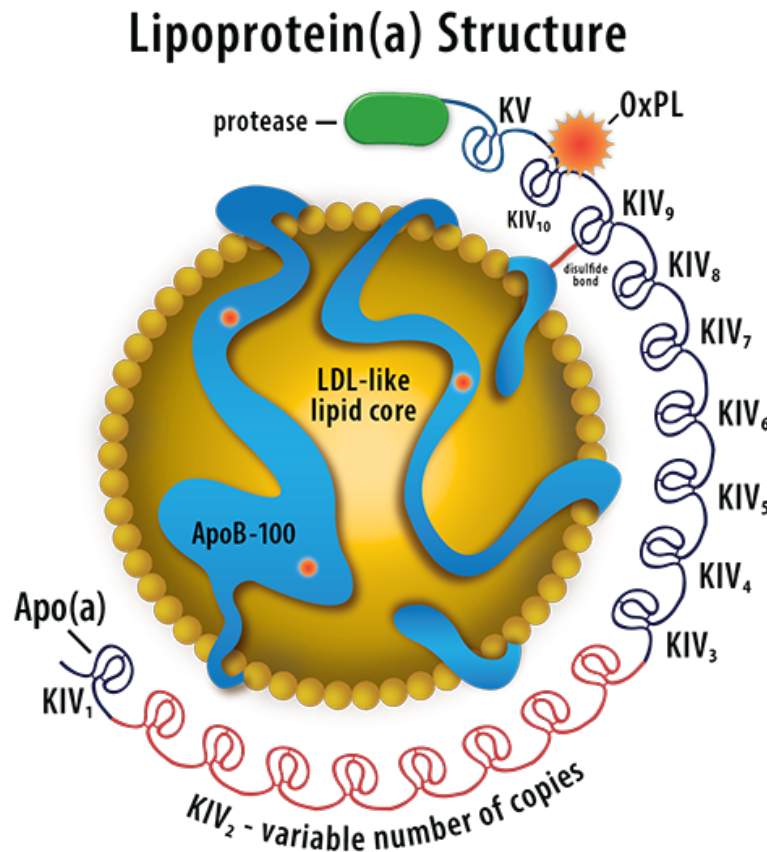


Figure 1. Structure of lipoprotein(a) (from www.familyheart.org).

In apo(a), the number of the fourth kringle domain is highly variable due to expansion and differentiation of KIV into 10 different types of KIV domains, called

KIV1-KIV10. While KIV1 and KIV3-KIV10 are present as single copies, kringle IV type 2 (KIV2) are further expanded, resulting in multiallelic copy number

variation (1 to >40 copies). This expansion of KIV2 leads to a size polymorphism of apo(a), ranging from 300-800 kDa (23). Circulating levels of lipoprotein(a) are determined by the number of KIV2 copies. A low number of KIV2 copies results in small apo(a) isoforms, which lead to efficient secretion and contribute to higher levels of lipoprotein(a). On the other hand, the high number of KIV2 copies leads to large apo(a) isoforms and low levels of circulating lipoprotein(a).

Apo(a) is mainly synthesized in the liver. Newly formed apo(a) is then bound to apo B-100 of LDL to become lipoprotein(a). The assembly of lipoprotein(a) particles is a two-step process (24). The first step is the non-covalent docking of the lysine-binding site at the KIV7-KIV8 domains of apo(a) to the lysine residues at the N-terminus of apo B-100. The second step is the covalent binding through the disulfide bond between the 2 free cysteines in the KIV-9 of apo(a) and apo B-100 (25). The site of lipoprotein(a) assembly has been controversial whether it occurs intracellularly or extracellularly (23,25,26), but a recent study using a hepatocyte cell model suggests that the first non-covalent step occurs intracellularly, whereas the second covalent bond formation occurs extracellularly (27,28).

FUNCTION

The physiological function of lipoprotein(a) remains obscure (23). Earlier, it has been suggested that lipoprotein(a) may assist in wound healing (16,29). Lipoprotein(a) can interact with fibrin and other components of the extracellular matrix (30) via the lysine-binding sites in its kringle domains and it delivers cholesterol to the site of injury. Besides carrying cholesterol esters, free cholesterol, triglycerides, and phospholipids, lipoprotein(a) is the main carrier of oxidized phospholipids in the circulation (15). Lipoprotein(a) might also act as a carrier/scavenger for oxidized lipids since oxidized

phospholipids and platelet-activating factor acetylhydrolase, an enzyme involved in hydrolyzing PAF, are found on lipoprotein(a) particles. In vitro, lipoprotein(a) can interfere with many steps of blood clotting and fibrinolysis (21), but the evidence for its thrombogenic role in vivo is less convincing (16).

In the Finnish population, loss-of-function variants in the *LPA* gene have been found (31). Although these subjects have very low levels of lipoprotein(a), no identifiable clinical abnormalities have been demonstrated (31). An increased risk of type 2 diabetes has been reported in those who have very low levels of lipoprotein(a) (32-36). Whether low levels of lipoprotein(a) are causally associated with type 2 diabetes is still unclear.

METABOLISM

Circulating levels of lipoprotein(a) are primarily determined by isoform size-dependent production rate and not catabolism (37). Fractional catabolic rates for lipoprotein(a) with short and long isoforms have been shown to be relatively indifferent (37). Liver is the main site of lipoprotein(a) catabolism, with a minor contribution from the kidney (26). Apo(a), apo B-100 and oxidized phospholipids carried on lipoprotein(a) may play a role in catabolism of lipoprotein(a) particles by acting as ligands for various receptors. A number of receptors have been shown to be associated with clearance of lipoprotein(a), including lipoprotein receptors, scavenger receptors, plasminogen receptors, Toll-like receptors (TLRs), and carbohydrate receptors or lectins (38). However, the relative contribution of these different receptors in lipoprotein(a) clearance remains to be explored. The lack of suitable animal models and the conflicting data on the role of certain receptors on the catabolism of lipoprotein(a) also make it difficult to conclude the definite role of these receptors. Following uptake into the cells, it has been shown that lipoprotein(a) dissociates into 2 components, with LDL being

degraded in lysosomes and apo(a) being recycled to be re-secreted (39). It has been estimated that approximately 30% of apo(a) is recycled after lipoprotein(a) internalization into the cells (39), which could potentially contribute to the circulating level of lipoprotein(a).

GENETICS

Lipoprotein(a) levels are strongly determined by the genetic locus at the *LPA* gene on chromosome 6, which encodes apo(a). The *LPA* gene is closely related to the *PLG* gene, which encodes plasminogen. These 2 genes diverged about 40 million years ago with the loss of KI-KIII and the expansion and differentiation of KIV domain (23). The major genetic determinant is a copy number variation of the KIV2 repeat, which explains approximately 30-70% of the variability in lipoprotein(a) levels, depending on ethnicity (40). The apo(a) size is highly variable among individuals and depends on the number of KIV2 repeats in the *LPA* gene. Expression of a low number (10-22) of KIV2 repeats is characterized by small apo(a) isoforms and higher lipoprotein(a) levels, whereas a higher number (>23) of KIV2 repeats results in large apo(a) isoforms and lower lipoprotein(a) levels. Smaller apo(a) isoforms are associated with higher apo(a) production rates from the liver (41), whereas larger isoforms are more susceptible to proteosomal degradation in the endoplasmic reticulum (42). Subjects who carry a low number of KIV repeats have 4-5 times higher median lipoprotein(a) levels than those with a high number of KIV repeats (43).

Because every individual has 2 copies of this gene, 2 different isoforms may be present in plasma. In general, plasma levels of lipoprotein(a) are determined by the net production of apo(a) in each isoform. In Caucasians, with an increasing number of KIV repeats, and hence the larger apo(a) isoform, the frequency of the non-expressed allele is also

increasing (44). As a result, the major isoform in circulation is mainly driven by the smaller ones. However, in about one-quarter of Caucasians, the larger allele is reported to be the dominant one (44) so the smaller allele is not always dominant (45). The frequency of the non-expressed alleles in Caucasians was highest in the mid-range whereas in African Americans, the non-expressed alleles were fairly distributed across apo(a) sizes (44).

It is of note that among those who carry the same number of KIV-2 repeats, there is a wide range of variability in the lipoprotein(a) levels. This could be explained by the presence of other genetic variants beyond the KIV repeat polymorphism that are also known to influence lipoprotein(a) levels (23,43,45) with a variable impact among various populations. A large genome-wide association meta-analysis has identified a number of independent single nucleotide polymorphisms (SNPs) around the *LPA* gene which are significantly associated with lipoprotein(a) levels (46). Certain SNPs are functionally lipoprotein(a)-increasing, such as rs1800769 and rs1853021, whereas other SNPs, such as rs10455872 and rs3798220, have no functional effect, but they are in linkage disequilibrium with other small apo(a) isoforms or other variants associated with elevated lipoprotein(a) levels (47).

On the contrary, other genetic variants of the *LPA* gene are associated with low levels of lipoprotein(a), such as the common splice variants, 4733G>A (48) and 4925G>A (49) in the KIV-2 repeat, and the missense variant rs41267813 (50). Other SNPs are null alleles which decrease lipoprotein(a) levels, such as rs41272114, rs41259144 and rs139145675. Individuals who carry these variants are found to be protected against the development of ASCVD.

Other genes, besides the *LPA* gene, have also been shown to influence lipoprotein(a) levels (45) although a meta-analysis has not confirmed the findings (51),

suggesting that further studies with large sample sizes are required to replicate these findings. A recent genome-wide association study from the UK Biobank in almost 300,000 individuals has identified *APOE*, *APOH*, and *CETP* as additional loci that affect lipoprotein(a) levels (52).

Although lipoprotein(a) is under a strong genetic regulation, currently, there is no recommendation or advice to perform genetic testing for the *LPA* gene. Measuring lipoprotein(a) level in the circulation is considered sufficient since it reflects the overall genetic interaction of all variants.

LIPOPROTEIN(A) LEVEL

The distribution of lipoprotein(a) level in plasma is highly skewed with a tail toward higher levels as

shown in Figure 2 (16,17,53). The range varies widely from <0.1 mg/dL to >300 mg/dL (<0.2 – 750 nmol/L). In people of European descent, 80% of the population have a serum level of lipoprotein(a) <40 mg/dL or 90 nmol/L (18). It is well known that plasma levels of lipoprotein(a) are different among various ethnicities, which are predominantly determined by lipoprotein(a) isoform size and other genetic variants in the *LPA* locus (45). Data from the UK Biobank showed that the mean lipoprotein(a) levels were lowest in Chinese individuals (16 nmol/L), followed by White (19 nmol/L), South Asian (31 nmol/L), and highest in Black individuals (75 nmol/L) (17). Data from subjects with various ethnicities have demonstrated that the level of lipoprotein(a) is slightly higher in women than in men (17,53-56), although other studies have shown a lack of difference between men and women (57,58).

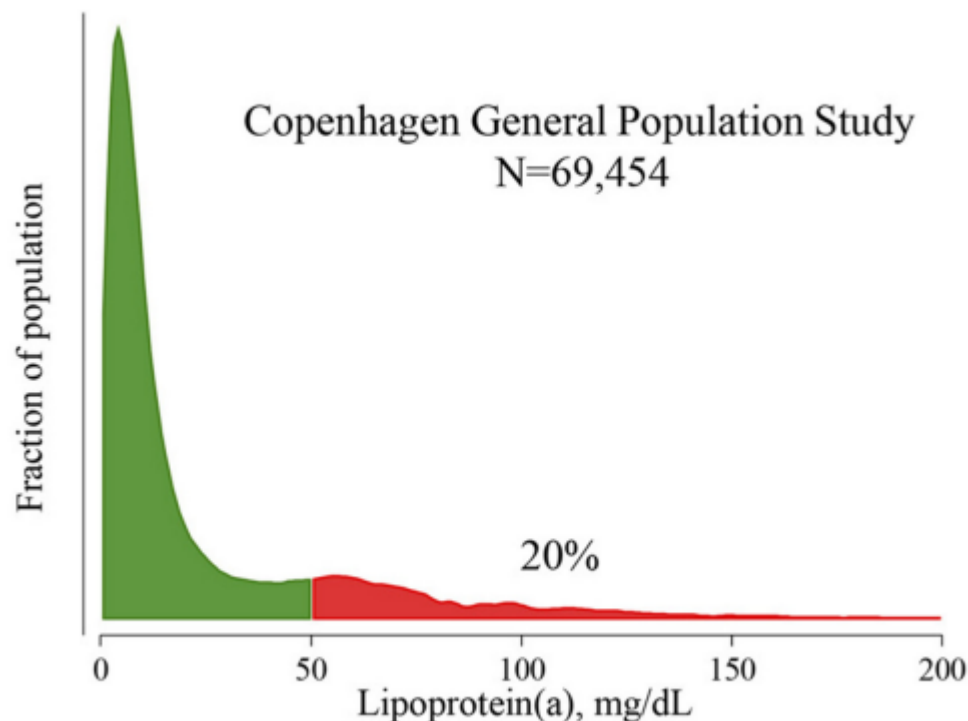


Figure 2. Distribution of lipoprotein(a) in the Danish general population (from (16)).

Lipoprotein(a) level is fully expressed by the age of 2 years and the adult levels are usually achieved by 5 years (59). The level of lipoprotein(a) seems to be stable throughout life because it is under a strong genetic influence (60). Except for certain medical conditions, plasma lipoprotein(a) levels are relatively stable across the lifespan independent of lifestyle. A long-term study over a period of 15 years has shown that the overall absolute change in lipoprotein(a) levels is relatively modest but may be more pronounced in subjects with very high lipoprotein(a) levels (60). The level is also not affected by fasting (61).

Because lipoprotein(a) levels are predominantly determined by genetics, lifestyle modifications appear to have minimal effects (45). A low carbohydrate/high saturated fat diet was shown to result in a 15% decrease in lipoprotein(a) levels (62), whereas a decrease in saturated fat was associated with a 10-15% increase in lipoprotein(a) levels (63). Dietary changes may affect lipoprotein(a) levels in the opposite direction to LDL-C. Physical activity and exercise may affect lipoprotein(a) levels but the results are inconsistent and it may depend on the host, type, intensity, and duration (64).

As lipoprotein(a) is produced by the liver, a reduction in lipoprotein(a) levels is observed in liver disease (65,66). Liver transplantation has been shown to change apo(a) isoform to that of the donor with corresponding changes in lipoprotein(a) levels (67). In contrast, elevations of lipoprotein(a) levels are shown in nephrotic syndrome and chronic kidney diseases, either from impaired catabolism or increased hepatic production in response to protein loss in urine or in dialysis (68,69). A large increase is found among subjects who carry large apo(a) isoform sizes (70). Initiation of dialysis has no effect on lipoprotein(a) levels (71). Kidney transplantation can rapidly normalize lipoprotein(a) levels within several weeks (72-74).

Infection and inflammation also affect lipoprotein(a) levels. In acute and chronic inflammatory conditions, such as autoimmune diseases, lipoprotein(a) levels were increased (10,75), but in severe life-threatening conditions, such as sepsis and burns, lipoprotein(a) levels were decreased (76). Lipoprotein(a) levels increased during COVID infections, which might be responsible for increased thromboembolic events (77,78). The *LPA* gene contains interleukin-6 response elements (79) and elevated lipoprotein(a) levels could be decreased using interleukin-6 receptor blockade by tocilizumab (80). Following acute myocardial infarction, earlier results on the changes in lipoprotein(a) were conflicting, which could be due to differences in assay system (81,82).

Changes in endogenous sex hormones, including menopause and ovariectomy, have been found to have minimal effects on lipoprotein(a) levels (83,84), although a 27% increase after menopause has also been reported (85). Castration and orchidectomy have been shown to slightly increase lipoprotein(a) levels (86,87). Hormone replacement therapy in postmenopausal women reduces lipoprotein(a) levels by approximately 12-25% (85,88).

Longitudinal studies during pregnancy have shown that lipoprotein(a) levels are increased during the first trimester, peak at the middle of the second trimester and return to baseline after childbirth (89-91). Other studies, however, report no changes in lipoprotein(a) during pregnancy (92,93).

Hyperthyroidism is associated with a reduction in lipoprotein(a) level and treatment is found to increase it (94). Hypothyroidism is also associated with an elevation in lipoprotein(a) level and treatment with thyroxine can reduce it (94). Growth hormone (GH) therapy for GH-deficient adults can markedly increase lipoprotein(a) levels (95).

A decrease in lipoprotein(a) level has been reported in several genetic disorders of lipoprotein metabolism including abetalipoproteinemia, lecithin-cholesterol acyltransferase (LCAT) deficiency, and lipoprotein lipase deficiency (96). In contrast, an increase in lipoprotein(a) level is observed in familial

hypercholesterolemia (FH) and familial defective apo B (96).

Conditions that have been reported to increase or decrease lipoprotein(a) levels are shown in Table 1.

Table 1. Conditions Associated with Changes in Lipoprotein(a) Levels		
Increase	Decrease	No change
High carbohydrate/low fat diet (10-15%)	Low carbohydrate/high fat diet (10-15%)	Lifestyle intervention
Hypothyroidism (5-20%)	Hyperthyroidism (20-25%)	Alcohol consumption
Pregnancy (200%)	Hormone replacement therapy (25%)	Fasting
Castration/ovariectomy (small)	Severe acute-phase reactions (burn/sepsis)	Endogenous sex hormone
Growth hormone therapy (25-100%)	Tocilizumab (30-40%)	Menopause
Chronic kidney disease (200-400%)	Hepatitis/cirrhosis	
Nephrotic syndrome (300-500%)		
Severe inflammatory condition		
Protease inhibitors/antiretroviral therapy		

ISSUES IN LIPOPROTEIN(A) MEASUREMENT AND REPORTING

The wide variation in apo(a) isoform size among individuals poses challenges in measuring and reporting lipoprotein(a) levels. Most commercially available immunoassays use polyclonal antibodies which may cross-react with multiple KIV2 repeats (97). As a result, it may overestimate or underestimate lipoprotein(a) levels in subjects with large or small apo(a) isoforms, respectively. Currently, the latex-enhanced immunoturbidimetric method by Denka Seiken, Japan, has been shown to be less affected to apo(a) isoform size variability with high concordance

of values when compared with the reference enzyme-linked immunosorbent assay (ELISA) method (98,99). Although the antibodies used in the Denka assay are still isoform dependent, the impact of apo(a) size variation is minimized by the use of five different calibrators (99). Nevertheless, results comparing six commercially available immunoassays, all of which use five-point calibrators, show a wide range of discrepancy among various assays (100). The reference ELISA method using monoclonal antibodies developed by a group at the University of Washington is considered the least apo(a) isoform size-sensitive immunoassay available (98,99). Recently, a newly developed LC-MS/MS method has been shown to be

unaffected by the apo(a) isoform size polymorphism and proposed as a candidate reference method for standardization of lipoprotein(a) assay (101).

Besides the issues in measuring lipoprotein(a) levels, the reporting of lipoprotein(a) levels is also challenging. Currently, there are 2 types of commercially available assays to measure and report lipoprotein(a) levels. The first one reports the level in total lipoprotein(a) mass concentrations, which include the mass of apo(a), apo B-100, lipid, and carbohydrate components. The values are based on assay calibrators and are expressed in mg/dL. In the first method, there is no traceability of the various calibrators to the reference material (102). In the second method, the level is reported in lipoprotein(a) particle number and expressed in nmol/L of apo(a). The assay calibrators used in the second approach are traceable to the World Health Organization/International Federation of Clinical Chemistry and Laboratory Medicine (WHO/IFCCCLM) secondary reference material (98) and the values are compared to the “gold standard” monoclonal antibody-based ELISA developed by Marcovina et al. (103). It is recommended that lipoprotein(a) levels should be measured with an assay which is least subjected to apo(a) isoform size and has been calibrated with the WHO/IFCCCLM reference material. Current recommendations also encourage the reporting of lipoprotein(a) levels in molar units, but if it is not available, the units in which the assay is calibrated should be used for reporting (59,104,105).

It is known that different apo(a) isoform sizes give different molecular weights (106), therefore, direct conversion between molar and mass concentrations (i.e. nmol/L and mg/dL) using a single conversion factor could be misleading and is discouraged (59,99,106). Nevertheless, a factor of 2.0-2.5 is traditionally used to convert from a mass unit to a molar unit (97), although it may vary from 1.85 for a large apo(a) size to 2.85 for a small apo(a) size (99).

Since lipoprotein(a) and LDL have relatively similar size and density, cholesterol contained in lipoprotein(a) particles cannot be separated from that in LDL particles and is therefore collectively reported as LDL-C concentration. Previous experiments of isolated lipoprotein(a) particles showed that cholesterol accounted for approximately 30% of lipoprotein(a) mass concentration, therefore, lipoprotein(a)-cholesterol could be estimated by multiplying lipoprotein(a) mass (mg/dL) by 0.3 and used to correct LDL-C (lipoprotein(a)-cholesterol-corrected LDL-C) (59). However, a recent study directly measured lipoprotein(a)-cholesterol relative to lipoprotein(a) mass demonstrated that the percentage varied widely, ranging from 5.8% to 57.3% with a median of 17.3% (107), therefore, routine correction of LDL-C for lipoprotein(a)-cholesterol is currently not recommended in clinical practice (59). There are certain exceptions to this. First, in patients with clinically suspected familial hypercholesterolemia (FH) and elevated lipoprotein(a) levels, measurement of lipoprotein(a)-cholesterol may be warranted since the corrected value may help exclude the diagnosis of FH and avoid unnecessary genetic testing (108). Second, correcting LDL-C for lipoprotein(a)-cholesterol may help explain the suboptimal response or resistance to statin therapy. High levels of lipoprotein(a) result in falsely elevated LDL-C. Since statins do not lower lipoprotein(a) levels, cholesterol in lipoprotein(a) is considered a statin-resistant fraction of LDL-C.

EFFECTS OF LIPOPROTEIN(A) ON VASCULAR DISEASE

Lipoprotein(a) exerts multiple effects that could be proatherogenic, proinflammatory, and prothrombotic.

Lipoprotein(a) could be atherogenic since lipoprotein(a) is small enough (<70 nm in diameter) to enter and become trapped in the vascular wall.

Cholesterol carried on lipoprotein(a) particle could then be deposited in the arterial intima and aortic valvular leaflets. However, the number of circulating lipoprotein(a) particles is substantially lower than that of LDL particles. As a result, the amount of cholesterol deposited from lipoprotein(a) is expected to be much lower than that from LDL (109). Apo(a), the main protein of lipoprotein(a), also contains lysine-binding sites that could tightly bind to exposed surface of denuded endothelium of the vascular wall or the aortic valve leaflets. In an animal experiment of endothelial injury, it was found that lipoprotein(a) preferentially accumulated at injured sites, compared with LDL (110). These findings suggest that accumulation of lipoprotein(a) at the site of vascular injury could be the primary mechanism by which elevated lipoprotein(a) causes cardiovascular disease.

There is increasing evidence that oxidized phospholipids carried on lipoprotein(a) play a major role in atherogenesis and valvular calcification. In plasma, lipoprotein(a) is the main carrier of oxidized phospholipids (15). Interaction between oxidized phospholipids and apo(a) is mediated by the histidine residues in the KIV-10 domain of apo(a) (111,112). These oxidized phospholipids are both proatherogenic and proinflammatory (113). Oxidized phospholipids can induce inflammation by binding TLR2, TLR4, CD14 and CD36 on monocytes, macrophages, and endothelial cells (79,114). The result is an activation of multiple cytokines, chemokines, and adhesion molecules that mediate monocyte activation and migration into the vascular wall, endothelial dysfunction and proliferation, proliferation and migration of vascular smooth muscle cells into the atheromatous plaques, generation of reactive oxygen species, progression of vascular wall inflammation, and cell apoptosis that could lead to plaque rupture (115,116).

Structurally, apo(a) is similar to plasminogen, but the protease domain of apo(a) is catalytically inactive.

Therefore, apo(a) may inhibit binding of plasminogen to endothelial cell surface receptor, compete with plasminogen for fibrin affinity sites, and interfere with fibrinolytic activity of plasminogen through a molecular mimicry mechanism (21). However, lowering lipoprotein(a) levels does not affect *ex vivo* fibrinolysis (117), suggesting that the role of lipoprotein(a) in thrombosis may involve other mechanisms beyond fibrinolysis (118). Lipoprotein(a) has also been shown to induce tissue factor expression, inhibit tissue factor pathway inhibitor, promote platelet activation and aggregation, and alter the structure of fibrin, which ultimately leads to thrombosis (118).

It is of note that these proatherogenic, proinflammatory, and prothrombotic effects of lipoprotein(a) have been demonstrated mainly from *in vitro* studies, and the clinical significance of these findings needs to be established from human studies.

LIPOPROTEIN(A) AND CARDIOVASCULAR DISEASE

Over the past two decades, data from epidemiological studies, meta-analyses, genome-wide association studies, and Mendelian randomization studies, have provided conclusive evidence that elevated lipoprotein(a) levels are associated with a higher risk of ASCVD (16,18,47,119-121). This is true in all ethnicities studied to date (17,55,122). The result of a genome-wide association study revealed that the most potent genetic association with coronary artery disease (CAD) was the *LPA* locus (121). A number of Mendelian randomization studies have shown that genetic variants associated with high lipoprotein(a) levels are more prevalent in subjects with ASCVD (18,47), whereas genetic variants associated with low lipoprotein(a) levels are protective against the development of ASCVD (31,49).

Several epidemiological studies, both in primary prevention and secondary prevention settings, have

shown an association between lipoprotein(a) levels and ASCVD (17,19,55,120,123). The association is continuous and linear in different ethnicities without evidence of a threshold effect (17,120). Data from a large prospective cohort study from the UK Biobank showed a broadly linear relationship between lipoprotein(a) levels and ASCVD with an 11% increased risk of ASCVD with every 50 nmol/L increase in lipoprotein(a) levels (17). Another study also reported a relatively similar result, showing a 2.9% increased risk of CVD with every 18 nmol/L (10 mg/dL) increment in lipoprotein(a) levels (124).

Results from the clinical trials suggest that lipoprotein(a) might be a determinant of residual risk of ASCVD in patients who achieved low levels of LDL-C. For example, in the JUPITER trial using high-intensity rosuvastatin, on-statin lipoprotein(a) levels were associated with a residual risk of ASCVD even at low LDL-C levels (125). Similarly, findings from the FOURIER and ODYSSEY-OUTCOMES trials, using statins and PCSK9 inhibitors evolocumab and alirocumab, respectively, also demonstrated that patients with the higher baseline lipoprotein(a) levels were at an elevated risk of ASCVD irrespective of LDL-C levels (126,127). Lipoprotein(a) level is not associated with coronary artery calcium score, but both are independently associated with ASCVD risk (128). Elevated levels of lipoprotein(a) are associated with accelerated progression of atherosclerotic plaque (129).

The association between lipoprotein(a) levels and ASCVD is strongest for MI, atherosclerotic stenosis, and calcific aortic valvular disease (CAVD) (16). Additionally, very high levels of lipoprotein(a) levels are also associated with an increased risk of ischemic stroke (120,130) and heart failure (131), although the associations are weaker.

Not only that lipoprotein(a) is a determinant of ASCVD in patients with lower risk of ASCVD, but in subjects

who are at higher risk of ASCVD, such as those with FH, elevated lipoprotein(a) levels have also been shown to be associated with a higher risk of ASCVD (132,133). Lipoprotein(a) is also an independent predictor of MI and mortality in patients with CKD (134).

Regarding prothrombotic effects of lipoprotein(a), although *in vitro* data demonstrated that lipoprotein(a) might impair fibrinolysis, a potential role for lipoprotein(a) in prothrombotic and antifibrinolytic activity *in vivo* remains unproven (21). Epidemiological studies and Mendelian randomization studies have failed to establish the major role of lipoprotein(a) in venous thrombosis in adults (135,136). In children, however, there is some evidence that elevated lipoprotein(a) level is a risk factor for arterial ischemic stroke and venous thromboembolism (137).

LIPOPROTEIN(A) AND CALCIFIC AORTIC VALVULAR DISEASE

Calcific aortic valvular disease (CAVD) is the disease of the aortic valve that includes early valvular sclerosis and advanced aortic valvular stenosis. CAVD is the leading cause of aortic valve replacement in developed countries, but there is currently no available medical treatment for CAVD. CAVD is characterized by thickening of the aortic valve leaflets with progressive stenosis of the aortic valve. Although the early stages of CAVD are asymptomatic, severe aortic stenosis may lead to significant left ventricular outflow obstruction and subsequent development of syncope, angina and heart failure.

Early cross-sectional studies have shown a strong association between elevated lipoprotein(a) and CAVD (138,139). Such association, however, cannot be used to indicate that lipoprotein(a) is causal for CAVD. In 2013, a genome-wide association study in subjects of European ancestry reported an association between genetic variants in the *LPA* locus and CAVD

(20), which was also confirmed across multiple ethnic groups (20,140). Subsequent cohort and case-control studies have verified this finding and further linked lipoprotein(a) levels and oxidized phospholipids to CAVD (141-144). Lipoprotein(a) is now considered as a new causal risk factor for CAVD (16). Two recent meta-analyses show that plasma lipoprotein(a) levels ≥ 50 mg/dL are associated with a 1.76-1.79-fold increased risk of CAVD (145,146). Elevated lipoprotein(a) levels have also been associated with the faster progression of CAVD and the increased risk for aortic valve replacement and cardiovascular death (143,146-149). In contrast, genetically lowered levels of lipoprotein(a) are associated with a 37% lower risk of aortic stenosis (150).

The normal aortic valve consists of endothelial cells and valvular interstitial cells. In the early stage of CAVD, increased permeability of valvular endothelial cells occurs and results in endothelial barrier dysfunction. Mechanical shear stress may cause further injury to the valvular endothelial cells, leading to endothelium denudation. As a result, lipid infiltration by LDL and lipoprotein(a) follows, similar to the development of atherosclerosis. Inflammatory responses ensue and induce the valvular interstitial cells to gain a myofibroblast-like phenotype and release collagen matrix along with other bone-related proteins. The later stage of CAVD is characterized by the osteogenic differentiation of the valvular interstitial cells, resulting in progressive calcification of the aortic valve. Apoptosis of the valvular interstitial cells can lead to formation of hydroxyapatite crystals and further calcification, creating the propagation of both inflammation and calcification. Progressive fibrosis and widespread calcification ultimately result in thickening and dysfunction of the aortic valvular leaflets.

The role of lipoprotein(a) in the molecular pathogenesis of CAVD is now accumulating. Apo(a) may increase the endothelial cell permeability through

the Rho/RhoK signaling pathway, which is dependent on the lysine-binding site in the KIV10 domain. Since lipoprotein(a) is a major carrier of oxidized phospholipids in plasma, infiltration of lipoprotein(a) in the valvular tissue can deliver oxidized phospholipids to the valve. Oxidized phospholipids can directly attract monocytes and promote the transformation into macrophages. Oxidized phospholipids can then interact with various receptors on the macrophage, resulting in the release of several pro-inflammatory cytokines and subsequent formation of foam cells. Lipoprotein-associated phospholipase A2 (Lp-PLA2) from the macrophage carried on lipoprotein(a) can also act on oxidized phospholipids and generate lysophosphatidylcholine. Autotaxin, a lysophospholipase D enzyme secreted by the valvular interstitial cells and carried on lipoprotein(a) particles (151), can convert lysophosphatidylcholine into lysophosphatidic acid. Lysophosphatidic acid is both pro-inflammatory and pro-calcifying. By binding the lysophospholipid receptor on the valvular interstitial cells, it can activate the nuclear factor kappa B (NF- κ B) and the Wnt- β -catenin pathways, leading to increased transcripts of IL-6 and various osteogenic genes, including runt-related transcription factor 2 (RUNX2) and bone morphogenetic protein 2 (BMP2). The result is the production of alkaline phosphatase, calcium deposition, inflammation, and calcification of the aortic valve (152).

These molecular pathways involved in the pathogenesis of CAVD provide several targets of interest, in addition to lipoprotein(a), that could be targeted and may lead to novel therapies for CAVD in the future.

GUIDELINE RECOMMENDATIONS FOR MEASUREMENT OF LIPOPROTEIN(A) LEVELS

Measurement of lipoprotein(a) levels could help refine the cardiovascular risk in certain conditions and various professional societies have recommended

specific clinical conditions that warrant the measurement of lipoprotein(a) levels (59,105,153-156) as shown in Table 2.

Table 2. Guideline Recommendations for Lipoprotein(a) Measurement						
Indications	AHA 2018	HEART UK 2019	NLA 2019	CCS 2021	BHS 2022	EAS 2022
1. Familial hypercholesterolemia		✓	✓	All individuals	✓	All adults
2. Family history (1 st degree relatives) of premature ASCVD	✓	✓	✓		✓	
3. Family history (1 st degree relatives) of elevated lipoprotein(a)		✓	✓		✓	
4. Personal history of premature ASCVD		✓	✓			
5. Recurrent CVD despite optimal statin treatment			✓			
6. Inadequate LDL-C reduction in response to statin			✓			
7. Borderline or intermediate risk of ASCVD	✓	✓	✓		✓	
8. Calcific valvular aortic stenosis		✓	✓		✓	

It has been pointed out that different recommendations on measurement of lipoprotein(a) among various guidelines may be related to when the guidelines have been written (157). Most of the earlier guidelines list a number of conditions in which lipoprotein(a) should be measured, but the 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) dyslipidemia guidelines have simplified this and recommended that lipoprotein(a) measurement should be considered at

least once in each adult person's lifetime (158). The rationale behind this recommendation is to identify individuals with very high levels of lipoprotein(a), i.e., >180 mg/dL or >430 nmol/L, who have a lifetime risk of ASCVD equivalent to that of heterozygous FH (158). Thus, measuring lipoprotein(a) levels in those with very high levels could make a significant contribution in the overall management to reduce cardiovascular risk. For the latest EAS lipoprotein(a) consensus statement published in 2022, it is

recommended that lipoprotein(a) levels should be measured at least once in every adult (59). Incorporating lipoprotein(a) levels in the cardiovascular risk assessment could help improve risk stratification and provide comprehensive ASCVD risk evaluation. In addition, failure to consider an individual's lipoprotein(a) level could lead to an underestimate of the absolute cardiovascular risk (59). For example, in a person with baseline risk of ASCVD events of 25%, a lipoprotein(a) level of 150 mg/dL will substantially increase the risk to 68% (59). A new risk calculator incorporating lipoprotein(a) levels and other traditional cardiovascular risk factors is now publicly available at <http://www.lipaclinicalguidance.com>.

Elevated lipoprotein(a) level is transmitted as a co-dominant trait. When an index subject is found to have high lipoprotein(a) level, screening for high lipoprotein(a) level in other family members is recommended and could help identify other affected family members (59). This approach is relatively similar to cascade screening in FH, except that genetic testing is not required. For children, there is a recommendation that children who have history of hemorrhagic or ischemic stroke, children of a parent with premature ASCVD and no other identifiable risk factors, and children of a parent with high levels of lipoprotein(a) should have lipoprotein(a) testing (59,154).

In general, the higher the lipoprotein(a) level, the greater risk for ASCVD. Therefore, the use of a specific threshold is biologically implausible and not appropriate. However, clinical practice guidelines prefer the use of a certain threshold for therapeutic decisions. An early study in patients who suffered acute MI proposed the lipoprotein(a) level of >30 mg/dL to reflect a higher risk of MI (5), and this cutoff values have been referred to in several guideline recommendations from various international societies (156,159,160). Another threshold level of lipoprotein(a) that has been used by other professional

societies to confer an increased risk of ASCVD is 50 mg/dL or 100-125 nmol/L (153,154), which corresponds to the 80th percentile in the European descent (45). A recent 2022 consensus statement from the EAS proposed a threshold of ≥ 50 mg/dL (125 nmol/L) to rule in and <30 mg/dL (75 nmol/L) to rule out cardiovascular risk, whereas levels between 30-50 mg/dL (75-125 nmol/L) are grey zones (59). Different thresholds according to ethnicities have been proposed (161), although a large study from the UK Biobank has shown that the ASCVD risk among various ethnicities is similar when using a uniform threshold of ≥ 150 nmol/L (17). At present, current management should remain the same regardless of ethnicity.

Interestingly, an inverse relationship between lipoprotein(a) levels and the risk of type 2 diabetes has been demonstrated from various studies and subjects with very low levels of lipoprotein(a) are at increased risk of diabetes (32-36,162). Some, but not all, genetic studies also suggest that low lipoprotein(a) level is causally associated with the risk of diabetes (33-35). The exact mechanism underlying this association is currently unclear. Whether potent specific lipoprotein(a)-lowering therapy might increase the risk of diabetes remains to be determined.

LIPOPROTEIN(A)-LOWERING TREATMENT

Currently, there is no approved medication for lowering lipoprotein(a) levels. Currently available lipid-lowering medications result in modest (10-30%) reduction in lipoprotein(a) levels (table 3) (163). Data from the Mendelian randomization studies have suggested that lowering lipoprotein(a) levels by approximately 100 mg/dL (215 nmol/L) would produce a similar benefit of reducing ASCVD risk by 22% as shown by lowering LDL-C levels by 38.6 mg/dL (1 mmol/L) using statin therapy (164). A separate analysis using data from primary prevention studies suggested that this number might be overestimated

and lowering lipoprotein(a) levels by 65 mg/dL would be enough to give 22% ASCVD risk reduction (165,166). Similarly, data from the Copenhagen General Population Study demonstrated that lowering lipoprotein(a) by 50 mg/dL (105 nmol/L) within a 5-year period would produce a 20% reduction in major adverse cardiovascular events for secondary prevention (167). It is of note that lowering LDL-C levels of 38.6 mg/dL to give a reduction of an adverse cardiovascular event of 22% was used only as a benchmark and it is possible that lowering lipoprotein(a) levels by smaller amount may also be beneficial as previously shown for LDL-C lowering.

Although early studies report an increase in lipoprotein(a) levels after statin therapy, recent meta-analyses of statin therapy show that there is heterogeneity across studies. In addition, the changes in lipoprotein(a) levels are relatively small and may not be clinically meaningful (168,169). Currently, it is widely accepted that the benefits of statin in lowering LDL-C levels and decreasing ASCVD risk outweigh the potential risk associated with a small increase in lipoprotein(a) levels.

PCSK9 inhibitors, including evolocumab, alirocumab and inclisiran, can lower lipoprotein(a) levels by 10-30% and the absolute reduction is greatest in those with high lipoprotein(a) levels at baseline (126,127,170). A post-hoc analysis from the FOURIER trial using evolocumab reported a 23% decrease in adverse cardiovascular events in those with a baseline lipoprotein(a) level >37 nmol/L and a 7% reduction in those with <37 nmol/L (126). A significant relationship between a 15% lower risk per 25 nmol/L reduction of lipoprotein(a) levels was also observed. These data suggest that a small lowering in lipoprotein(a) level might have a clinical benefit. Results from the ODYSSEY Outcomes trial using alirocumab also showed a significant reduction in major cardiovascular events among those in the two

highest quartiles of baseline lipoprotein(a) levels (127).

Interestingly, an exploratory analysis of the FOURIER trial further showed that lipoprotein(a) level was associated with future aortic stenosis (AS) events (new or worsening CAVD or aortic valve replacement) and that evolocumab therapy beyond one year might reduce these AS events (171). However, it should be noted that this post hoc analysis was performed in only a small number of subjects and the original trial was not designed to evaluate the impact of PCSK9 inhibitors on CAVD.

Other lipid-lowering medications, such as fibrates, ezetimibe, bempedoic acid and bile acid sequestrants, also have modest effects on lipoprotein(a) levels (163). Niacin can lower lipoprotein(a) levels by 20% due to decreased *LPA* mRNA and apo(a) production rate (172). Mipomersen and CETP inhibitors also decrease lipoprotein(a) levels by 20-30% (173). Currently, the use of these medications to lower lipoprotein(a) level is not advised.

Lipoprotein apheresis is an option to lower lipoprotein(a) levels in clinical practice, although levels of all apoB-containing lipoproteins are reduced after treatment (174). A median reduction in lipoprotein(a) level by 70% was observed (175) but the time-averaged reduction was around 30-35% (176). Notably, a reduction in CAD events has been reported from several retrospective studies (177-180). Lipoprotein apheresis could therefore be considered in those with very high levels of lipoprotein(a) and progressive cardiovascular disease despite optimal management of other risk factors (174). Worldwide, lipoprotein apheresis is not commonly performed except in Germany where it is approved for ASCVD patients who have elevated lipoprotein(a) levels (>120 nmol/L or >60 mg/dL) and recurrent ASCVD events, irrespective of LDL-C levels (175). Recently, it is also approved in the United States for patients with

lipoprotein(a) levels >60 mg/dL and LDL-C levels >100 mg/dL with documented CAD or peripheral arterial disease (163).

Without specific lipoprotein(a)-lowering therapy yet available, in subjects with elevated lipoprotein(a) levels, intensive risk factor management, such as healthy diet and lifestyle behavior modifications, is recommended along with the intensification of statin therapy to lower the risk of ASCVD (59). Data from the EPIC-Norfolk population-based study showed that in subjects with elevated lipoprotein(a) above 50 mg/dL, those who modified their lifestyles to maintain ideal cardiovascular health had about one third of cardiovascular risk compared to those with poor cardiovascular health (181). These modifiable cardiovascular health scores included body mass index, healthy diet, physical activity, smoking status, high blood pressure, diabetes and cholesterol concentration (181). In those whose LDL-C target levels are not achieved, ezetimibe or PCSK9 inhibitors could be considered (154).

Aspirin has been shown to be associated with a cardiovascular risk reduction in subjects who carried the SNP rs3798220-C with elevated lipoprotein(a) levels from the Women's Health Study and the Aspirin in Reducing Events in the Elderly (APREE) trial (182). However, this SNP was present in only a small percentage of Caucasian subjects (approximately 3-4%) in these 2 trials. Therefore, further studies with a larger number of subjects in broader populations are needed to confirm the benefits of aspirin.

NEW SPECIFIC LIPOPROTEIN(A)-LOWERING TREATMENT

Since apo(a) is exclusively produced by the liver, novel therapies targeting hepatic apo(a) production using antisense oligonucleotide (ASO) and small interfering RNA (siRNA) technologies are under active investigation.

Pelacarsen, formerly known as TQJ230, IONIS-APO(a)-LRx and AKCEA-APO(a)-LRx, is a second generation of apo(a) ASO, conjugated with *N*-acetylgalactosamine (GalNAc). Since GalNAc is preferentially bound to asialoglycoprotein receptor on the cell surface of hepatocytes, the design of this GalNAc-conjugated molecule will ensure the selective uptake by hepatocytes. Administered by subcutaneous injection every 4 weeks, it can bind apo(a) RNA in the hepatocytes, leading to an approximately 80% reduction in lipoprotein(a) levels in subjects with lipoprotein(a) level >150 nmol/L or approximately 60 mg/dL (183). Pelacarsen is generally well tolerated with the most frequently reported adverse event being injection site reactions. Currently, a phase 3 Lp(a)-HORIZON (NCT04023552) cardiovascular outcome study is underway to investigate the efficacy and safety of pelacarsen at the dose of 80 mg monthly for 4 years in subjects with ASCVD and lipoprotein(a) \geq 70 mg/dL.

Olpasiran, formerly known as AMG890 and ARO-LPA, is a GalNAc-conjugated siRNA that could be given every 3-6 months and result in a greater (>90%) reduction in lipoprotein(a) levels in subjects with lipoprotein(a) level >150 nmol/L or approximately 70 mg/dL (184). The most common adverse events were injection site reactions and hypersensitivity reactions. A cardiovascular outcome study (NCT05581303) is currently investigating the effects of olpasiran given every 12 weeks for 4 years in subjects with ASCVD and lipoprotein(a) levels \geq 200 nmol/L.

Zerlasiran, also known as SLN360, is another GalNAc-conjugated siRNA (185). A Phase 1 study investigated the safety and tolerability of zerlasiran after single ascending doses and multiple doses in healthy subjects with elevated lipoprotein(a) level \geq 150 nmol/L. A dose-dependent and sustained reduction in lipoprotein(a) level has been observed with a 98% reduction in the group receiving 600 mg of zerlasiran (185). A phase 2 ALPACAR-360 study

(NCT05537571) to evaluate the Lipoprotein (a) lowering efficacy, safety and tolerability of zerlasiran in adult participants with elevated lipoprotein(a) (≥ 125 nmol/L) at high risk of ASCVD is now underway.

Besides nucleic acid therapeutics to inhibit hepatic production of apo(a), small molecule inhibitors of lipoprotein(a) formation have been developed. Muvalaplin, an oral small molecule that blocks the

initial noncovalent binding between apo(a) and apo B-100, thus disrupting lipoprotein(a) formation, has been reported to lower lipoprotein(a) level by 65% after 14 days of daily dosing in a phase 1 study (186). No serious adverse effects have been noted.

The effect of lipid-lowering medications on lipoprotein(a) levels is shown in Table 3.

Table 3. Effect of Lipid-Lowering Medications on Lipoprotein(a) Levels	
Statins	No effect or slight increase
Ezetimibe	No effect or slight increase
Fibrates	No effect
Bempedoic acid	Minimal effect
Bile acid sequestrants	Minimal effect
Omega-3 fatty acids	No effect
Niacin	Decrease 15-25%
Lomitapide	Decrease 15-20%
Mipomersen*	Decrease 20-30%
CETP inhibitors*	Decrease 20-30%
Estrogen	Decrease 20-35%
PCSK9 inhibitors	Decrease 10-30%
Apo(a) ASO*	Decrease 80%
Apo(a) siRNA*	Decrease 90-98%
Apo(a) small molecule inhibitor*	Decrease 65%

*not currently available

The results of these ongoing and future clinical trials of lipoprotein(a) reduction are eagerly awaited and are expected to be the last piece of evidence supporting and confirming the causal relationship between lipoprotein(a) and ASCVD. Until a specific therapy for elevated lipoprotein(a) is available, intensive management of other modifiable cardiovascular risk factors is strongly recommended. Whether these lipoprotein(a)-lowering treatments would also be beneficial in CAVD remains to be further explored.

CONCLUSION

After 60 years of its discovery, several issues of lipoprotein(a) remain unresolved, including its function and metabolism. While the causality of lipoprotein(a) in ASCVD and CAVD has now been firmly established by epidemiological, genetic association, and Mendelian randomization studies, the next challenge is to prove that lowering lipoprotein(a) levels also leads to cardiovascular benefit in patients with elevated lipoprotein(a) levels.

REFERENCES

- Berg K. A new serum type system in man--the Lp system. *Acta Pathol Microbiol Scand.* 1963;59:369-382.
- Ehnholm C, Garoff H, Simons K, Aro H. Purification and quantitation of the human plasma lipoprotein carrying the Lp(a) antigen. *Biochim Biophys Acta.* 1971;236(2):431-439.
- Frick MH, Dahlen G, Furberg C, Ericson C, Wiljasalo M. Serum pre-beta-1 lipoprotein fraction in coronary atherosclerosis. *Acta Med Scand.* 1974;195(5):337-340.
- Berg K, Dahlen G, Frick MH. Lp(a) lipoprotein and pre-beta1-lipoprotein in patients with coronary heart disease. *Clin Genet.* 1974;6(3):230-235.
- Kostner GM, Avogaro P, Cazzolato G, Marth E, Bittolo-Bon G, Qunici GB. Lipoprotein Lp(a) and the risk for myocardial infarction. *Atherosclerosis.* 1981;38(1-2):51-61.
- Eaton DL, Fless GM, Kohr WJ, McLean JW, Xu QT, Miller CG, Lawn RM, Scanu AM. Partial amino acid sequence of apolipoprotein(a) shows that it is homologous to plasminogen. *Proc Natl Acad Sci U S A.* 1987;84(10):3224-3228.
- McLean JW, Tomlinson JE, Kuang WJ, Eaton DL, Chen EY, Fless GM, Scanu AM, Lawn RM. cDNA sequence of human apolipoprotein(a) is homologous to plasminogen. *Nature.* 1987;330(6144):132-137.
- Utermann G, Menzel HJ, Kraft HG, Duba HC, Kemmler HG, Seitz C. Lp(a) glycoprotein phenotypes. Inheritance and relation to Lp(a)-lipoprotein concentrations in plasma. *J Clin Invest.* 1987;80(2):458-465.
- Rosengren A, Wilhelmsen L, Eriksson E, Risberg B, Wedel H. Lipoprotein (a) and coronary heart disease: a prospective case-control study in a general population sample of middle aged men. *BMJ.* 1990;301(6763):1248-1251.
- Dahlen GH, Guyton JR, Attar M, Farmer JA, Kautz JA, Gotto AM, Jr. Association of levels of lipoprotein Lp(a), plasma lipids, and other lipoproteins with coronary artery disease documented by angiography. *Circulation.* 1986;74(4):758-765.
- Bostom AG, Cupples LA, Jenner JL, Ordovas JM, Seman LJ, Wilson PW, Schaefer EJ, Castelli WP. Elevated plasma lipoprotein(a) and coronary heart disease in men aged 55 years and younger. A prospective study. *JAMA.* 1996;276(7):544-548.
- Seman LJ, DeLuca C, Jenner JL, Cupples LA, McNamara JR, Wilson PW, Castelli WP, Ordovas JM, Schaefer EJ. Lipoprotein(a)-cholesterol and coronary heart disease in the Framingham Heart Study. *Clin Chem.* 1999;45(7):1039-1046.
- Ridker PM, Hennekens CH, Stampfer MJ. A prospective study of lipoprotein(a) and the risk of myocardial infarction. *JAMA.* 1993;270(18):2195-2199.
- Ridker PM, Stampfer MJ, Hennekens CH. Plasma concentration of lipoprotein(a) and the risk of future stroke. *JAMA.* 1995;273(16):1269-1273.
- Bergmark C, Dewan A, Orsoni A, Merki E, Miller ER, Shin MJ, Binder CJ, Horkko S, Krauss RM, Chapman MJ, Witztum JL, Tsimikas S. A novel function of lipoprotein [a] as a preferential carrier of oxidized phospholipids in human plasma. *J Lipid Res.* 2008;49(10):2230-2239.
- Nordestgaard BG, Langsted A. Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology. *J Lipid Res.* 2016;57(11):1953-1975.
- Patel AP, Wang M, Pirruccello JP, Ellinor PT, Ng K, Kathiresan S, Khera AV. Lp(a) (Lipoprotein[a]) Concentrations and Incident Atherosclerotic Cardiovascular Disease: New Insights From a Large National Biobank. *Arterioscler Thromb Vasc Biol.* 2021;41(1):465-474.
- Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA.* 2009;301(22):2331-2339.
- Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. *Circulation.* 2008;117(2):176-184.
- Thanassoulis G, Campbell CY, Owens DS, Smith JG, Smith AV, Peloso GM, Kerr KF, Pechlivanis S, Budoff MJ, Harris TB, Malhotra R, O'Brien KD, Kamstrup PR, Nordestgaard BG, Tybjaerg-Hansen A, Allison MA, Aspelund T, Criqui MH, Heckbert SR, Hwang SJ, Liu Y, Sjogren M, van der Pals J, Kalsch H, Muhleisen TW, Nothen MM, Cupples LA, Caslake M, Di Angelantonio E, Danesh J, Rotter JJ, Sigurdsson S, Wong Q, Erbel R, Kathiresan S, Melander O, Gudnason V, O'Donnell CJ, Post WS, Group CECW. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med.* 2013;368(6):503-512.
- Boffa MB, Koschinsky ML. Lipoprotein (a): truly a direct prothrombotic factor in cardiovascular disease? *J Lipid Res.* 2016;57(5):745-757.
- Lawn RM, Schwartz K, Patthy L. Convergent evolution of apolipoprotein(a) in primates and hedgehog. *Proc Natl Acad Sci U S A.* 1997;94(22):11992-11997.
- Schmidt K, Noureen A, Kronenberg F, Utermann G. Structure, function, and genetics of lipoprotein (a). *J Lipid Res.* 2016;57(8):1339-1359.
- Trieu VN, McConathy WJ. A two-step model for lipoprotein(a) formation. *J Biol Chem.* 1995;270(26):15471-15474.
- Dieplinger H, Utermann G. The seventh myth of lipoprotein(a): where and how is it assembled? *Curr Opin Lipidol.* 1999;10(3):275-283.
- Kostner KM, Kostner GM. Lipoprotein (a): a historical appraisal. *J Lipid Res.* 2017;58(1):1-14.
- Youssef A, Clark JR, Marcovina SM, Boffa MB, Koschinsky ML. Apo(a) and ApoB Interact Noncovalently Within Hepatocytes: Implications for Regulation of Lp(a) Levels by Modulation of ApoB Secretion. *Arterioscler Thromb Vasc Biol.* 2022;42(3):289-304.
- Boffa MB, Koschinsky ML. Understanding the ins and outs of lipoprotein (a) metabolism. *Curr Opin Lipidol.* 2022;33(3):185-192.
- Brown MS, Goldstein JL. Plasma lipoproteins: teaching old dogmas new tricks. *Nature.* 1987;330(6144):113-114.
- van der Hoek YY, Sangrar W, Cote GP, Kastelein JJ, Koschinsky ML. Binding of recombinant apolipoprotein(a) to extracellular matrix proteins. *Arterioscler Thromb.* 1994;14(11):1792-1798.
- Lim ET, Wurtz P, Havulinna AS, Palta P, Tukiainen T, Rehnstrom K, Esko T, Magi R, Inouye M, Lappalainen T, Chan Y, Salem RM, Lek M, Flannick J, Sim X, Manning A, Ladenvall C, Bumpstead S,

- Hamalainen E, Aalto K, Maksimow M, Salmi M, Blankenberg S, Ardisino D, Shah S, Horne B, McPherson R, Hovingh GK, Reilly MP, Watkins H, Goel A, Farrall M, Girelli D, Reiner AP, Stitzel NO, Kathiresan S, Gabriel S, Barrett JC, Lehtimäki T, Laakso M, Groop L, Kaprio J, Perola M, McCarthy MI, Boehnke M, Altshuler DM, Lindgren CM, Hirschhorn JN, Metspalu A, Freimer NB, Zeller T, Jalkanen S, Koskinen S, Raitakari O, Durbin R, MacArthur DG, Salomaa V, Ripatti S, Daly MJ, Palotie A, Sequencing Initiative Suomi P. Distribution and medical impact of loss-of-function variants in the Finnish founder population. *PLoS Genet*. 2014;10(7):e1004494.
32. Mora S, Kamstrup PR, Rifai N, Nordestgaard BG, Buring JE, Ridker PM. Lipoprotein(a) and risk of type 2 diabetes. *Clin Chem*. 2010;56(8):1252-1260.
33. Kamstrup PR, Nordestgaard BG. Lipoprotein(a) concentrations, isoform size, and risk of type 2 diabetes: a Mendelian randomisation study. *Lancet Diabetes Endocrinol*. 2013;1(3):220-227.
34. Ye Z, Haycock PC, Gurdasani D, Pomilla C, Boekholdt SM, Tsimikas S, Khaw KT, Wareham NJ, Sandhu MS, Forouhi NG. The association between circulating lipoprotein(a) and type 2 diabetes: is it causal? *Diabetes*. 2014;63(1):332-342.
35. Gudbjartsson DF, Thorgerirsson G, Sulem P, Helgadottir A, Gylfason A, Saemundsdottir J, Bjornsson E, Norddahl GL, Jonasdottir A, Jonasdottir A, Eggertsson HP, Gretarsdottir S, Thorleifsson G, Indridason OS, Palsson R, Jonasson F, Jonsdottir I, Eyjolfsson GI, Sigurdardottir O, Olafsson I, Danielsen R, Matthiasson SE, Kristmundsdottir S, Halldorsson BV, Hreidarsson AB, Valdimarsson EM, Gudnason T, Benediktsson R, Steinthorsdottir V, Thorsteinsdottir U, Holm H, Stefansson K. Lipoprotein(a) Concentration and Risks of Cardiovascular Disease and Diabetes. *J Am Coll Cardiol*. 2019;74(24):2982-2994.
36. Paige E, Masconi KL, Tsimikas S, Kronenberg F, Santer P, Weger S, Willeit J, Kiechl S, Willeit P. Lipoprotein(a) and incident type-2 diabetes: results from the prospective Bruneck study and a meta-analysis of published literature. *Cardiovasc Diabetol*. 2017;16(1):38.
37. Rader DJ, Cain W, Ikewaki K, Talley G, Zech LA, Usher D, Brewer HB, Jr. The inverse association of plasma lipoprotein(a) concentrations with apolipoprotein(a) isoform size is not due to differences in Lp(a) catabolism but to differences in production rate. *J Clin Invest*. 1994;93(6):2758-2763.
38. McCormick SPA, Schneider WJ. Lipoprotein(a) catabolism: a case of multiple receptors. *Pathology*. 2019;51(2):155-164.
39. Sharma M, Redpath GM, Williams MJ, McCormick SP. Recycling of Apolipoprotein(a) After PlgRKT-Mediated Endocytosis of Lipoprotein(a). *Circ Res*. 2017;120(7):1091-1102.
40. Scholz M, Kraft HG, Lingenhel A, Delport R, Vorster EH, Bickeboller H, Utermann G. Genetic control of lipoprotein(a) concentrations is different in Africans and Caucasians. *Eur J Hum Genet*. 1999;7(2):169-178.
41. Chan DC, Watts GF, Coll B, Wasserman SM, Marcovina SM, Barrett PHR. Lipoprotein(a) Particle Production as a Determinant of Plasma Lipoprotein(a) Concentration Across Varying Apolipoprotein(a) Isoform Sizes and Background Cholesterol-Lowering Therapy. *J Am Heart Assoc*. 2019;8(7):e011781.
42. White AL, Guerra B, Wang J, Lanford RE. Presecretory degradation of apolipoprotein [a] is mediated by the proteasome pathway. *J Lipid Res*. 1999;40(2):275-286.
43. Coassin S, Kronenberg F. Lipoprotein(a) beyond the kringle IV repeat polymorphism: The complexity of genetic variation in the LPA gene. *Atherosclerosis*. 2022;349:17-35.
44. Rubin J, Paultre F, Tuck CH, Holleran S, Reed RG, Pearson TA, Thomas CM, Ramakrishnan R, Berglund L. Apolipoprotein [a] genotype influences isoform dominance pattern differently in African Americans and Caucasians. *J Lipid Res*. 2002;43(2):234-244.
45. Enkhmaa B, Anuurad E, Berglund L. Lipoprotein (a): impact by ethnicity and environmental and medical conditions. *J Lipid Res*. 2016;57(7):1111-1125.
46. Mack S, Coassin S, Rueedi R, Yousri NA, Seppala I, Gieger C, Schonherr S, Forer L, Erhart G, Marques-Vidal P, Ried JS, Waeber G, Bergmann S, Dahnhardt D, Stockl A, Raitakari OT, Kahonen M, Peters A, Meitinger T, Strauch K, Kedenko L, Paulweber B, Lehtimäki T, Hunt SC, Vollenweider P, Lamina C, Kronenberg F. A genome-wide association meta-analysis on lipoprotein (a) concentrations adjusted for apolipoprotein (a) isoforms. *J Lipid Res*. 2017;58(9):1834-1844.
47. Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, Parish S, Barlera S, Franzosi MG, Rust S, Bennett D, Silveira A, Malarstig A, Green FR, Lathrop M, Gigante B, Leander K, de Faire U, Seedorf U, Hamsten A, Collins R, Watkins H, Farrall M, Consortium P. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med*. 2009;361(26):2518-2528.
48. Schachtl-Riess JF, Kheirkhah A, Gruneis R, Di Maio S, Schoenherr S, Streiter G, Losso JL, Paulweber B, Eckardt KU, Kottgen A, Lamina C, Kronenberg F, Coassin S, Investigators G. Frequent LPA KIV-2 Variants Lower Lipoprotein(a) Concentrations and Protect Against Coronary Artery Disease. *J Am Coll Cardiol*. 2021;78(5):437-449.
49. Coassin S, Erhart G, Weissensteiner H, Eca Guimaraes de Araujo M, Lamina C, Schonherr S, Forer L, Haun M, Losso JL, Kottgen A, Schmidt K, Utermann G, Peters A, Gieger C, Strauch K, Finkstedt A, Bale R, Zoller H, Paulweber B, Eckardt KU, Huttenhofer A, Huber LA, Kronenberg F. A novel but frequent variant in LPA KIV-2 is associated with a pronounced Lp(a) and cardiovascular risk reduction. *Eur Heart J*. 2017;38(23):1823-1831.
50. Said MA, Yeung MW, van de Vegte YJ, Benjamins JW, Dullaart RPF, Ruotsalainen S, Ripatti S, Natarajan P, Juarez-Orozco LE, Verweij N, van der Harst P. Genome-Wide Association Study and Identification of a Protective Missense Variant on Lipoprotein(a) Concentration: Protective Missense Variant on Lipoprotein(a) Concentration-Brief Report. *Arterioscler Thromb Vasc Biol*. 2021;41(5):1792-1800.
51. Zabaneh D, Kumari M, Sandhu M, Wareham N, Wainwright N, Papamarkou T, Hopewell J, Clarke R, Li K, Palmen J, Talmud PJ, Kronenberg F, Lamina C, Summerer M, Paulweber B, Price J, Fowkes G, Stewart M, Drenos F, Shah S, Shah T, Casas JP, Kivimäki M, Whittaker J, Hingorani AD, Humphries SE. Meta analysis of candidate gene variants outside the LPA locus with Lp(a) plasma levels in 14,500 participants of six White European cohorts. *Atherosclerosis*. 2011;217(2):447-451.

52. Hoekstra M, Chen HY, Rong J, Dufresne L, Yao J, Guo X, Tsai MY, Tsimikas S, Post WS, Vasan RS, Rotter JI, Larson MG, Thanassoulis G, Engert JC. Genome-Wide Association Study Highlights APOH as a Novel Locus for Lipoprotein(a) Levels-Brief Report. *Arterioscler Thromb Vasc Biol.* 2021;41(1):458-464.
53. Varvel S, McConnell JP, Tsimikas S. Prevalence of Elevated Lp(a) Mass Levels and Patient Thresholds in 532 359 Patients in the United States. *Arterioscler Thromb Vasc Biol.* 2016;36(11):2239-2245.
54. Nago N, Kayaba K, Hiraoka J, Matsuo H, Goto T, Kario K, Tsutsumi A, Nakamura Y, Igarashi M. Lipoprotein(a) levels in the Japanese population: influence of age and sex, and relation to atherosclerotic risk factors. The Jichi Medical School Cohort Study. *Am J Epidemiol.* 1995;141(9):815-821.
55. Virani SS, Brautbar A, Davis BC, Nambi V, Hoogeveen RC, Sharrett AR, Coresh J, Mosley TH, Morrisett JD, Catellier DJ, Folsom AR, Boerwinkle E, Ballantyne CM. Associations between lipoprotein(a) levels and cardiovascular outcomes in black and white subjects: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation.* 2012;125(2):241-249.
56. Gurdasani D, Sjouke B, Tsimikas S, Hovingh GK, Luben RN, Wainwright NW, Pomilla C, Wareham NJ, Khaw KT, Boekholdt SM, Sandhu MS. Lipoprotein(a) and risk of coronary, cerebrovascular, and peripheral artery disease: the EPIC-Norfolk prospective population study. *Arterioscler Thromb Vasc Biol.* 2012;32(12):3058-3065.
57. Jenner JL, Ordovas JM, Lamon-Fava S, Schaefer MM, Wilson PW, Castelli WP, Schaefer EJ. Effects of age, sex, and menopausal status on plasma lipoprotein(a) levels. The Framingham Offspring Study. *Circulation.* 1993;87(4):1135-1141.
58. Cobbaert C, Kesteloot H. Serum lipoprotein(a) levels in racially different populations. *Am J Epidemiol.* 1992;136(4):441-449.
59. Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, Dweck MR, Koschinsky M, Lambert G, Mach F, McNeal CJ, Moriarty PM, Natarajan P, Nordestgaard BG, Parhofer KG, Virani SS, von Eckardstein A, Watts GF, Stock JK, Ray KK, Tokgozoglu LS, Catapano AL. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. *Eur Heart J.* 2022;43(39):3925-3946.
60. Deshotels MR, Sun C, Nambi V, Virani SS, Matsushita K, Yu B, Ballantyne CM, Hoogeveen RC. Temporal Trends in Lipoprotein(a) Concentrations: The Atherosclerosis Risk in Communities Study. *J Am Heart Assoc.* 2022;11(21):e026762.
61. Langsted A, Kamstrup PR, Nordestgaard BG. Lipoprotein(a): fasting and nonfasting levels, inflammation, and cardiovascular risk. *Atherosclerosis.* 2014;234(1):95-101.
62. Ebbeling CB, Knapp A, Johnson A, Wong JMW, Greco KF, Ma C, Mora S, Ludwig DS. Effects of a low-carbohydrate diet on insulin-resistant dyslipoproteinemia-a randomized controlled feeding trial. *Am J Clin Nutr.* 2022;115(1):154-162.
63. Enkhmaa B, Petersen KS, Kris-Etherton PM, Berglund L. Diet and Lp(a): Does Dietary Change Modify Residual Cardiovascular Risk Conferred by Lp(a)? *Nutrients.* 2020;12(7).
64. Enkhmaa B, Berglund L. Non-genetic influences on lipoprotein(a) concentrations. *Atherosclerosis.* 2022;349:53-62.
65. Feely J, Barry M, Keeling PW, Weir DG, Cooke T. Lipoprotein(a) in cirrhosis. *BMJ.* 1992;304(6826):545-546.
66. Alessandri C, Basili S, Maurelli M, Andreozzi P, Violi F, Cordova C. Relationship between lipoprotein(a) levels in serum and some indices of protein synthesis in liver cirrhosis. *Clin Chim Acta.* 1994;224(2):125-129.
67. Kraft HG, Menzel HJ, Hoppichler F, Vogel W, Utermann G. Changes of genetic apolipoprotein phenotypes caused by liver transplantation. Implications for apolipoprotein synthesis. *J Clin Invest.* 1989;83(1):137-142.
68. Kronenberg F. Causes and consequences of lipoprotein(a) abnormalities in kidney disease. *Clin Exp Nephrol.* 2014;18(2):234-237.
69. Hopewell JC, Haynes R, Baigent C. The role of lipoprotein (a) in chronic kidney disease. *J Lipid Res.* 2018;59(4):577-585.
70. Kronenberg F, Lingenhel A, Lhotta K, Rantner B, Kronenberg MF, Konig P, Thiery J, Koch M, von Eckardstein A, Dieplinger H. The apolipoprotein(a) size polymorphism is associated with nephrotic syndrome. *Kidney Int.* 2004;65(2):606-612.
71. Barbagallo CM, Averna MR, Sparacino V, Galione A, Caputo F, Scafidi V, Amato S, Mancino C, Cefalu AB, Notarbartolo A. Lipoprotein (a) levels in end-stage renal failure and renal transplantation. *Nephron.* 1993;64(4):560-564.
72. Kronenberg F, Konig P, Lhotta K, Ofner D, Sandholzer C, Margreiter R, Dosch E, Utermann G, Dieplinger H. Apolipoprotein(a) phenotype-associated decrease in lipoprotein(a) plasma concentrations after renal transplantation. *Arterioscler Thromb.* 1994;14(9):1399-1404.
73. Black IW, Wilcken DE. Decreases in apolipoprotein(a) after renal transplantation: implications for lipoprotein(a) metabolism. *Clin Chem.* 1992;38(3):353-357.
74. Segarra A, Chacon P, Vilardell M, Piera LL. Cyclosporin and serum lipids in renal transplant recipients. *Lancet.* 1993;341(8847):766; author reply 767.
75. Missala I, Kassner U, Steinhagen-Thiessen E. A Systematic Literature Review of the Association of Lipoprotein(a) and Autoimmune Diseases and Atherosclerosis. *Int J Rheumatol.* 2012;2012:480784.
76. Mooser V, Berger MM, Tappy L, Cayeux C, Marcovina SM, Darioli R, Nicod P, Chiolero R. Major reduction in plasma Lp(a) levels during sepsis and burns. *Arterioscler Thromb Vasc Biol.* 2000;20(4):1137-1142.
77. Feingold KR. Lipid and Lipoprotein Levels in Patients with COVID-19 Infections. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J, Kalra S, Kaltsas G, Kapoor N, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrere B, Levy M, McGee EA, McLachlan R, New M, Purnell J, Sahay R, Shah AS, Singer F, Sperling MA, Stratakis CA, Trencle DL, Wilson DP, eds. Endotext. South Dartmouth (MA)2000.
78. Moriarty PM, Gorby LK, Stroes ES, Kastelein JP, Davidson M, Tsimikas S. Lipoprotein(a) and Its Potential Association with Thrombosis and Inflammation in COVID-19: a Testable Hypothesis. *Curr Atheroscler Rep.* 2020;22(9):48.
79. Dzobo KE, Kraaijenhof JM, Stroes ESG, Nurmohamed NS, Kroon J. Lipoprotein(a): An underestimated inflammatory mastermind. *Atherosclerosis.* 2022;349:101-109.
80. Schultz O, Oberhauser F, Saech J, Rubbert-Roth A, Hahn M, Krone W, Laudes M. Effects of inhibition of interleukin-6 signalling

- on insulin sensitivity and lipoprotein (a) levels in human subjects with rheumatoid diseases. *PLoS One*. 2010;5(12):e14328.
81. Maeda S, Abe A, Seishima M, Makino K, Noma A, Kawade M. Transient changes of serum lipoprotein(a) as an acute phase protein. *Atherosclerosis*. 1989;78(2-3):145-150.
 82. Andreassen AK, Berg K, Torsvik H. Changes in Lp(a) lipoprotein and other plasma proteins during acute myocardial infarction. *Clin Genet*. 1994;46(6):410-416.
 83. Derby CA, Crawford SL, Pasternak RC, Sowers M, Sternfeld B, Matthews KA. Lipid changes during the menopause transition in relation to age and weight: the Study of Women's Health Across the Nation. *Am J Epidemiol*. 2009;169(11):1352-1361.
 84. Anagnostis P, Antza C, Trakatelli C, Lambrinoudaki I, Goulis DG, Kotsis V. The effect of menopause on lipoprotein (a) concentrations: A systematic review and meta-analysis. *Maturitas*. 2023;167:39-45.
 85. Simony SB, Mortensen MB, Langsted A, Afzal S, Kamstrup PR, Nordestgaard BG. Sex differences of lipoprotein(a) levels and associated risk of morbidity and mortality by age: The Copenhagen General Population Study. *Atherosclerosis*. 2022;355:76-82.
 86. Denti L, Pasolini G, Cortellini P, Ferretti S, Sanfelici L, Ablondi F, Valenti G. Effects of androgen suppression by gonadotropin-releasing hormone agonist and flutamide on lipid metabolism in men with prostate cancer: focus on lipoprotein(a). *Clin Chem*. 1996;42(8 Pt 1):1176-1181.
 87. Henriksson P, Angelin B, Berglund L. Hormonal regulation of serum Lp (a) levels. Opposite effects after estrogen treatment and orchidectomy in males with prostatic carcinoma. *J Clin Invest*. 1992;89(4):1166-1171.
 88. Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, Salpeter EE. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. *Diabetes Obes Metab*. 2006;8(5):538-554.
 89. Zechner R, Desoye G, Schweditsch MO, Pfeiffer KP, Kostner GM. Fluctuations of plasma lipoprotein-A concentrations during pregnancy and post partum. *Metabolism*. 1986;35(4):333-336.
 90. Sattar N, Clark P, Greer IA, Shepherd J, Packard CJ. Lipoprotein (a) levels in normal pregnancy and in pregnancy complicated with pre-eclampsia. *Atherosclerosis*. 2000;148(2):407-411.
 91. Manten GT, Franx A, van der Hoek YY, Hameeteman TM, Voorbij HA, Smolders HC, Westers P, Visser GH. Changes of plasma lipoprotein(a) during and after normal pregnancy in Caucasians. *J Matern Fetal Neonatal Med*. 2003;14(2):91-95.
 92. Rymer J, Constable S, Lumb P, Crook M. Serum lipoprotein (A) and apolipoproteins during pregnancy and postpartum in normal women. *J Obstet Gynaecol*. 2002;22(3):256-259.
 93. Chiang AN, Yang ML, Hung JH, Chou P, Shyn SK, Ng HT. Alterations of serum lipid levels and their biological relevances during and after pregnancy. *Life Sci*. 1995;56(26):2367-2375.
 94. Kotwal A, Cortes T, Genere N, Hamidi O, Jasim S, Newman CB, Prokop LJ, Murad MH, Alahdab F. Treatment of Thyroid Dysfunction and Serum Lipids: A Systematic Review and Meta-analysis. *J Clin Endocrinol Metab*. 2020;105(12).
 95. Eden S, Wiklund O, Oscarsson J, Rosen T, Bengtsson BA. Growth hormone treatment of growth hormone-deficient adults results in a marked increase in Lp(a) and HDL cholesterol concentrations. *Arterioscler Thromb*. 1993;13(2):296-301.
 96. Kronenberg F, Utermann G. Lipoprotein(a): resurrected by genetics. *J Intern Med*. 2013;273(1):6-30.
 97. Kronenberg F. Lipoprotein(a) measurement issues: Are we making a mountain out of a molehill? *Atherosclerosis*. 2022;349:123-135.
 98. Marcovina SM, Albers JJ, Scanu AM, Kennedy H, Giaculli F, Berg K, Couderc R, Dati F, Rifai N, Sakurabayashi I, Tate JR, Steinmetz A. Use of a reference material proposed by the International Federation of Clinical Chemistry and Laboratory Medicine to evaluate analytical methods for the determination of plasma lipoprotein(a). *Clin Chem*. 2000;46(12):1956-1967.
 99. Marcovina SM, Albers JJ. Lipoprotein (a) measurements for clinical application. *J Lipid Res*. 2016;57(4):526-537.
 100. Scharnagl H, Stojakovic T, Dieplinger B, Dieplinger H, Erhart G, Kostner GM, Herrmann M, Marz W, Grammer TB. Comparison of lipoprotein (a) serum concentrations measured by six commercially available immunoassays. *Atherosclerosis*. 2019;289:206-213.
 101. Marcovina SM, Clouet-Foraison N, Koschinsky ML, Lowenthal MS, Orquillas A, Boffa MB, Hoofnagle AN, Vaisar T. Development of an LC-MS/MS Proposed Candidate Reference Method for the Standardization of Analytical Methods to Measure Lipoprotein(a). *Clin Chem*. 2021;67(3):490-499.
 102. Tsimikas S, Fazio S, Ferdinand KC, Ginsberg HN, Koschinsky ML, Marcovina SM, Moriarty PM, Rader DJ, Remaley AT, Reyes-Soffer G, Santos RD, Thanassoulis G, Witztum JL, Danthi S, Olive M, Liu L. NHLBI Working Group Recommendations to Reduce Lipoprotein(a)-Mediated Risk of Cardiovascular Disease and Aortic Stenosis. *J Am Coll Cardiol*. 2018;71(2):177-192.
 103. Marcovina SM, Albers JJ, Gabel B, Koschinsky ML, Gaur VP. Effect of the number of apolipoprotein(a) kringle 4 domains on immunochemical measurements of lipoprotein(a). *Clin Chem*. 1995;41(2):246-255.
 104. Reyes-Soffer G, Ginsberg HN, Berglund L, Duell PB, Heffron SP, Kamstrup PR, Lloyd-Jones DM, Marcovina SM, Yeang C, Koschinsky ML, American Heart Association Council on Arteriosclerosis T, Vascular B, Council on Cardiovascular R, Intervention, Council on Peripheral Vascular D. Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2022;42(1):e48-e60.
 105. Cegla J, Neely RDG, France M, Ferns G, Byrne CD, Halcox J, Datta D, Capps N, Shoulders C, Qureshi N, Rees A, Main L, Cramb R, Viljoen A, Payne J, Soran H, Heart Uk Medical S, Research C. HEART UK consensus statement on Lipoprotein(a): A call to action. *Atherosclerosis*. 2019;291:62-70.
 106. Tsimikas S, Fazio S, Viney NJ, Xia S, Witztum JL, Marcovina SM. Relationship of lipoprotein(a) molar concentrations and mass according to lipoprotein(a) thresholds and apolipoprotein(a) isoform size. *J Clin Lipidol*. 2018;12(5):1313-1323.
 107. Yeang C, Witztum JL, Tsimikas S. Novel method for quantification of lipoprotein(a)-cholesterol: implications for improving accuracy of LDL-C measurements. *J Lipid Res*. 2021;62:100053.
 108. Langsted A, Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. High lipoprotein(a) as a possible cause of clinical familial hypercholesterolaemia: a prospective cohort study. *Lancet Diabetes Endocrinol*. 2016;4(7):577-587.

109. Nielsen LB, Gronholdt ML, Schroeder TV, Stender S, Nordestgaard BG. In vivo transfer of lipoprotein(a) into human atherosclerotic carotid arterial intima. *Arterioscler Thromb Vasc Biol.* 1997;17(5):905-911.
110. Nielsen LB, Stender S, Kjeldsen K, Nordestgaard BG. Specific accumulation of lipoprotein(a) in balloon-injured rabbit aorta in vivo. *Circ Res.* 1996;78(4):615-626.
111. Leibundgut G, Scipione C, Yin H, Schneider M, Boffa MB, Green S, Yang X, Dennis E, Witztum JL, Koschinsky ML, Tsimikas S. Determinants of binding of oxidized phospholipids on apolipoprotein (a) and lipoprotein (a). *J Lipid Res.* 2013;54(10):2815-2830.
112. Koschinsky ML, Boffa MB. Oxidized phospholipid modification of lipoprotein(a): Epidemiology, biochemistry and pathophysiology. *Atherosclerosis.* 2022;349:92-100.
113. van der Valk FM, Bekkering S, Kroon J, Yeang C, Van den Bossche J, van Buul JD, Ravandi A, Nederveen AJ, Verberne HJ, Scipione C, Nieuwdorp M, Joosten LA, Netea MG, Koschinsky ML, Witztum JL, Tsimikas S, Riksen NP, Stroes ES. Oxidized Phospholipids on Lipoprotein(a) Elicit Arterial Wall Inflammation and an Inflammatory Monocyte Response in Humans. *Circulation.* 2016;134(8):611-624.
114. Seimon TA, Nadolski MJ, Liao X, Magallon J, Nguyen M, Feric NT, Koschinsky ML, Harkewicz R, Witztum JL, Tsimikas S, Golenbock D, Moore KJ, Tabas I. Atherogenic lipids and lipoproteins trigger CD36-TLR2-dependent apoptosis in macrophages undergoing endoplasmic reticulum stress. *Cell Metab.* 2010;12(5):467-482.
115. Simantiris S, Antonopoulos AS, Papastamos C, Benetos G, Koumallos N, Tsioufis K, Tousoulis D. Lipoprotein(a) and inflammation- pathophysiological links and clinical implications for cardiovascular disease. *J Clin Lipidol.* 2023;17(1):55-63.
116. Coassin S, Kronenberg F. Mechanistic insights into lipoprotein(a): from infamous to 'inflammatory'. *Eur Heart J.* 2020;41(24):2272-2274.
117. Boffa MB, Marar TT, Yeang C, Viney NJ, Xia S, Witztum JL, Koschinsky ML, Tsimikas S. Potent reduction of plasma lipoprotein (a) with an antisense oligonucleotide in human subjects does not affect ex vivo fibrinolysis. *J Lipid Res.* 2019;60(12):2082-2089.
118. Boffa MB. Beyond fibrinolysis: The confounding role of Lp(a) in thrombosis. *Atherosclerosis.* 2022;349:72-81.
119. Tsimikas S. A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies. *J Am Coll Cardiol.* 2017;69(6):692-711.
120. Emerging Risk Factors C, Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, Marcovina SM, Collins R, Thompson SG, Danesh J. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA.* 2009;302(4):412-423.
121. Consortium CAD, Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, Ingelsson E, Saleheen D, Erdmann J, Goldstein BA, Stirrups K, Konig IR, Cazier JB, Johansson A, Hall AS, Lee JY, Willer CJ, Chambers JC, Esko T, Folkersen L, Goel A, Grundberg E, Havulinna AS, Ho WK, Hopewell JC, Eriksson N, Kleber ME, Kristiansson K, Lundmark P, Lytikainen LP, Rafelt S, Shungin D, Strawbridge RJ, Thorleifsson G, Tikkanen E, Van Zuydam N, Voight BF, Waite LL, Zhang W, Ziegler A, Absher D, Altshuler D, Balmforth AJ, Barroso I, Braund PS, Burgdorf C, Claudi-Boehm S, Cox D, Dimitriou M, Do R, Consortium D, Consortium C, Doney AS, El Mokhtari N, Eriksson P, Fischer K, Fontanillas P, Franco-Cereceda A, Gigante B, Groop L, Gustafsson S, Hager J, Hallmans G, Han BG, Hunt SE, Kang HM, Illig T, Kessler T, Knowles JW, Kolovou G, Kuusisto J, Langenberg C, Langford C, Leander K, Lokki ML, Lundmark A, McCarthy MI, Meisinger C, Melander O, Mihailov E, Maouche S, Morris AD, Muller-Nurasyid M, Mu TC, Nikus K, Peden JF, Rayner NW, Rasheed A, Rosinger S, Rubin D, Rumpf MP, Schafer A, Sivananthan M, Song C, Stewart AF, Tan ST, Thorgerirsson G, van der Schoot CE, Wagner PJ, Wellcome Trust Case Control C, Wells GA, Wild PS, Yang TP, Amouyel P, Arveiler D, Basart H, Boehnke M, Boerwinkle E, Brambilla P, Cambien F, Cupples AL, de Faire U, Dehghan A, Diemert P, Epstein SE, Evans A, Ferrario MM, Ferrieres J, Gauguier D, Go AS, Goodall AH, Gudnason V, Hazen SL, Holm H, Iribarren C, Jang Y, Kahonen M, Kee F, Kim HS, Klopp N, Koenig W, Kratzer W, Kuulasmaa K, Laakso M, Laaksonen R, Lee JY, Lind L, Ouwehand WH, Parish S, Park JE, Pedersen NL, Peters A, Quertermous T, Rader DJ, Salomaa V, Schadt E, Shah SH, Sinisalo J, Stark K, Stefansson K, Tregouet DA, Virtamo J, Wallentin L, Wareham N, Zimmermann ME, Nieminen MS, Hengstenberg C, Sandhu MS, Pastinen T, Syvanen AC, Hovingh GK, Dedoussis G, Franks PW, Lehtimäki T, Metspalu A, Zalloua PA, Siegbahn A, Schreiber S, Ripatti S, Blankenberg SS, Perola M, Clarke R, Boehm BO, O'Donnell C, Reilly MP, Marz W, Collins R, Kathiresan S, Hamsten A, Kooner JS, Thorsteinsdottir U, Danesh J, Palmer CN, Roberts R, Watkins H, Schunkert H, Samani NJ. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet.* 2013;45(1):25-33.
122. Cai DP, He YM, Yang XJ, Zhao X, Xu HF. Lipoprotein (a) is a risk factor for coronary artery disease in Chinese Han ethnic population modified by some traditional risk factors: A cross-sectional study of 3462 cases and 6125 controls. *Clin Chim Acta.* 2015;451(Pt B):278-286.
123. Pare G, Caku A, McQueen M, Anand SS, Enas E, Clarke R, Boffa MB, Koschinsky M, Wang X, Yusuf S, Investigators I. Lipoprotein(a) Levels and the Risk of Myocardial Infarction Among 7 Ethnic Groups. *Circulation.* 2019;139(12):1472-1482.
124. Welsh P, Welsh C, Celis-Morales CA, Brown R, Ho FK, Ferguson LD, Mark PB, Lewsey J, Gray SR, Lyall DM, Gill JMR, Pell JP, de Lemos JA, Willeit P, Sattar N. Lipoprotein(a) and cardiovascular disease: prediction, attributable risk fraction, and estimating benefits from novel interventions. *Eur J Prev Cardiol.* 2021;28(18):1991-2000.
125. Khera AV, Everett BM, Caulfield MP, Hantash FM, Wohlgemuth J, Ridker PM, Mora S. Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER Trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). *Circulation.* 2014;129(6):635-642.
126. O'Donoghue ML, Fazio S, Giugliano RP, Stroes ESG, Kanevsky E, Gouni-Berthold I, Im K, Lira Pineda A, Wasserman SM, Ceska R, Ezhov MV, Jukema JW, Jensen HK, Tokgozoglu SL, Mach F, Huber K, Sever PS, Keech AC, Pedersen TR, Sabatine MS. Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk. *Circulation.* 2019;139(12):1483-1492.
127. Bittner VA, Szarek M, Aylward PE, Bhatt DL, Diaz R, Edelberg JM, Fras Z, Goodman SG, Halvorsen S, Hanotin C, Harrington RA,

- Jukema JW, Loizeau V, Moriarty PM, Moryusef A, Pordy R, Roe MT, Sinnaeve P, Tsimikas S, Vogel R, White HD, Zahger D, Zeiher AM, Steg PG, Schwartz GG, Committees OO, Investigators. Effect of Alirocumab on Lipoprotein(a) and Cardiovascular Risk After Acute Coronary Syndrome. *J Am Coll Cardiol*. 2020;75(2):133-144.
128. Mehta A, Vasquez N, Ayers CR, Patel J, Hooda A, Khera A, Blumenthal RS, Shapiro MD, Rodriguez CJ, Tsai MY, Sperling LS, Virani SS, Blaha MJ, Joshi PH. Independent Association of Lipoprotein(a) and Coronary Artery Calcification With Atherosclerotic Cardiovascular Risk. *J Am Coll Cardiol*. 2022;79(8):757-768.
 129. Kaiser Y, Daghem M, Tzolos E, Meah MN, Doris MK, Moss AJ, Kwiecinski J, Kroon J, Nurmohamed NS, van der Harst P, Adamson PD, Williams MC, Dey D, Newby DE, Stroes ESG, Zheng KH, Dweck MR. Association of Lipoprotein(a) With Atherosclerotic Plaque Progression. *J Am Coll Cardiol*. 2022;79(3):223-233.
 130. Langsted A, Nordestgaard BG, Kamstrup PR. Elevated Lipoprotein(a) and Risk of Ischemic Stroke. *J Am Coll Cardiol*. 2019;74(1):54-66.
 131. Kamstrup PR, Nordestgaard BG. Elevated Lipoprotein(a) Levels, LPA Risk Genotypes, and Increased Risk of Heart Failure in the General Population. *JACC Heart Fail*. 2016;4(1):78-87.
 132. Seed M, Hoppichler F, Reaveley D, McCarthy S, Thompson GR, Boerwinkle E, Utermann G. Relation of serum lipoprotein(a) concentration and apolipoprotein(a) phenotype to coronary heart disease in patients with familial hypercholesterolemia. *N Engl J Med*. 1990;322(21):1494-1499.
 133. Holmes DT, Schick BA, Humphries KH, Frohlich J. Lipoprotein(a) is an independent risk factor for cardiovascular disease in heterozygous familial hypercholesterolemia. *Clin Chem*. 2005;51(11):2067-2073.
 134. Bajaj A, Damrauer SM, Anderson AH, Xie D, Budoff MJ, Go AS, He J, Lash JP, Ojo A, Post WS, Rahman M, Reilly MP, Saleheen D, Townsend RR, Chen J, Rader DJ. Chronic Renal Insufficiency Cohort Study I. Lipoprotein(a) and risk of myocardial infarction and death in chronic kidney disease: findings from the CRIC study (Chronic Renal Insufficiency Cohort). *Arterioscler Thromb Vasc Biol*. 2017;37(10):1971-1978.
 135. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Genetic evidence that lipoprotein(a) associates with atherosclerotic stenosis rather than venous thrombosis. *Arterioscler Thromb Vasc Biol*. 2012;32(7):1732-1741.
 136. Helgadottir A, Gretarsdottir S, Thorleifsson G, Holm H, Patel RS, Gudnason T, Jones GT, van Rij AM, Eapen DJ, Baas AF, Tregouet DA, Morange PE, Emmerich J, Lindblad B, Gottsater A, Kiemeny LA, Lindholt JS, Sakalihasan N, Ferrell RE, Carey DJ, Elmore JR, Tsao PS, Grarup N, Jorgensen T, Witte DR, Hansen T, Pedersen O, Pola R, Gaetani E, Magnadottir HB, Wijmenga C, Tromp G, Ronkainen A, Ruigrok YM, Blankensteijn JD, Mueller T, Wells PS, Corral J, Soria JM, Souto JC, Peden JF, Jalilzadeh S, Mayosi BM, Keavney B, Strawbridge RJ, Sabater-Lleal M, Gertow K, Baldassarre D, Nyyssönen K, Rauramaa R, Smit AJ, Mannarino E, Giral P, Tremoli E, de Faire U, Humphries SE, Hamsten A, Haraldsdottir V, Olafsson I, Magnusson MK, Samani NJ, Levey AI, Markus HS, Kostulas K, Dichgans M, Berger K, Kühlenbaumer G, Ringelstein EB, Stoll M, Seedorf U, Rothwell PM, Powell JT, Kuivaniemi H, Onundarson PT, Valdimarsson E, Matthiasson SE, Gudbjartsson DF, Thorgeirsson G, Quyyumi AA, Watkins H, Farrall M, Thorsteinsdottir U, Stefansson K. Apolipoprotein(a) genetic sequence variants associated with systemic atherosclerosis and coronary atherosclerotic burden but not with venous thromboembolism. *J Am Coll Cardiol*. 2012;60(8):722-729.
 137. Kenet G, Lutkhoff LK, Albisetti M, Bernard T, Bonduel M, Brandao L, Chabrier S, Chan A, deVeber G, Fiedler B, Fullerton HJ, Goldenberg NA, Grabowski E, Gunther G, Heller C, Holzhauer S, Iorio A, Journeycake J, Junker R, Kirkham FJ, Kurnik K, Lynch JK, Male C, Manco-Johnson M, Mesters R, Monagle P, van Ommen CH, Raffini L, Rostasy K, Simioni P, Strater RD, Young G, Nowak-Gottl U. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. *Circulation*. 2010;121(16):1838-1847.
 138. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, Kitzman DW, Otto CM. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol*. 1997;29(3):630-634.
 139. Gotoh T, Kuroda T, Yamasawa M, Nishinaga M, Mitsunashi T, Seino Y, Nagoh N, Kayaba K, Yamada S, Matsuo H, et al. Correlation between lipoprotein(a) and aortic valve sclerosis assessed by echocardiography (the JMS Cardiac Echo and Cohort Study). *Am J Cardiol*. 1995;76(12):928-932.
 140. Cairns BJ, Coffey S, Travis RC, Prendergast B, Green J, Engert JC, Lathrop M, Thanassoulis G, Clarke R. A Replicated, Genome-Wide Significant Association of Aortic Stenosis With a Genetic Variant for Lipoprotein(a): Meta-Analysis of Published and Novel Data. *Circulation*. 2017;135(12):1181-1183.
 141. Arsenault BJ, Boekholdt SM, Dube MP, Rheault E, Wareham NJ, Khaw KT, Sandhu MS, Tardif JC. Lipoprotein(a) levels, genotype, and incident aortic valve stenosis: a prospective Mendelian randomization study and replication in a case-control cohort. *Circ Cardiovasc Genet*. 2014;7(3):304-310.
 142. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. *J Am Coll Cardiol*. 2014;63(5):470-477.
 143. Capoulade R, Chan KL, Yeang C, Mathieu P, Bosse Y, Dumesnil JG, Tam JW, Teo KK, Mahmut A, Yang X, Witztum JL, Arsenault BJ, Despres JP, Pibarot P, Tsimikas S. Oxidized Phospholipids, Lipoprotein(a), and Progression of Calcific Aortic Valve Stenosis. *J Am Coll Cardiol*. 2015;66(11):1236-1246.
 144. Kamstrup PR, Hung MY, Witztum JL, Tsimikas S, Nordestgaard BG. Oxidized Phospholipids and Risk of Calcific Aortic Valve Disease: The Copenhagen General Population Study. *Arterioscler Thromb Vasc Biol*. 2017;37(8):1570-1578.
 145. Liu Q, Yu Y, Xi R, Li J, Lai R, Wang T, Fan Y, Zhang Z, Xu H, Ju J. Association Between Lipoprotein(a) and Calcific Aortic Valve Disease: A Systematic Review and Meta-Analysis. *Front Cardiovasc Med*. 2022;9:877140.
 146. Pantelidis P, Oikonomou E, Lampsas S, Zakynthinos GE, Lysandrou A, Kalogeris K, Katsianos E, Theofilis P, Siasos G, Vavuranakis MA, Antonopoulos AS, Tousoulis D, Vavouranakis M. Lipoprotein(a) and calcific aortic valve disease initiation and progression: a systematic review and meta-analysis. *Cardiovasc Res*. 2023;119(8):1641-1655.

147. Zheng KH, Tsimikas S, Pawade T, Kroon J, Jenkins WSA, Doris MK, White AC, Timmers N, Hjortnaes J, Rogers MA, Aikawa E, Arsenault BJ, Witztum JL, Newby DE, Koschinsky ML, Fayad ZA, Stroes ESG, Boekholdt SM, Dweck MR. Lipoprotein(a) and Oxidized Phospholipids Promote Valve Calcification in Patients With Aortic Stenosis. *J Am Coll Cardiol*. 2019;73(17):2150-2162.
148. Perez de Isla L, Watts GF, Alonso R, Diaz-Diaz JL, Muniz-Grijalvo O, Zambon D, Fuentes F, de Andres R, Padro T, Lopez-Miranda J, Mata P. Lipoprotein(a), LDL-cholesterol, and hypertension: predictors of the need for aortic valve replacement in familial hypercholesterolaemia. *Eur Heart J*. 2021;42(22):2201-2211.
149. Capoulade R, Yeang C, Chan KL, Pibarot P, Tsimikas S. Association of Mild to Moderate Aortic Valve Stenosis Progression With Higher Lipoprotein(a) and Oxidized Phospholipid Levels: Secondary Analysis of a Randomized Clinical Trial. *JAMA Cardiol*. 2018;3(12):1212-1217.
150. Emdin CA, Khera AV, Natarajan P, Klarin D, Won HH, Peloso GM, Stitzel NO, Nomura A, Zekavat SM, Bick AG, Gupta N, Asselta R, Duga S, Merlini PA, Correa A, Kessler T, Wilson JG, Bown MJ, Hall AS, Braund PS, Samani NJ, Schunkert H, Marrugat J, Elosua R, McPherson R, Farrall M, Watkins H, Willer C, Abecasis GR, Felix JF, Vasan RS, Lander E, Rader DJ, Danesh J, Ardisson D, Gabriel S, Saleheen D, Kathiresan S, Consortium CH-HF, Consortium CAE. Phenotypic Characterization of Genetically Lowered Human Lipoprotein(a) Levels. *J Am Coll Cardiol*. 2016;68(25):2761-2772.
151. Bourgeois R, Devillers R, Perrot N, Despres AA, Boulanger MC, Mitchell PL, Guertin J, Couture P, Boffa MB, Scipione CA, Pibarot P, Koschinsky ML, Mathieu P, Arsenault BJ. Interaction of Autotaxin With Lipoprotein(a) in Patients With Calcific Aortic Valve Stenosis. *JACC Basic Transl Sci*. 2020;5(9):888-897.
152. Mathieu P, Boulanger MC. Autotaxin and Lipoprotein Metabolism in Calcific Aortic Valve Disease. *Front Cardiovasc Med*. 2019;6:18.
153. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Jr., Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73(24):3168-3209.
154. Wilson DP, Jacobson TA, Jones PH, Koschinsky ML, McNeal CJ, Nordestgaard BG, Orringer CE. Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association. *J Clin Lipidol*. 2019;13(3):374-392.
155. Pearson GJ, Thanassoulis G, Anderson TJ, Barry AR, Couture P, Dayan N, Francis GA, Genest J, Gregoire J, Grover SA, Gupta M, Hegele RA, Lau D, Leiter LA, Leung AA, Lonn E, Mancini GBJ, Manjoo P, McPherson R, Ngui D, Piche ME, Poirier P, Sievenpiper J, Stone J, Ward R, Wray W. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. *Can J Cardiol*. 2021;37(8):1129-1150.
156. Li JJ, Ma CS, Zhao D, Yan XW, Beijing Heart S, Expert C. Lipoprotein(a) and Cardiovascular Disease in Chinese Population: A Beijing Heart Society Expert Scientific Statement. *JACC Asia*. 2022;2(6):653-665.
157. Kronenberg F, Mora S, Stroes ESG. Consensus and guidelines on lipoprotein(a) - seeing the forest through the trees. *Curr Opin Lipidol*. 2022;33(6):342-352.
158. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglul, Wiklund O, Group ESCSD. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111-188.
159. Anderson TJ, Gregoire J, Pearson GJ, Barry AR, Couture P, Dawes M, Francis GA, Genest J, Jr., Grover S, Gupta M, Hegele RA, Lau DC, Leiter LA, Lonn E, Mancini GB, McPherson R, Ngui D, Poirier P, Sievenpiper JL, Stone JA, Thanassoulis G, Ward R. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Can J Cardiol*. 2016;32(11):1263-1282.
160. Joint committee for guideline r. 2016 Chinese guidelines for the management of dyslipidemia in adults. *J Geriatr Cardiol*. 2018;15(1):1-29.
161. Guan W, Cao J, Steffen BT, Post WS, Stein JH, Tattersall MC, Kaufman JD, McConnell JP, Hoefner DM, Warnick R, Tsai MY. Race is a key variable in assigning lipoprotein(a) cutoff values for coronary heart disease risk assessment: the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2015;35(4):996-1001.
162. Ding L, Song A, Dai M, Xu M, Sun W, Xu B, Sun J, Wang T, Xu Y, Lu J, Wang W, Bi Y, Ning G. Serum lipoprotein (a) concentrations are inversely associated with T2D, prediabetes, and insulin resistance in a middle-aged and elderly Chinese population. *J Lipid Res*. 2015;56(4):920-926.
163. Schwartz GG, Ballantyne CM. Existing and emerging strategies to lower Lipoprotein(a). *Atherosclerosis*. 2022;349:110-122.
164. Burgess S, Ference BA, Staley JR, Freitag DF, Mason AM, Nielsen SF, Willeit P, Young R, Surendran P, Karthikeyan S, Bolton TR, Peters JE, Kamstrup PR, Tybjaerg-Hansen A, Benn M, Langsted A, Schnohr P, Vedel-Krogh S, Kobylecki CJ, Ford I, Packard C, Trompet S, Jukema JW, Sattar N, Di Angelantonio E, Saleheen D, Howson JMM, Nordestgaard BG, Butterworth AS, Danesh J, European Prospective Investigation Into C, Nutrition-Cardiovascular Disease C. Association of LPA Variants With Risk of Coronary Disease and the Implications for Lipoprotein(a)-Lowering Therapies: A Mendelian Randomization Analysis. *JAMA Cardiol*. 2018;3(7):619-627.
165. Lamina C, Kronenberg F, Lp GC. Estimation of the Required Lipoprotein(a)-Lowering Therapeutic Effect Size for Reduction in Coronary Heart Disease Outcomes: A Mendelian Randomization Analysis. *JAMA Cardiol*. 2019;4(6):575-579.
166. Kronenberg F. Therapeutic lowering of lipoprotein(a): How much is enough? *Atherosclerosis*. 2019;288:163-165.
167. Madsen CM, Kamstrup PR, Langsted A, Varbo A, Nordestgaard BG. Lipoprotein(a)-Lowering by 50 mg/dL (105 nmol/L) May Be Needed to Reduce Cardiovascular Disease 20% in Secondary

- Prevention: A Population-Based Study. *Arterioscler Thromb Vasc Biol.* 2020;40(1):255-266.
168. de Boer LM, Oorthuys AOJ, Wiegman A, Langendam MW, Kroon J, Spijker R, Zwinderman AH, Hutten BA. Statin therapy and lipoprotein(a) levels: a systematic review and meta-analysis. *Eur J Prev Cardiol.* 2022;29(5):779-792.
169. Willeit P, Ridker PM, Nestel PJ, Simes J, Tonkin AM, Pedersen TR, Schwartz GG, Olsson AG, Colhoun HM, Kronenberg F, Drechsler C, Wanner C, Mora S, Lesogor A, Tsimikas S. Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials. *Lancet.* 2018;392(10155):1311-1320.
170. Leiter LA, Teoh H, Kallend D, Wright RS, Landmesser U, Wijngaard PLJ, Kastelein JJP, Ray KK. Inclisiran Lowers LDL-C and PCSK9 Irrespective of Diabetes Status: The ORION-1 Randomized Clinical Trial. *Diabetes Care.* 2019;42(1):173-176.
171. Bergmark BA, O'Donoghue ML, Murphy SA, Kuder JF, Ezhov MV, Ceska R, Gouni-Berthold I, Jensen HK, Tokgozoglu SL, Mach F, Huber K, Gaciong Z, Lewis BS, Schiele F, Jukema JW, Pedersen TR, Giugliano RP, Sabatine MS. An exploratory analysis of proprotein convertase subtilisin/kexin type 9 inhibition and aortic stenosis in the FOURIER trial. *JAMA Cardiol.* 2020;5(6):709-713.
172. Chemello K, Chan DC, Lambert G, Watts GF. Recent advances in demystifying the metabolism of lipoprotein(a). *Atherosclerosis.* 2022;349:82-91.
173. Santos RD, Raal FJ, Catapano AL, Witztum JL, Steinhagen-Thiessen E, Tsimikas S. Mipomersen, an antisense oligonucleotide to apolipoprotein B-100, reduces lipoprotein(a) in various populations with hypercholesterolemia: results of 4 phase III trials. *Arterioscler Thromb Vasc Biol.* 2015;35(3):689-699.
174. Waldmann E, Parhofer KG. Lipoprotein apheresis to treat elevated lipoprotein (a). *J Lipid Res.* 2016;57(10):1751-1757.
175. Schettler VJJ, Neumann CL, Peter C, Zimmermann T, Julius U, Roeseler E, Heigl F, Grutzmacher P, Blume H, Vogt A, Scientific Board of GftGAWG. The German Lipoprotein Apheresis Registry (GLAR) - almost 5 years on. *Clin Res Cardiol Suppl.* 2017;12(Suppl 1):44-49.
176. Julius U, Tselmin S, Schatz U, Fischer S, Birkenfeld AL, Bornstein SR. Actual situation of lipoprotein apheresis in patients with elevated lipoprotein(a) levels. *Atheroscler Suppl.* 2019;40:1-7.
177. Jaeger BR, Richter Y, Nagel D, Heigl F, Vogt A, Roeseler E, Parhofer K, Ramlow W, Koch M, Utermann G, Labarrere CA, Seidel D, Group of Clinical I. Longitudinal cohort study on the effectiveness of lipid apheresis treatment to reduce high lipoprotein(a) levels and prevent major adverse coronary events. *Nat Clin Pract Cardiovasc Med.* 2009;6(3):229-239.
178. Leebmann J, Roeseler E, Julius U, Heigl F, Spitthoever R, Heutling D, Breitenberger P, Maerz W, Lehmacher W, Heibges A, Klingel R, ProLiFe Study G. Lipoprotein apheresis in patients with maximally tolerated lipid-lowering therapy, lipoprotein(a)-hyperlipoproteinemia, and progressive cardiovascular disease: prospective observational multicenter study. *Circulation.* 2013;128(24):2567-2576.
179. Roeseler E, Julius U, Heigl F, Spitthoever R, Heutling D, Breitenberger P, Leebmann J, Lehmacher W, Kamstrup PR, Nordestgaard BG, Maerz W, Noureen A, Schmidt K, Kronenberg F, Heibges A, Klingel R, ProLiFe-Study G. Lipoprotein Apheresis for Lipoprotein(a)-Associated Cardiovascular Disease: Prospective 5 Years of Follow-Up and Apolipoprotein(a) Characterization. *Arterioscler Thromb Vasc Biol.* 2016;36(9):2019-2027.
180. Moriarty PM, Gray JV, Gorby LK. Lipoprotein apheresis for lipoprotein(a) and cardiovascular disease. *J Clin Lipidol.* 2019;13(6):894-900.
181. Perrot N, Verbeek R, Sandhu M, Boekholdt SM, Hovingh GK, Wareham NJ, Khaw KT, Arsenault BJ. Ideal cardiovascular health influences cardiovascular disease risk associated with high lipoprotein(a) levels and genotype: The EPIC-Norfolk prospective population study. *Atherosclerosis.* 2017;256:47-52.
182. Bhatia HS. Aspirin and lipoprotein(a) in primary prevention. *Curr Opin Lipidol.* 2023;34(5):214-220.
183. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, Tardif JC, Baum SJ, Steinhagen-Thiessen E, Shapiro MD, Stroes ES, Moriarty PM, Nordestgaard BG, Xia S, Guerriero J, Viney NJ, O'Dea L, Witztum JL, Investigators AK-A-LS. Lipoprotein(a) Reduction in Persons with Cardiovascular Disease. *N Engl J Med.* 2020;382(3):244-255.
184. O'Donoghue ML, Rosenson RS, Gencer B, Lopez JAG, Lepor NE, Baum SJ, Stout E, Gaudet D, Knusel B, Kuder JF, Ran X, Murphy SA, Wang H, Wu Y, Kassahun H, Sabatine MS, Investigators O-DT. Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease. *N Engl J Med.* 2022;387(20):1855-1864.
185. Nissen SE, Wolski K, Balog C, Swerdlow DI, Scrimgeour AC, Rambaran C, Wilson RJ, Boyce M, Ray KK, Cho L, Watts GF, Koren M, Turner T, Stroes ES, Melgaard C, Campion GV. Single Ascending Dose Study of a Short Interfering RNA Targeting Lipoprotein(a) Production in Individuals With Elevated Plasma Lipoprotein(a) Levels. *JAMA.* 2022;327(17):1679-1687.
186. Nicholls SJ, Nissen SE, Fleming C, Urva S, Suico J, Berg PH, Linnebjerg H, Ruotolo G, Turner PK, Michael LF. Muvalaplin, an Oral Small Molecule Inhibitor of Lipoprotein(a) Formation: A Randomized Clinical Trial. *JAMA.* 2023;330(11):1042-1053.