Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Lp(a) Therapies

Evidence Summary

Robust lowering of Lp(a) >80% has been observed with therapies currently in clinical development. They show good safety, but their impact on long-term cardiovascular risk remains to be determined.

Neuroprotective Benefit: Lp(a) shows complex vessel dependent relationships with stroke risk and possibly a modest protective effect with dementia risk. The effect of drug-based Lp(a) lowering on cerebrovasculature pathology hasn't been tested.

Aging and related health concerns: Lp(a) therapies show robust, durable, and reversible lowering of Lp(a) in clinical trials. Due to its association with residual risk, this is expected to reduce adverse cardiovascular outcomes, but needs to be confirmed.

Safety: Lp(a) lowering therapies have shown good safety without clear evidence of hepatic toxicity in Phase 2 trials. Mild injection side reactions have been the most common adverse events. Longer term studies are ongoing.

Availability: Currently being tested in clinical trials.	**Dose**: Clinically effective doses for CVD have not yet been established. Pelacarsen, olpasiran, lepodisiran, and zerlasiran are administered subcutaneously. Muvalaplin is administered orally.
Half-life: Pelacarsen: ~30 days Muvalaplin: 70 to 414 hours (in Phase 1 study) Olpasiran: 3 to 8 hours (in serum in Phase 1 study) Lepodisiran: levels undetectable by 48 hours post administration (Phase 1 study) Zerlasiran: 2.4 to 5.9 hours in plasma/56 hours in liver (in cynomolgus monkeys)	**BBB**: Pelacarsen – liver targeted ASO. Olpasiran, Lepodisiran, and Zerlasiran- liver targeted siRNAs. Muvalaplin – small molecule, penetrance has not been described.
Clinical trials: Phase 1 and 2 RCTs have been conducted for pelacarsen, muvalaplin, olpasiran, lepodisiran, and zerlasiran. Phase 3 trials are underway for pelacarsen (n=8,323), olpasiran (n=7,297), and lepodisiran (n=12,500).	**Observational studies**: Elevated Lp(a) is associated with residual cardiovascular risk and shows mixed associations with stroke depending on subtype.

What is it?

Lipoprotein(a) (Lp(a) – pronounced "Lp little a") is a lipoprotein similar to LDL with regards to its lipid composition and the presence of an ApoB100 molecule [1]. However, it also contains a unique glycoprotein, apolipoprotein(a) (apo(a) – not to be confused with apoA1). Apo(a) proteins have various numbers of kringle-domain type 2 repeats depending on the *LPA* allele leading to high heterogeneity between individuals in a population. Lp(a) levels are largely determined genetically and remain stable throughout life. Levels also vary by ethnic populations with higher levels in those of African descent than those of European or Asian descent. The population distribution of Lp(a) levels is characterized by a long tail.

LPA is expressed in the liver, though where Lp(a) lipoproteins are assembled is still not fully resolved. Plasma Lp(a) levels are determined by the amount of Lp(a) production and not necessarily clearance. Lp(a) is cleared by the liver through unelucidated mechanisms. One of the difficulties in determining

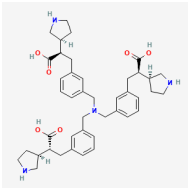
how Lp(a) is produced and cleared is the lack of animal research since the *LPA* gene is only present in Old World monkeys and humans [2].

Levels of Lp(a) above 30 mg/dL are associated with an increased risk for cardiovascular diseases, and is considered a factor contributing to residual risk in individuals treated with traditional lipid-lowering therapies [1].

There are currently no approved therapies indicated for lowering Lp(a), however, there are several Lp(a) lowering therapies in clinical development for patients with cardiovascular disease and elevated Lp(a).

Pelacarsen, originally called AKCEA-APO(a)-LRx, is an antisense oligonucleotide (ASO) that was developed by Akcea Therapeutics. Akcea was acquired by and became a subsidiary of Ionis Pharmaceuticals in 2020. Following its testing in Phase 2 trials, pelacarsen was licensed to Novartis in 2023, which is advancing the clinical development and commercialization of pelacarsen, including overseeing the Phase 3 HORIZON clinical trial (NCT04023552). that is currently underway (Press release).

Muvalaplin (LY3473329) is a small molecule inhibitor of Lp(a) formation in clinical development by Eli Lilly. It has been tested in Phase 1 and Phase 2 trials thus far. (Formula: $C_{42}H_{54}N_4O_6$, Molecular weight: 710.9 g/mol, Image source: Pubchem).



Olpasiran, formerly called AMG 890 was developed by Arrowhead Pharmaceuticals where it was referred to as ARO-LPA, and was licensed to Amgen in 2016 (Press release). It is the first in class short interfering RNA (siRNA) targeting *LPA* mRNA. Amgen is overseeing its clinical development and commercialization. Olpasiran has been tested in the Phase 2 OCEAN-DOSE trial and is currently being tested in the Phase 3 OCEAN(a)) Outcomes trial (NCT05581303).

Lepodisiran (LY3819469) is a siRNA targeting *LPA* mRNA that is in clinical development by Eli Lilly. It has been tested in Phase 1 and Phase 2 trials and is currently being tested in the Phase 3 ACCLAIM-Lp(a) trial (NCT06292013).

Zerlasiran, formerly called SLN360, is an siRNA targeting *LPA* mRNA developed by Silence Therapeutics. It has been tested in Phase 1 and Phase 2 trials thus far.

Neuroprotective Benefit for: Lp(a) shows complex vessel dependent relationships with stroke risk and possibly a modest protective effect with dementia risk. The effect of drug-based Lp(a) lowering on cerebrovasculature pathology hasn't been tested.

Types of evidence:

- 1 meta-analysis of studies assessing relationship between Lp(a) and stroke risk
- 1 Mendelian randomization study of Lp(a) and stroke risk
- 2 Mendelian randomization studies of Lp(a) and dementia risk
- 3 observational studies of Lp(a) and stroke risk/outcomes
- 1 case-control study of Lp(a) levels and stroke risk in a diverse cohort
- 2 cohort studies of Lp(a) and dementia
- 3 observational studies of Lp(a) and cognition
- 3 case control studies for Lp(a) and ApoE4

The evidence regarding the role of Lp(a) on the development of cerebrovascular pathology and cognitive decline is mixed. The relationships vary depending on the type of cerebrovascular pathology, suggesting that Lp(a) plays multiple, yet to be defined, vessel specific roles, such that higher levels may be protective in some contexts and pathogenic in others. The overall link of Lp(a) with cognitive decline appears to be weak, such that many studies fail to find a significant association, while those that show associations tend to be of borderline significance. This may stem from the mixed roles of Lp(a) in the cerebrovasculature or brain. Additionally, levels of Lp(a) are influenced by ethnicity, such that some of the associations may be influenced by the ethnic makeup of the cohorts analyzed.

Stroke: HIGH LP(a) ASSOCIATED WITH INCREASED RISK FOR LARGE ARTERY STROKE
Observational and Mendelian randomization studies have indicated a divide between the associations of Lp(a) with stroke depending on the size of the vessel, such that large vessel stroke shows positive associations while small vessel stroke shows inverse associations with levels of Lp(a).

The REGARDS (Reasons for Geographic and Racial Differences in Stroke) study included 30,239 Black and White adults aged ≥45 in the United States. A case-control study, including 572 cases of incident ischemic stroke and a 967-person cohort random sample, identified elevated Lp(a) as a risk factor for ischemic stroke [3]. Median Lp(a) levels in the cohort sample varied based on sex and race, with levels increasing from lowest to highest in the order of White men (8.8 mg/dL), White women (11.0 mg/dL),

Black men (26.7 mg/dL), and Black women (32.8 mg/dL). The association with stroke was stronger in Black individuals, but did not significantly differ based on sex.

A meta-analysis including 41 studies involving 7,874 ischemic stroke patients and 32,138 controls along with seven studies including 871 intracerebral hemorrhage (ICH) patients and 2,865 controls found there was a significant association between elevated Lp(a) and the risk for ischemic stroke [4]. Based on subtype, high Lp(a) was significantly associated with increased risk for large artery atherosclerosis ischemic stroke and ICH.

A Mendelian randomization study in 446,696 European individuals found that genetically predicted 1-standard deviation log-transformed increase in Lp(a) concentration was associated with an increased risk of large artery stroke (Odds Ratio [OR]: 1.20, 95% Confidence Interval [CI] 1.11 to 1.30), but was associated with a reduced risk of small vessel stroke (OR: 0.92, 95% CI 0.88 to 0.97) [5].

An observational study in 3,059 community-dwelling participants aged 50-79 in the Polyvascular Evaluation for Cognitive Impairment and Vascular Events study in China identified a similar dichotomy, such that relative to those with the lowest tertile Lp(a) levels, higher levels of Lp(a) were associated with the increased odds of having intracranial plaques (OR: 1.34 to 1.37) and elevated intracranial atherosclerotic burden [6]. However, those with the highest tertile Lp(a) levels had lower odds of having cerebral small vessel disease (OR: 0.74) and a lower burden of cerebral small vessel disease. Similarly, a retrospective observational study in China including 111 patients with Alzheimer's disease found that those with the highest tertile levels of Lp(a) were less likely to have features of cerebral small vessel disease [7].

An observational study including 1,017 patients from the Third China National Stroke Registry who experienced an acute ischemic stroke, or a transient ischemic attack ("mini stroke") also found an association between Lp(a) and cognitive outcomes for the large artery atherosclerosis stroke subtype [8]. For this subtype, a greater percentage of participants with the highest quartile levels of Lp(a) experienced cognitive impairment in the year following the stroke (adjusted OR: 2.63, 95% CI 1.05 to 6.61) and were less likely to show cognitive improvement. A similar trend was not observed in participants with the small artery occlusion stroke subtype.

Dementia: LP(a) MAY BE ASSOCIATED WITH REDUCED RISK, BUT THE RELATIONSHIP IS UNCLEAR
Prospective studies and Mendelian randomization studies suggest that high levels of Lp(a) may be associated with a reduced risk of Alzheimer's disease. Case-control studies have mixed results on the association of Lp(a) and dementia with some showing increased Lp(a) increasing risk, some showing decreased Lp(a) increasing risk, and some show no significant effect. However, these studies are limited by the potential confounders with case-control studies [5]. Notably, one cohort study found that the reduced risk of Alzheimer's was no longer significant when controlling for cardiovascular disease or all-cause mortality [9], suggesting the possibility that individuals who survive without cardiovascular disease may be more protected from Alzheimer's.

The mechanisms underlying the potential protective effects of Lp(a) are unclear. Lp(a) levels in the CSF were correlated with plasma levels of Lp(a) which could mean it crosses the blood/CSF barrier. In the brain, Apo-A1 regulates cholesterol levels, amyloid levels, and neurogenesis, and possibly Lp(a) may also influence lipoprotein dynamics or ApoE metabolism in the brain [5].

In a prospective cohort study of 2,532 men in eastern Finland (avg. age at baseline 53; avg. follow-up 24.9 years), comparing the top quartile of Lp(a) levels to the bottom quartile was associated with a reduced risk of dementia (Hazard Ratio [HR]: 0.68, 95% CI 0.47 to 0.99) [9]. However, these results were attenuated, and no longer statistically significant when controlling for all-cause mortality (HR: 0.91, p=0.781) and cardiovascular disease-related mortality (HR: 0.71; p=0.124), suggesting the potentially protective effect was mitigated when taking into account the known vascular risk of high Lp(a) levels.

In a Mendelian randomization study including and 54,162 European individuals, genetically predicted 1-standard deviation log-transformed increase in Lp(a) concentration was associated with a reduced risk of Alzheimer's disease (OR: 0.94, 95% CI 0.91 to 0.97) [5].

A separate Mendelian randomization study including 367,586 unrelated European-descent participants from the UK Biobank did not find a significant relationship between LPA genetic variants with Alzheimer's disease or vascular dementia, but did find a weak inverse association between genetically predicated Lp(a) levels and self-reported parental history of dementia (OR: 0.96, 95% CI 0.94 to 0.99) [10].

No significant associations between Lp(a) levels and dementia risk (HR: 0.96, 95% CI 0.87 to 1.07) were observed in a cohort study with an 11.8 year follow-up including 254,575 women and 214,891 men from the UK Biobank [11].

Cognition: RELATIONSHIP WITH LP(a) IS UNCLEAR
The relationship between Lp(a) and cognition is unclear, as there is variation across studies that may be related to composition of the study populations and the type of cognitive measures assessed.

A prospective cohort study of 9,350 participants (avg. age 63.4) in the Atherosclerosis Risk in Communities (ARIC) cohort with a mean follow-up of 15 years fount that each 10 mg/dL increase in Lp(a) was associated with an improved global cognitive z score (0.007; p=0.04) and those in the highest Lp(a) quintiles had improved cognitive scores than those in the lowest quintile [12]. These effects were more pronounced in those taking statins.

In contrast, a nested case-control study including 434 cases of incident cognitive impairment and 557 controls from the REGARDS study found that each standard deviation increase in Lp(a) was associated with increased odds for cognitive impairment (adjusted OR: 1.15, 95% CI 1.01 to 1.30) [13]. The association was strongest in Black participants (OR: 1.39, 95% CI 1.05 to 1.84), and did not reach statistical significance in White participants (OR: 1.03, 95% CI 0.87 to 1.21).

A cross sectional observational study including 1,130 participants ≥60 years of age from the Berlin Aging Study II found that male participants with the lowest quintile of Lp(a) levels showed better cognitive performance on measures related to executive function and processing speed [14]. Lp(a) levels were not significantly associated with cognition in women in this study.

Parkinson's disease: MODEST ASSOCIATIONS/UNCLEAR RELATIONSHIP
The relationships between Lp(a) and Parkinson's disease risk or progression are not well understood. There have been a limited number of preliminary observational studies. One study found that Lp(a) levels were positively associated with Hamilton depression rating scale (HAMD) scores [15], while another case-control study found that Lp(a) levels were weakly associated with UDPRS III scores [16].

ApoE4 interactions

An observational study including 915 participants examined the relationship between ApoE genotype and the circulating lipid profile [17]. ApoE4 carriers were found to have higher levels of total cholesterol, LDL, ApoB, and Lp(a) along with a more pro-inflammatory lipid profile.

Only a few case-control studies have examined the association with Lp(a) levels and ApoE4 genotype. One study reported that higher Lp(a) increased the risk of Alzheimer's disease in ApoE4 carriers, but not in ApoE4 negative carriers, but this was only significant in patients >75 years of age [18].

Another case-control study suggested that Lp(a) levels (70.0-355.0mg/l) were associated with an increased risk of Alzheimer's disease, though the increased risk was independent of ApoE status, and, the risk dropped in those with the highest Lp(a) levels [19].

A third case-control study suggested that those with an Lp(a) null genotype had a later age-of-onset for Alzheimer's disease than those with at least some Lp(a) (76.8 vs 66.9 years) [20]. This association was also independent of ApoE4 status.

Aging and related health concerns: Lp(a) therapies show robust, durable, and reversible lowering of Lp(a) in clinical trials. Due to its association with residual risk, this is expected to reduce adverse cardiovascular outcomes, but needs to be confirmed.

Types of evidence:

- 3 clinical trials for pelacarsen (Phase 1, 2a, and 2b)
- 2 clinical trials for muvalaplin (Phase 1 and 2)
- 3 clinical trials for olpasiran (Phase 1 and 2)
- 1 clinical trial for lepodisiran (Phase 1)
- 2 clinical trials for zerlasiran (Phase 1 and 2)
- 4 Mendelian randomization studies
- 2 observational/epidemiological studies on Lp(a) and CVD risk
- 1 society consensus statement
- 4 reviews on Lp(a) and CVD

Cardiovascular disease: POTENTIAL BENEFIT

Epidemiological and genetic links between Lp(a) and cardiovascular disease

Many individuals experience adverse cardiovascular events despite treatment with lipid lowering therapies, such as high-dose statins, suggesting that additional risk factors remain unaddressed. This is referred to as residual risk [21]. Lp(a) has emerged as a candidate factor involved in residual risk for cardiovascular disease, particularly related to atherosclerotic pathology [22].

A participant-level meta-analysis including 27,658 participants from six placebo-controlled statin trials found that both LDL-C and Lp(a) were independently associated with atherosclerotic cardiovascular disease (ASCVD) risk [23]. Regardless of the degree of LDL-C lowering, the risk for ASCVD remained elevated in statin-treated participants with Lp(a) levels >50 mg/dL (≈125 nmol/L). The overall degree of risk was greatest in those with both elevated Lp(a) and LDL-C, but a 38% increase in relative risk was still observed in those achieving the greatest degree of LDL-C lowering (to levels <77.34 mg/dL) when Lp(a) was high (>50 mg/dL). This suggests that both LDL-C and Lp(a) need to be controlled in order to adequately mitigate ASCVD risk.

Many epidemiology studies have found that high Lp(a) levels are associated with an increased risk for cardiovascular diseases such as myocardial infarction, atherosclerosis, and aortic valve stenosis [1]. For example, Lp(a) levels were found to be associated with arterial calcification in the population-based Rotterdam study including 2,354 participants [24]. Arterial calcification refers to the buildup of calcium deposits in artery walls and is considered a hallmark of atherosclerosis. Higher Lp(a) levels were associated with larger volumes of arterial calcification, with the association more pronounced in women.
More recently, Mendelian randomization studies provide evidence for a causal role for high Lp(a) in cardiovascular disease [1].

A cross-sectional Mendelian randomization analysis based on individual-level data from 139,362 White British participants from the UK Biobank found that genetic based Lp(a) levels were inversely associated with parental lifespan and healthspan [25]. Similarly, an analysis including 18,720 participants from EPIC-Norfolk prospective cohort found that the mortality risk for individuals with ≥95th percentile Lp(a) levels was equivalent to being 1.5 years older. Lp(a) levels >50 mg/dL was associated with increased risk for all-

cause mortality (HR: 1.17, 95% CI 1.08 to 1.27) and cardiovascular mortality (HR: 1.54, 95% CI 1.37 to 1.72) [25].

The physiological function of Lp(a) is not yet clear, but it is speculated to be involved with wound healing by binding of fibrin to its kringle domains, transporting it to the site of injury and inhibiting fibrinolysis [1]. There are evolutionary similarities between apo(a) and plasminogen, a precursor of plasmin that breaks down fibrin deposits and removes blood clots, such that apo(a) may inhibit plasminogen activation [26]. Though these antifibrinolytic effects may prevent bleeding, in old age it could increase the risk of thrombosis [1].
The pathophysiological role of Lp(a) may stem from its effects on the stability of atherosclerotic plaques [27]. Lp(a) can influence the inflammatory environment of vessels through chemotaxic properties, promoting the expression of adhesion molecules on vascular endothelial cells and promote the recruitment of inflammatory immune populations, such as macrophages and neutrophils [27]. Lp(a) can interact with oxidized phospholipids, and at low concentrations Lp(a) is an efficient scavenger of oxidized phospholipids [2]. However, at high levels it may be more likely to deliver oxidized phospholipids to vascular lesions and exacerbate vascular inflammation.

Various Mendelian randomization studies have attempted to determine the degree of Lp(a) lowering that would be necessary to reduce the risk for adverse cardiovascular outcomes [28]. The estimates vary across studies, which may stem from differences in populations or underlying assumptions. These studies are contingent on the assumption that the proportions for genetically based lifetime risk reduction and short-term therapeutic based risk reductions for Lp(a) would be comparable to what has been observed for LDL-C [29]. This assumption remains to be validated in Phase 3 clinical trials.

Burgess et al., conducted a Mendelian randomization study using 43 LPA SNPs to assess the effect of Lp(a) reduction on coronary heart disease (CHD) outcomes [30]. A genetically predicted 10 mg/dL reduction in Lp(a) was associated with a 5.8% reduced risk of CHD (OR: 0.942, 95% CI 0.933 to 0.951) while a 10 mg/dL reduction in LDL-C was associated with a 14.5% reduced risk of CHD (OR: 0.85, 95% CI 0.818 to 0.893). With respect to LDL-C, they found that genetically based lowering by 38.67 mg/dL was associated with a 45% reduction in lifetime CHD risk, while the short-term risk reduction stemming from therapeutic lowering of LDL-C by 38.67 mg/dL was approximately 22%. Thus, a 101.5mg/dL decrease in Lp(a) was required for the same risk reduction as a 38.6 7mg/dL (1 mmol/L) decrease in LDL-C.
A separate Mendelian randomization study found that a lowering of Lp(a) to 65.7 mg/dL (95% CI 46.3 to 88.3) was required to reach the same impact on clinical outcomes as achieved by lowering LDL-C by

38.67 mg/dL [29]. Their meta-analysis of 27 LPA SNPs found that genetically estimated Lp(a) levels lower by 10 mg/dL were associated with an 8.8% lifetime lower risk of CHD, and a 3.7% lower short-term risk. Thus, lowering Lp(a) to 65.7 mg/dL would correspond to a 45% lifetime and 22% short-term risk reduction for CHD.
In terms of secondary prevention, a Mendelian randomization analysis from the Copenhagen General Population Study including participants with cardiovascular disease, estimated that Lp(a) would need to be lowered by 50 mg/dL to achieve a 20% risk reduction for major adverse cardiovascular events (MACE) [28].

Challenges, clinical guidelines, and measurement of Lp(a)

Various organizations, such as the European Atherosclerosis Society and US National Lipid Association have issued statements recognizing Lp(a) as a causal risk factor for ASCVD and providing recommendations regarding testing [28]. For example, the 2022 consensus statement from the European Atherosclerosis society recommends all adults have their Lp(a) levels checked at least once, to be included as part of the global cardiovascular risk assessment [31]. Since Lp(a) levels tend to be relatively stable over time, repeat assessments are not considered necessary for most people.

There are various challenges toward developing standards for the testing and management of Lp(a). Around 90% of Lp(a) levels are genetically determined, and they are largely resistant to most lifestyle modifications [28]. Lp(a) levels are primarily related to differences in the expression of different apo(a) isoforms. The isoforms vary by size depending on the number of Kringle IV repeats, and those expressing smaller isoforms (>22 Kringle IV) generally have higher concentrations of Lp(a) [32]. However, there are additional regulatory variables involved, as Lp(a) levels can vary around 2.5-fold between individuals in families sharing the same LPA alleles [31]. Due to these size and structure differences in apo(a), the accurate measurement of Lp(a) is technically challenging, and standardization is needed. Most assays use polyclonal antibodies to different epitopes and can over or underestimate levels depending on the relative contribution of small and large isoforms [31]. These assays are either reported in mg/dL or they approximate nmol/L levels via comparison with apo(a) isoform-insensitive reference methods. The use of a standard conversion factor, typically 2 to 2.5, is not recommended as it can lead to inaccuracies due to assay variability. It has been recommended that clinical assays use an antibody with a unique non-repetitive epitope in apo(a) that recognizes each Lp(a) particle only once and report levels as nmol/L [31].

Levels of Lp(a) vary across ethnicities, but ASCVD risk estimates for every 50 nmol/L increase in Lp(a) are highly similar, suggesting that Lp(a) may play a heightened contribution to ASCVD risk in populations with genetically higher levels of Lp(a) [28]. Population-based studies have found that average levels of Lp(a) are for 15 nmol/L for East Asians, 20 nmol/L for Latinos, 25 nmol/L for Whites, 30 nmol/L for South Asians, and 75 nmol/L for Blacks [28]. Lp(a) levels tend to be the highest and most variable in Black populations, who exhibit a less direct relationship between isoform size and circulating Lp(a) levels [28]. A variety of gene variants have been identified that have been linked with variation in Lp(a) levels in population studies. But the directions of the associations are not necessarily consistent, since the phenotypes associated with different LPA genetic variants can also differ across ethnicities. For example, rs10455872 and rs3798220 are two of the best studied LPA variants, which have been associated with small apo(a) isoforms, elevated Lp(a) levels, and elevated risk for ASCVD and cardiovascular-related mortality in predominantly White/Caucasian populations [28]. Meanwhile, the Dallas Heart Study found that the rs3798220 variant was more prevalent in Hispanic populations, but was associated with larger apo(a) isoforms and lower levels [33].

Observational studies have found that women are more prone to having elevated levels of Lp(a) [27]. For example, an assessment of 37,545 women and 32,497 men from the Copenhagen General Population Study found that while Lp(a) levels tend to increase with age in both sexes, women experience an additional menopause-related increase in Lp(a) (around age 50) [34]. This increase was attenuated in women taking hormone replacement therapy. The level of risk for cardiovascular events and mortality associated with elevated Lp(a) (>40 mg/dL) was similar for men and women. This suggests that relative to men, a greater proportion of women >50 years of age are at risk for adverse cardiovascular events related to elevated Lp(a). Additionally, it suggests that testing recommendations may need to be updated to reflect that Lp(a) levels are less stable over a woman's lifespan and should be tested both before and after menopause [34].

The presence of other cardiovascular risk factors in addition to Lp(a) can also influence an individual's risk for adverse cardiovascular events. For example, an individual with Lp(a) levels of 150 mg/dL and a very low 5% baseline risk (based on other traditional risk factors) will have an absolute risk for cardiovascular disease of around 14%. However, an individual with the same Lp(a) level of 150 mg/dL but a high baseline risk of 25% will have an absolute risk for cardiovascular disease of 68% [35]. Due to the additive effects of independent risk factors, these other risk factors may need to be managed more aggressively in individuals with elevated Lp(a), since current therapies do not meaningfully reduce Lp(a) and potent Lp(a) lowering therapies are still in clinical development.

The European Atherosclerosis Society recommends more intensive management of other cardiovascular risk factors, such as LDL-C lowering, in individuals with elevated Lp(a) [31]. Observational data from the ELITE study including 4,602 participants from rural northwestern Germany found that 19.8% of participants had elevated Lp(a), as defined by levels >75 nmol/L (~30 mg/dL) [36]. Those with the highest levels of Lp(a) (>120 nmol/L) were more likely to have elevated LDL-C and hypertension that were inadequately controlled by medication, suggesting that cardiovascular risk is not being properly managed in this population.

These factors make it challenging to use the presence of genetic variants, traditional risk factors, and defined cutoffs for Lp(a) levels in determining eligibility for Lp(a) lowering therapies. Currently, most clinical trials primarily use the somewhat arbitrary cutoff of 50 mg/dL (~125 nmol/L), based off of a Danish population study in which 20% of the population had Lp(a) levels >50 mg/dL [1]. However, the risk for cardiovascular disease is increased at Lp(a) levels above 30 mg/dL (~75 nmol/L). The relative risk is continuous with increasing levels, such that compared to individuals with the median level of 7 mg/dL, having Lp(a) levels of 30 mg/dL, 50 mg/dL, 75 mg/dL, 100 mg/dL, and 150 mg/dL is associated with an increased relative risk of 1.22-fold, 1.40-fold, 1.65-fold, 1.95-fold, and 2.72-fold, respectively [35]. The absolute risk depends on the presence of other risk factors.

Reducing Lp(a)

Traditional lipid-lowering therapies currently in clinical use have marginal effects on Lp(a) [37]. Most do not appreciably reduce Lp(a), and statins can increase Lp(a) levels in some patients. The degree of lowering observed PCSK9 inhibitors can reach up to 35%, but the effects are less robust in those with Lp(a) levels >50 mg/dL, only reducing levels by around 14% As such, these reductions have generally not been clinically meaningful [38].

A variety of Lp(a)-targeted therapies in clinical development generally aim to reduce levels of apo(a) and/or inhibit Lp(a) formation [28]. These include the antisense oligonucleotide (ASO) targeting *LPA* mRNA, pelacarsen, the small molecule inhibitor of Lp(a) formation, muvalaplin, as well as the short interfering RNAs (siRNAs) targeting *LPA* mRNA, lepodisiran, olpasiran, and zerlasiran. They have also demonstrated robust lowering of Lp(a) levels, however, their ability to reduce adverse cardiovascular outcomes has not yet been clinically validated. Ongoing Phase 3 trials should provide evidence toward their ability to reduce cardiovascular risk.

Antisense oligonucleotides (ASOs):

Pelacarsen, originally called, AKCEA-APO(a)-L_{Rx}, is an antisense oligonucleotide (ASO) that targets hepatic *LPA* messenger RNA [39]. It is a second-generation ASO conjugated with a triantennary N-acetylgalactosamine ($GalNAc_3$) moiety. $GalNAc_3$ targets the ASO to the asialoglycoprotein receptor on the surface of hepatocytes which reduces systemic exposure and leads to 15x to 30x increased potency. Pelacarsen was found to reduce Lp(a) levels in a Phase 1 single ascending dose (SAD) study and multiple dose study in 29 healthy Japanese volunteers [40]. In the SAD study, reductions in Lp(a) at day 30 were -55.4%, -58.9%, and -73.7% for the 20 mg, 40 mg, and 80 mg doses of pelacarsen, relative to placebo, respectively. All doses were administered subcutaneously. The multiple dosing study tested pelacarsen at a dose of 80 mg administered monthly for a total of four doses. The placebo-corrected reductions in Lp(a) reached -106.2% by day 85 (around three months). Lp(a) started increasing back toward baseline following the cessation of treatment, though reductions of -55.8% were maintained for nearly three months after the last dose.

A Phase 2a study reported that weekly dosing of pelacarsen reduced Lp(a) levels by 66%-92% with a half-life of approximately one month [41]. Therefore, a Phase 2b study (NCT03070782) was conducted with a more infrequent dosing schedule over six months in 286 patients with established cardiovascular disease and elevated levels of Lp(a) (>60mg/dl). Most of the patients were also taking lipid-lowering therapies and platelet aggregation inhibitors [39].

Results:

Percent change	20 mg every 4 weeks (n=48)	40 mg every 4 weeks (n=48)	20 mg every 2 weeks (n=48)	60 mg every 4 weeks (n=47)	20 mg every week (n=48)	Placebo (n=47)
Lp(a)	-35%	-56%	-58%	-72%	-80%	-6%
OxPL-apoB	-37%	-57%	-64%	-79%	-88%	+14%
OxPL-apo(a)	-28%	-49%	-45%	-63%	-70%	-20%

US guidelines recommend a target of <50mg/dl (125nmol/l) for circulating Lp(a) levels. The percentage of patients reaching the recommended Lp(a) levels were:

Lp(a)	23%	62%	65%	81%	98%	6%

Baseline Lp(a) levels in the study were ~230 nmol/l (~95mg/dL using 2.4 as a conversion factor – Lp(a) conversions are imprecise), so the reduction in Lp(a) in mg/dl ranged from ~33-76mg/dl, suggesting a risk reduction of ~8%-19% for CHD over a five-year trial period, based on the analysis from the Mendelian randomization study by Burgess et al, 2018.

Levels of LDL and ApoB were also slightly reduced after treatment (up to ~20%) with no change in HDL, triglycerides, or the inflammation marker high-sensitivity C-relative protein (hsCRP).

Trial participants were selected based on levels of Lp(a). Levels of Lp(a) can vary based on the presence of LPA genetic variants that tend to affect isoform size. An analysis of data from four trials testing pelacarsen including 455 participants assessed whether the performance of the apo(a)- targeted ASO was affected by genetic background [42]. As expected, the presence of genetic variants associated with elevated Lp(a) (i.e. rs10455872 and rs3798220) was most common in those with the highest levels of Lp(a), as they were present in 25.9% in patients with Lp(a) in the 75 to <125 nmol/L range and in 77.1% of patients with Lp(a) ≥375 nmol/L. The ability of pelacarsen to lower Lp(a) and oxidized phospholipids was found to be independent of LPA genetic variants and isoform size, suggesting that it may have broad utility for Lp(a) lowering.

LDL-C and ApoB are not directly targeted by pelacarsen, or other Lp(a)-targeted therapies currently in clinical development, thus the reductions observed could stem from an artifact of laboratory measures [43]. An analysis from this trial assessed the effect of pelacarsen on directly measured Lp(a)-C and LDL-C corrected for its Lp(a)-C content [43]. Lp(a)-C was measured on isolated Lp(a) using LPA4-magnetic beads directed to apo(a). Pelacarsen led to mean percent changes in LDL-C of −2% to −19% via direct Lp(a) corrected measures, in comparison to a reduction of −7% to −26% based on laboratory reported LDL-C, and 3.1% to 28.3% increases in LDL-C estimated by the Dahlén formula, which uses a fixed 30% correction of Lp(a) mass to estimate Lp(a)-C. The direct Lp(a) corrected LDL-C correlated with total ApoB and non-Lp(a)-ApoB. This analysis suggests that LDL-C assessments using the Dahlén formula are likely to be inaccurate when assessing the impact of targeted Lp(a) lowering therapies. Meanwhile the laboratory measures reported in most Lp(a) lowering clinical trials modestly overestimate the effect on LDL-C, thus should be interpreted with caution [43].

Based on the results from the Phase 2 study, pelacarsen is currently being tested in the randomized double-blind, placebo-controlled Phase 3 Lp(a)HORIZON trial in 8,323 patients with established

cardiovascular disease and elevated Lp(a) (>70 mg/dL) (NCT04023552). Pelacarsen is being administered subcutaneously at a dose of 80 mg on a monthly basis.

Small molecule inhibitors:

Muvalaplin (LY3473329) is an orally bioavailable small molecule inhibitor of Lp(a) formation with sub-nanomolar potency. Apo(a), encoded by the LPA gene, initially binds non-covalently to lysine-rich regions in ApoB-100 through its KIV6–8 domains and then subsequently forms a covalent disulfide bond [44]. Genetic variants in the KIV8 domain are associated with lower levels of Lp(a), suggesting that this region is critical for the formation of Lp(a).
Compounds that bind the KIV7-8 lysine-binding domains of apo(a) were tested for their ability to lower Lp(a) in *in vitro* assays, human LPA expressing transgenic mice, and cynomolgus monkeys [45]. Potency is tied to valency, such that multivalent inhibitors, which allow for the engagement of multiple apo(a) KIV domains, had greater efficacy relative to monovalent compounds. The trimeric compound LY3473329, later named muvalaplin, was identified as the most potent inhibitor of Lp(a) formation in these models. It selectively binds the KIV8 domain with a potency of 22 nM, inhibits the formation of Lp(a) particles *in vitro* with an IC_{50} of 0.09 nM, and dose-dependently decreased median Lp(a) by up to 71% and 92% in cynomolgus monkeys and transgenic mice, respectively.
In the first-in-human Phase 1 trial, muvalaplin was tested in single oral doses from 1 mg to 800 mg and multiple oral doses from 30 mg to 800 mg for 14 days in 114 healthy volunteers in the Netherlands (NCT04472676) [44]. Lp(a) levels were reduced within 24 hours of the first dose, and declined further with additional doses. Baseline Lp(a) levels in the MAD cohort were 58.3 mg/dL (IQR: 38.4 to 79.8 mg/dL), Lp(a) reductions were observed up to 63% to 65%, with 93% of participants achieving Lp(a) lowering to the recommended target of <50 mg/dL.

In the Phase 2 placebo-controlled, randomized, double-blind trial (NCT05563246), muvalaplin was tested in oral doses of 10 mg, 60 mg, or 240 mg per day for 12 weeks [46]. Because traditional apo(a) antibody-based assays may overestimate serum Lp(a) levels in the presence of an inhibitor that binds apo(a), the trial used both a traditional apo(a)-based assay as well as a novel intact Lp(a) assay, which only detects apo(a) bound to an ApoB particle. Muvalaplin was associated with significant reductions in Lp(a) using both assays.

Results:

Percent change (95% CI)	10 ng (n=34)	60 mg (n=63)	240 mg (n=68)	Placebo (n=67)
Lp(a) Traditional apo(a) assay	42.3% (−50.4% to −32.7%)	−70.9% (−74.0% to −67.4%)	−69.9% (−73.0% to −66.4%)	−3.2% (−13.1% to 8.0%)
Lp(a) Novel Lp(a) assay	47.4% (−56.0% to −37.0%)	−81.6% (−83.8% to −79.0%)	−85.7% (−87.4% to −83.8%)	0.5% (−11.4% to 13.9%)

Exploratory endpoints also assessed the effects on oxidized phospholipids, which were reduced with muvalaplin.

Placebo-adjusted Percent change (95% CI)	10 ng (n=34)	60 mg (n=63)	240 mg (n=68)
OxPL-apoB	−35.0% (−56.0% to −3.9%)	−67.2% (−76.3% to −54.5%)	−58.8% (−70.3% to −43.0%)
OxPL-apo(a)	−23.7% (−43.0% to 2.2%)	−70.9% (−77.2% to −62.8%)	−73.0% (−78.8% to −65.7%)

Muvalaplin also led to reductions in placebo-corrected levels of LDL-C levels ranging from −11.2% to −21.3%, and placebo-corrected levels of ApoB from −8.9% to -16.1%.

SiRNAs:

Olpasiran (AMG 890) is the first-in-class synthetic, double-stranded siRNA targeted to *LPA* (encoding for apo(a)) that is conjugated to N-acetylgalactosamine, which enhances hepatic uptake. [47] Inside the hepatocytes, it is loaded onto the RNA-induced silencing complex (RISC) and binds to *LPA* mRNA, leading to its degradation [48]. It is designed to inhibit the translation of *LPA* mRNA in hepatocytes, and thus limit the production of Lp(a). Single doses of olpasiran dose-dependently reduced levels of Lp(a) up to 80% in preclinical models of *LPA*-expressing transgenic mice and cynomolgus monkeys [47].

In a Phase 1 dose-escalation trial (NCT03626662) in 79 participants with elevated Lp(a), subcutaneous administration of single doses of olpasiran were associated with reductions in Lp(a) of 71-97%, which persisted for several months in those treated with doses of 9 mg or higher [47]. Due to ethnicity-related differences in Lp(a) levels and isoforms, it is important to determine whether the performance of Lp(a) lowering therapies is impacted by ethnicity. In an open-label Phase 1 study (n=27), olpasiran was tested in single doses ranging from 3 to 225 mg in healthy Japanese participants and at a dose of 75 mg in healthy non-Japanese participants [49]. Mean Lp(a) reductions ranged from 56% to 99%, with no significant differences in the magnitude or durability of the responses between Japanese and non-Japanese participants. Reductions in Lp(a) became apparent by day four, with maximal responses observed at day 57. Reductions of ≥68% and ≥90% were sustained up to day 225 for the 75 mg and 225 mg doses, respectively.

In the Phase 2 randomized, double-blind, placebo-controlled, dosing finding OCEAN-DOSE trial (NCT04270760) including 281 patients with established ASCVD and Lp(a) levels of >150 nmol/L, olpasiran was administered subcutaneously at doses of 10 mg every 12 weeks, 75 mg every 12 weeks, 225 mg every 12 weeks, or 225 mg every 24 weeks for 48 weeks [48]. The majority of participants were taking other lipid-lowering therapies at baseline, including 88% taking statins, 52% taking ezetimibe, and 23% taking a PCSK9 inhibitor. The primary endpoint was the placebo-adjusted mean percent change in Lp(a) from baseline to week 36. Reductions in Lp(a) >90% were observed for the 75 mg and 225 mg dosing regimens.

Results:

Percent change (95% CI)	10 mg every 12 weeks (n=57)	75 mg every 12 weeks (n=57)	225 mg every 12 weeks (n=53)	225 mg every 24 weeks (n=53)	Placebo every 12 weeks (n=51)
Lp(a)	−66.9% (−70.4% to 63.4%)	−93.8% (−97.3% to 90.3%)	−97.5% (−100.0% to −94.0%)	−96.9% (−100.0% to 93.3%)	+3.6% (−0.1% to 7.3%)
% of patients achieving Lp(a) <125 nmol/L	67%	100%	100%	98%	0%

The degree of reduction in Lp(a) was similar at 48 weeks, with placebo-adjusted reductions of −68.5%, −96.1%, −100.9%, and −85.9% for the 10 mg, 75 mg, and 225 mg (12- and 24-week dosing) groups, respectively. Placebo-adjusted reductions in ApoB were observed in the range of −16.7% to −18.9%, while reductions in LDL-C were observed in the range of −22.6% to −24.8%, though these may be overestimates.

A long-term extension phase of the trial followed 276 participants for a median of 86 weeks (Q1-Q3: 79 to 99 weeks) [50]. Lp(a) levels returned toward baseline overtime, but reductions of 40-50% were maintained for over six months following the cessation of treatment in the higher dose groups.

Lp(a) Percent change	10 mg every 12 weeks (n=57)	75 mg every 12 weeks (n=57)	225 mg every 12 weeks (n=53)	225 mg every 24 weeks (n=53)	Placebo every 12 weeks (n=51)
48 weeks	-64.9%	-92.5%	-97.3%	-82.4%	+3.6%
60 weeks	-43.2%	-78.3%	-86.5%	-66.3%	-2.1%
72 weeks	-28.3%	-58.5%	-67.1%	-52%	-5.5%
84 weeks	-27.7%	-45.8%	-53.9%	-40%	-1.7%
96 weeks	-13.2%	-33.6%	-42.1%	-27.7%	-5.6%

Based on the results from the OCEAN-DOSE study, olpasiran is currently being tested in the Phase 3 OCEAN(a)-Outcomes trial (NCT05581303) in 7,297 patients with a history of ASCVD and Lp(a) >200 nmol/L. Olpasiran is being administered every 12 weeks via subcutaneous injection. The primary outcome is the time to coronary heart disease death, myocardial infarction, or urgent coronary revascularization over the time frame of approximately four years.

Lepodisiran (LY3819469) is an extended duration siRNA targeting the mRNA of *LPA* [51]. It is a Dicer substrate with tetraloop structure which contains three N-acetyl-galactosamine (GalNAc) conjugates, that allows for hepatic delivery.

In a Phase 1 dose ascending trial (NCT04914546) in 48 participants in the US and Singapore with elevated Lp(a) levels of 75 nmol/L or greater (or ≥30 mg/dL) but without cardiovascular disease, single subcutaneous doses of lepodisiran were administered at 4 mg, 12 mg, 32 mg, 96 mg, 304 mg, or 608 mg.

Participants were followed for 48 weeks [51]. The maximal median change in Lp(a) ranged from −41% (Interquartile range [IQR]: −47% to −20%) at the 4 mg dose to −97% (IQR: −98% to −96%) at the 608 mg dose, with no significant change in the placebo group. A similar degree of Lp(a) reduction was observed at the 304 mg and 608 mg doses, though durability was best at the 608 mg dose, for which reductions of −94% (IQR: −94% to −85%) were maintained out to 48 weeks.

Lepodisiran was tested in a Phase 2 randomized, double-blind, placebo-controlled trial (NCT05565742) in 216 adult patients ≥40 years old with Lp(a) levels ≥175 nmol/L. Participants received placebo or one of four lepodisiran dosing regimens and were followed out to 540 days. The trial was completed, but results have not yet been made available. The trial likely achieved its primary outcome of Lp(a) lowering because the Phase 3 randomized, double-blind, placebo-controlled ACCLAIM-Lp(a) trial (NCT06292013) was initiated in 2024. The trial includes 12,500 adult participants with Lp(a) ≥175 nmol/L, and either having established ASCVD with an event/revascularization, or being ≥55 years old at high risk for a first cardiovascular event. The primary outcome is the time to first event in a major adverse cardiac event (MACE-4) composite endpoint, comprised of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and urgent coronary revascularization over the study period of approximately 4.5 years.

Zerlasiran, originally called SLN360, is a 19-mer siRNA targeting *LPA* mRNA for degradation. It is conjugated to the tri-antennary N-acetyl-galactosamine (GalNAc) moiety, which enhances hepatic uptake due to its high affinity towards the asialoglycoprotein receptor in hepatocytes [52].
In a SAD Phase 1 trial conducted in the Netherlands, US, UK, and Australia (NCT04606602) including 32 participants with Lp(a) plasma concentrations of ≥150 nmol/L but without known clinically overt cardiovascular disease, zerlasiran was tested at doses of 30 mg, 100 mg, 300 mg, and 600 mg, administered subcutaneously [53]. The maximal median reductions in Lp(a) ranged from −89 nmol/L (IQR: −119 to −61) for the 30 mg dose to −227 nmol/L (IQR: −270 to −174) for the 600 mg dose, corresponding to percent reductions of −46% and -98%, respectively. The degree of reduction was similar for the 100, 300, and 600 mg doses, though the durability of the response was dose dependent. The MAD study included 37 participants who were treated with two doses of placebo or 200 mg zerlasiran at a four-week interval, or 300 mg or 450 mg doses of zerlasiran at an eight-week interval [52]. Maximal median changes in Lp(a) were 7% (IQR: −4% to 21%), −97% (IQR: −98% to −97%), −98% (IQR: −99% to −95%), and −99% (IQR: −99% to −98%) for the placebo, 200 mg, 300 mg, and 450 mg groups, respectively. Significant Lp(a) reductions of −60% (IQR: −71% to −40%), −90% (IQR: −91% to −74%), and −89% (IQR: −91% to −76%) were maintained out to 201 days for the 200 mg, 300 mg, and 450 mg groups, respectively.

Zerlasiran was tested in a randomized, double-blind, placebo-controlled Phase 2 trial (NCT05537571) including 178 patients in Europe and South Africa with stable ASCVD and serum Lp(a) concentrations ≥125 nmol/L [54]. Participants were administered placebo every 16 or 24 weeks, 300 mg zerlasiran every 16 or 24 weeks, or 450 mg zerlasiran every 24 weeks. The primary outcome was the time-averaged percent change in Lp(a) concentration from baseline to 36 weeks with follow-up out 60 weeks.

Results:

Placebo-adjusted Percent change (95% CI)	300 mg every 16 weeks: 3 doses (n=42)	300 mg every 24 weeks: 2 doses (n=44)	450 mg every 24 weeks: 2 doses (n=45)
Lp(a) 36 weeks	-82.8% (-88.2% to -77.4%)	-81.3% (-86.7% to -76.0%)	-85.6% (-90.9% to -80.3%)
Lp(a) 60 weeks	-79.2% (-85.3% to -73.1%)	-71.8% (-77.8% to -65.8%)	-77.1% (-83.1% to -71.2%)

Reported placebo-adjusted reductions in LDL-C ranged from 25.1% to 31.9%, while ApoB reductions ranged from 9.9% to 15% at 36 weeks. Based on these results, Silence Therapeutics is planning to test zerlasiran in a Phase 3 trial (Press release).

Safety: Lp(a) lowering therapies have shown good safety without clear evidence of hepatic toxicity in Phase 2 trials. Mild injection side reactions have been the most common adverse events. Longer term studies are ongoing.

Types of evidence:

- 3 clinical trials for pelacarsen (Phase 1, 2a, and 2b)
- 2 clinical trials for muvalaplin (Phase 1 and 2)
- 3 clinical trials for olpasiran (Phase 1 and 2)
- 1 clinical trial for lepodisiran (Phase 1)
- 2 clinical trials for zerlasiran (Phase 1 and 2)

To date Lpa(a) lowering therapies have generally been well-tolerated and shown a good safety profile in clinical trials. Injection site reactions are the most common adverse events for the subcutaneously administered therapies. Long term effects will be assessed in ongoing Phase 3 trials.

Observational studies have found that very low levels (<3 to 5 mg/dL) of Lp(a) is associated with increased incidence of type 2 diabetes, though the results of Mendelian randomization studies have been mixed [31]. It is unclear whether Lp(a) lowering therapies could increase the risk for diabetes, and may depend on whether these therapies can reduce Lp(a) to levels <5 mg/dL. To date, evidence for elevated diabetes risk has not been observed in clinical trials.

ASOs

Pelacarsen (AKCEA-APO(a)-LRx): The most common adverse events associated with pelacarsen are injection site reactions [39]. In a Phase 1 trial in healthy volunteers, there were no serious adverse events or clinically relevant abnormalities on laboratory measures [40]. In the Phase 2 trial, serious adverse events occurred in 10% of treated patients and 2% of placebo patients. The most common adverse event was injection-site reactions (27%) [39]. Other adverse events that occurred in at least 10% of treated patients and were more common than placebo included urinary tract infections (13% vs. 6%), myalgia (12% vs. 11%), and headache (11% vs. 8%).

Small molecule inhibitors

Muvalaplin (LY3473329): In a Phase 1 trial in healthy volunteers, muvalaplin was safe and well-tolerated [44]. Adverse events were generally mild, transient, and resolved on their own. There were no serious adverse events or clinically significant adverse events. In the SAD study, adverse events considered drug related were headache, fatigue, and vomiting, and primarily occurred at the highest tested dose (800 mg). In the multiple dosing study, the most common adverse events were headache, gastrointestinal events, and fatigue. There were no hematological or hepatic-related adverse events, and no evidence of QT prolongation.
In the Phase 2 trial in patients with ASCVD and elevated Lp(a) (≥175 nmol/L), treatment-emergent adverse events were similar across groups [46]. The most common (≥5%) adverse events across groups were diarrhea, nausea, influenza, back pain, myalgia, uterine leiomyoma, and anemia. There was no dose dependency to the adverse events. There were no instances of hepatic liver enzyme elevations coupled with elevations in bilirubin. There was one case of an elevation in ALT at >10 times the upper

limit of normal in a patients treated with 240 mg muvalaplin. The event occurred while the participant was taking penicillin for a tooth infection, and subsequently resolved. There were no changes in plasminogen.
In preclinical studies, muvalaplin inhibited plasminogen in rats, however, this is considered species-related effect, and evidence for a similar effect has not been observed in humans, to date [45].

siRNAs

Olpasiran (AMG 890): Olpasiran was generally found to be safe and well-tolerated in Phase 1 studies [47]. In an open-label Phase 1 study in healthy participants, there were no serious adverse events or clinically important changes in vital signs or laboratory measures [49].
In the Phase 2 OCEAN-DOSE trial in patients with established ASCVD and Lp(a) concentrations >150 nmol/L, the most common treatment-related adverse events were injection site reactions [48]. There were similar levels of study discontinuations related to adverse events across groups, as well as similar incidences of hyperglycemia, new-onset or worsening diabetes, and myalgias. Rates of liver-related adverse events, kidney-related adverse events, thrombocytopenia, and peripheral neuropathy were low (≤3%), and similar between placebo and olpasiran groups. Three patients in the placebo group and two patients treated with olpasiran experienced adjudicated cardiovascular events. No new safety concerns were identified during the trial extension period [50]. In contrast to the trial period, where rates of adverse events were balanced, there were numerically more cases of hyperglycemia and newly onset diabetes when including the extension period (8.8% vs 5.6%), but additional studies are needed to determine if this is a clinically meaningful difference.

Lepodisiran (LY3819469): In a Phase 1 dose ascending study with follow-up out to 48 weeks in adults with Lp(a) levels >75 nmol/L without cardiovascular disease, lepodisiran was generally safe and well-tolerated [51]. Injection site reactions were the most common adverse event in both active and placebo groups. There was one serious adverse event, an injury from a bicycle fall occurring 141 days after injection, not considered treatment related. Two participants receiving lepodisiran had elevations in liver aminotransaminases greater than three times the upper limit of normal, while three participants had elevations of creatine kinase five times greater than the upper limit of normal. These liver enzyme elevations were transient and resolved on their own. There were no cases of systemic hypersensitivity or cytokine storm reactions.

Zerlasiran (SNL360): In the Phase 1 dose ascending study in adults with plasma levels of Lp(a) >150 nmol/L without cardiovascular disease, zerlasiran was generally well-tolerated [52; 53]. There were two serious adverse events unrelated to the study drug, stemming from SARs-CoV2 vaccination and complications of cholecystitis, respectively. Treatment-emergent adverse events primarily consisted of Grade 1 or 2 mild injection site reactions and headache. There were no clinically relevant reductions in platelet counts or evidence of drug-related liver injury. The levels of the systemic inflammation marker, CRP, were elevated 24 hours following injection, but returned to normal range within seven days.
In the Phase 2 trial in patients with stable ASCVD and Lp(a) levels ≥125 nmol/L with follow-up to 60 weeks, injection site reactions and mild pain, occurring in 2.3% to 7.1% of participants following administration were the most common treatment-related adverse events [54]. The most common treatment-emergent adverse events were nasopharyngitis and urinary tract infection. None of the 20 reported serious adverse events were considered treatment related. Two participants, in the 450 mg every 24 weeks and 300 mg every 16 weeks groups, experienced transient elevations in liver aminotransferases three times greater than the upper limit of normal, but without concomitant elevations in bilirubin. The liver enzyme elevations resolved without intervention.

Drug interactions:
Drug interactions are currently for Lp(a) lowering therapies have not yet been established. To date, most trial participants have been treated with other lipid-lowering species without evidence of negative interactions, and the effects on other lipid species appear to be minimal. The ASOs and siRNAs are targeted to hepatocytes, so they may be contraindicated or require dose modification in individuals with hepatic impairment. Due to siRNA clearance by the kidneys, and potential renal toxicity with ASOs, these therapies may also be contraindicated or require dose modifications in individuals with kidney disease. Interactions with the small molecule muvalaplin will depend on its metabolic profile.

Sources and dosing:
There are several Lp(a) lowering therapies in clinical development, but to date none have been approved for clinical use outside of trials.
Muvalaplin is a small molecule in clinical development by Eli Lilly that is administered orally and has reduced Lp(a) levels >80% at doses of 60 mg and 240 mg in a Phase 2 trial.
Pelacarsen is an ASO in clinical development by Novartis that is administered subcutaneously. In the ongoing Phase 3 HORIZON trial, pelacarsen is being tested at a dose of 80 mg once per month.
Olpasiran is a siRNA in clinical development by Amgen that is administered subcutaneously. It demonstrated Lp(a) reductions >90% at doses of 75 mg or 225 mg every 12 weeks in the Phase 2

OCEAN-DOSE trial. The dose for the Phase 3 OCEAN(a) trial has not been made public, but it will be dosed at a schedule of every 12 weeks.
Lepodisiran is a siRNA in clinical development by Eli Lilly that is administered subcutaneously. It was tested at doses up to 608 mg in a Phase 1 study, but the doses tested in the completed Phase 2 trial or ongoing Phase 3 trial have not yet been made publicly available.
Zerlasiran is a siRNA in clinical development by Silence Therapeutics that is administered subcutaneously. It showed a similar level of Lp(a) lowering (>80%) in a Phase 2 trial at doses of 450 mg every 24 weeks and 300 mg every 16 or 24 weeks.

Research underway:

There are a variety of Phase 2 and Phase 3 trials planned or ongoing for Lp(a) lowering therapies.

Pelacarsen is currently being tested in:
The Phase 3 HORIZON trial in patients with established cardiovascular disease and elevated Lp(a). The trial has an expected completion date in 2025 (NCT04023552).
A Phase 3 trial in patients with hyperlipoproteinemia(a) and established cardiovascular disease currently undergoing lipoprotein apheresis in Germany. The trial has an expected completion date in 2025 (NCT05305664). There is also an open-label extension of this trial following participants for 60 months (NCT05900141).
A Phase 2 trial in patients with elevated Lp(a) (≥175 nmol/L) and mild or moderate calcific aortic valve stenosis. The trial has an expected completion date in 2029 (NCT05646381).
A Phase 3b trial in US Black/African American and Hispanic participants with established ASCVD and elevated levels of Lp(a) (≥ 125 nmol/L). The trial has an expected completion date in 2027 (NCT06267560).

Olpasiran is currently being tested in the randomized, double-blind, placebo-controlled Phase 3 OCEAN(a) Outcomes trial in participants at risk for coronary heart disease death, myocardial infarction, or urgent coronary revascularization in participants with ASCVD and elevated Lp(a) (≥ 200 nmol/L). The trial has an expected completion date in 2026 (NCT05581303).

Lepodisiran is currently being tested in the randomized, double-blind, placebo-controlled Phase 3 ACCLAIM-Lp(a) trial in patients with cardiovascular disease or are at risk of a heart attack or stroke and high Lp(a) (≥175 nmol/L). The trial has an expected completion date in 2029 (NCT06292013).

Search terms:

Pubmed, Google: Lp(a, pelacarsen (AKCEA-APO(a)-LRx), olapasiran (AMG 890), lepodisiran (LY3819469), zerlasiran (SLN360), muvalaplin (LY3473329) +

- Alzheimer's disease, dementia, cognition, stroke, cardiovascular disease, aging, lifespan, clinical trial, safety

Websites:

Clinicaltrials.gov (pelacarsen, muvalaplin, olpasiran, lepodisiran, zerlasiran)

Pubchem (muvalaplin)

Drugbank.ca (pelacarsen, olpasiran)

CafePharma (pelacarsen, muvalaplin, olpisaran, lepodisran)

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