

JACC FOCUS SEMINAR: EMERGING LIPID-LOWERING THERAPIES

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Emerging RNA Therapeutics to Lower Blood Levels of Lp(a)



JACC Focus Seminar 2/4

Sotirios Tsimikas, MD,^a Patrick M. Moriarty, MD,^b Erik S. Stroes, MD, PhD^c

ABSTRACT

Lipoprotein(a) [Lp(a)] has risen to the level of an accepted cardiovascular disease risk factor, but final proof of causality awaits a randomized trial of Lp(a) lowering. Inhibiting apolipoprotein(a) production in the hepatocyte with ribonucleic acid therapeutics has emerged as an elegant and effective solution to reduce plasma Lp(a) levels. Phase 2 clinical trials have shown that the antisense oligonucleotide pelacarsen reduced mean Lp(a) levels by 80%, allowing 98% of subjects to reach on-treatment levels of <125 nmol/L (~50 mg/dL). The phase 3 Lp(a)HORIZON (Assessing the Impact of Lipoprotein(a) Lowering With TQJ230 on Major Cardiovascular Events in Patients With CVD) outcomes trial is currently enrolling approximately 7,680 patients with history of myocardial infarction, ischemic stroke, and symptomatic peripheral arterial disease and controlled low-density lipoprotein cholesterol to pelacarsen versus placebo. The co-primary endpoints are major adverse cardiovascular events in subjects with Lp(a) >70 mg/dL and >90 mg/dL, in which either of the two being positive will lead to a successful trial. Additional ribonucleic acid-targeted therapies to lower Lp(a) are in preclinical and clinical development. The testing of the Lp(a) hypothesis will provide proof whether Lp(a)-mediated risk can be abolished by potent Lp(a) lowering. (J Am Coll Cardiol 2021;77:1576-89) © 2021 by the American College of Cardiology Foundation.

Lipoprotein(a) [Lp(a)] is composed of apolipoprotein(a) that is covalently linked to apolipoprotein B-100 (apoB-100) of a low-density lipoprotein (LDL)-like particle and has no known physiological function (Figure 1). The existence of Lp(a) was first described by Kare Berg in 1963 (1). He further went on to show this Lp(a) factor was associated with cardiovascular disease (CVD) risk (2). Unlike other lipoproteins in which both diet and genetics play a role in determining plasma levels, Lp(a) plasma levels are more than 90% genetically determined by constitutive hepatocyte production. Lp(a) levels in plasma are inversely associated with smaller number of kringle IV type 2 (KIV₂) repeats, and plasma levels

vary over 1,000-fold, from being absent in rare patients to up to 1,000 nmol/L. Levels at which Lp(a)-induced CVD risk is negligible are <30 mg/dL (<75 nmol/L), which is therefore often the metric reported as normal by clinical laboratories.

Since 1963, significantly more has been learned about Lp(a), including: 1) new and more accurate methods to measure Lp(a) showing that circulating Lp(a) is present in just about everyone; 2) epidemiological studies showing that risk is associated with CVD at levels >30 mg/dL (>75 nmol/L) in primary care populations (3) and >50 mg/dL (>125 nmol/L) in statin-treated patients (4); and 3) genome-wide association and Mendelian randomization studies demonstrating



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From the ^aDivision of Cardiovascular Medicine, Sulpizio Cardiovascular Center, University of California San Diego, La Jolla, California, USA; ^bDivision of Clinical Pharmacology, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Missouri, USA; and the ^cDepartment of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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HIGHLIGHTS

- Elevated blood levels of Lp(a) are a risk factor for atherosclerotic CVD and aortic stenosis, but currently there is no approved therapy.
- RNA therapeutics targeting hepatic synthesis of apolipoprotein(a) are under development.
- Multiple trials, including the phase 3 Lp(a)-HORIZON trial, are in progress to test the hypothesis that lowering Lp(a) could reduce cardiovascular risk.

probable causality by linking variability in the number of apolipoprotein(a) isoforms or various single nucleotide polymorphisms to plasma Lp(a) levels, and subsequently to CVD events, particularly myocardial infarction (5). Lp(a) has also been causally linked to aortic valve calcification (6), and through its content of oxidized phospholipids, to the progression and need for aortic valve replacement of pre-existing aortic stenosis (7), even in advanced stages with aortic valve areas near 1.0 cm² (8). Lp(a) is also associated with heart failure, which appears to be secondary to either myocardial infarction or aortic stenosis (9).

DETERMINANTS OF PLASMA Lp(a) CONCENTRATION AND IMPLICATIONS FOR THERAPEUTIC TARGETING

Apolipoprotein(a) is primarily synthesized in the liver and assembled with a LDL-like particle to form Lp(a) inside the hepatocyte or on the cell surface and is then secreted into the circulation. It is well established that the size of apolipoprotein(a) is inversely related to the plasma concentration of Lp(a), primarily owing to the fact that small isoforms can be synthesized and secreted at a faster rate compared with large isoforms. Differences in apolipoprotein(a) isoforms account for 30% to 70% of the influence on plasma Lp(a) levels (10). The remaining determinants are single nucleotide polymorphisms and effects on promoter activity by dietary factors, hormones, inflammatory mediators, and other unknown mechanisms. Clearance mechanisms do not seem to be significantly involved in determining plasma levels.

Figure 2 demonstrates the role of each allele on Lp(a) levels, with implications on developing therapeutic agents. The smaller isoforms are responsible for most of the plasma Lp(a), with the final plasma concentration being a combination of the production

rates of these 2 alleles, in addition to other influences noted above. In developing therapeutics for Lp(a), it is important that any therapy addresses the ability to inhibit all isoforms and any genetic variations such as common single nucleotide polymorphisms equally, and in particular treat patients with elevated Lp(a) irrespective of the drivers of elevated levels.

THERAPIES AFFECTING Lp(a) LEVELS

The development of therapies to lower Lp(a), and to test the “Lp(a) hypothesis,” namely that lowering levels of Lp(a) will reduce risk of CVD events and aortic stenosis progression, has been lagging behind until recently. Small molecules and monoclonal antibodies have not been found to have a role in treating elevated Lp(a) for 2 main reasons. Small molecules tend to affect enzyme activities or receptor function and neither of these are relevant to lowering Lp(a). Monoclonal antibodies would likely be both cost and safety prohibitive due to the large amount of Lp(a) in plasma that would need to be cleared as immune complexes.

Estrogen can lower Lp(a) ~20%, but as a pharmaceutical agent, it is limited to women and because of its potential for thromboembolic disease, it is less than ideal for treating an atherothrombotic risk factor (11). Niacin can lower Lp(a) 20% to 30% (12), but it is limited by side effects. Although early studies had suggested niacin reduces CVD events, most recently studies in subjects on statins showed no benefit of adding niacin to the regimen (13,14). However, it has to be acknowledged that these studies included patients with normal Lp(a) levels on average, and that subgroup analyses were underpowered, and niacin has only a modest effect on Lp(a). In these studies, elevated Lp(a) did remain a significant risk factor despite low-density lipoprotein cholesterol (LDL-C) <70 mg/dl (13).

Proprotein convertase subtilisin kexin type 9 inhibitors (PCSK9i) lower Lp(a) but are least effective in subjects with Lp(a) >50 mg/dl by achieving only a 14% reduction (15). In the 2 major PCSK9i trials, the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) and ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trials, the fourth quartile of Lp(a), approximately >120 nmol/l and >60 mg/dl in the placebo group and in the entire

ABBREVIATIONS AND ACRONYMS

apoB = apolipoprotein B-100

ASGPR = asialoglycoprotein receptor

ASO = antisense oligonucleotide

CVD = cardiovascular disease

GalNAc = N-acetyl-galactosamine

KIV₂ = kringle IV type 2

LDL = low-density lipoprotein

LDL-C = low-density lipoprotein cholesterol

Lp(a) = lipoprotein(a)

MACE = major adverse cardiovascular events

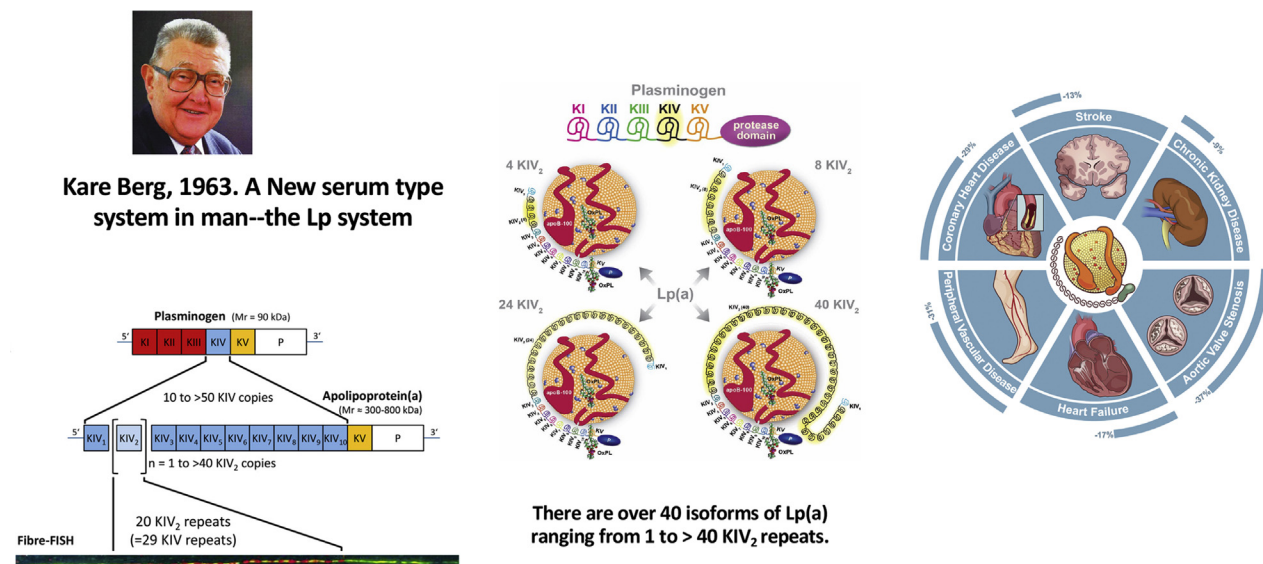
mRNA = messenger ribonucleic acid

OxPL-apo(a) = oxidized phospholipids on apolipoprotein(a)

OxPL-apoB = oxidized phospholipids on apolipoprotein B-100

PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor

FIGURE 1 Genetics of LPA Gene, Relationship to Plasminogen, Oxidized Phospholipids, and Clinical Phenotypes



The presence of lipoprotein [a] [Lp(a)] was reported by Kare Berg in 1963 (1). Apolipoprotein(a) is derived from kringle IV (KIV), KV, and the protease domain of the plasminogen gene. However, it differs from plasminogen in that the protease domain is inactive, and KIV is highly heterogeneous by containing 10 subtypes present in 1 copy, except for KIV₂, which is present in a variable number of over 40 different sized identical copies. The numbers in the wheel represent the impact of genetically mediated Lp(a) reductions per 1 SD of the listed phenotypes, with estimates derived from the UK Biobank study. Reprinted with permission from Schmidt et al. (10), Tsimikas (51), and Emdin et al. (52).

cohort, respectively, was associated with ~25% higher risk of major adverse cardiovascular events (MACE) than the lowest quartile. This suggests that in the setting of PCSK9i and very low achieved LDL-C, Lp(a)-mediated events continue to accrue (16,17). Importantly, in the ODYSSEY OUTCOMES trial, which had a higher risk population than the FOURIER trial by including post-acute coronary syndrome patients (17), a reduction in Lp(a) with alirocumab in subjects at the 75th percentile of Lp(a) accounted for 25% of the absolute benefit. In a more recent analysis in ODYSSEY OUTCOMES trial, baseline Lp(a) predicted total (first and subsequent) cardiovascular events in the placebo group, while higher baseline Lp(a) levels were associated with greater reduction in total cardiovascular events with alirocumab, with each 5-mg/dl reduction in Lp(a) predicting a 2.5% relative reduction in cardiovascular events (18).

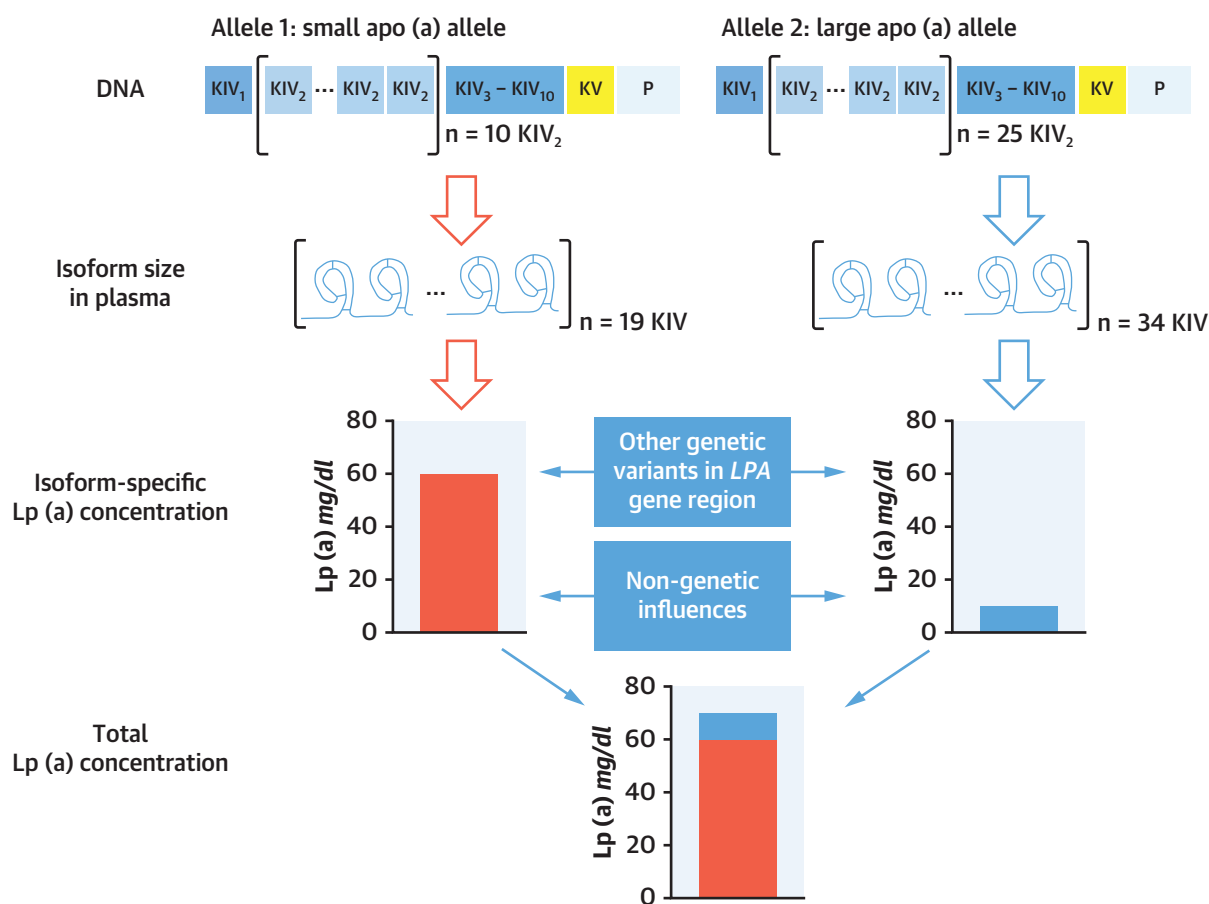
Lipid apheresis is highly effective in acutely lowering Lp(a), but owing to rapid hepatocyte synthesis, the levels generally return to baseline by 1 week, leading to a 30% to 35% time-averaged reduction in Lp(a) (19). Lipid apheresis is very infrequently used worldwide, except in Germany, and

retrospective or prospective observational studies have shown significantly higher event rates prior to compared with while on apheresis (20).

It should be clearly acknowledged that none of estrogen, niacin, PCSK9i, or lipid apheresis tested the Lp(a) hypothesis by enrolling, a priori, subjects with elevated Lp(a), randomizing to treatment versus no treatment and assessing outcomes. The only randomized, double blinded, placebo-controlled trials to date in Lp(a) patient have been with antisense oligonucleotides (ASOs), which will be reviewed subsequently. A randomized trial in lipid apheresis-eligible patients randomized to lipid apheresis versus no lipid apheresis, the MultiSELECT (Effect of Lipoprotein(a) Elimination by Lipoprotein Apheresis on Cardiovascular Outcomes) trial, is now ongoing (21).

A recent, large meta-analysis, that most statins may increase Lp(a) on average 8% to 24%, although significant heterogeneity in response is present (22). The clinical implications of this increase are not known, but it has been demonstrated in both statin (23) and PCSK9i trials (16,17), that subjects with elevated Lp(a), compared with low Lp(a), derive the least benefit from LDL-C lowering.

FIGURE 2 Scheme Illustrating the Determination of Lp(a) Plasma Levels by *LPA* Gene Variation



The major determinant of plasma Lp(a) levels is KIV₂ copy number variation that codes for apolipoprotein(a) isoform size. Because most (70-90%) individuals express 2 apolipoprotein(a) isoforms, a mixture of Lp(a) particles can be found in plasma with up to 40 isoforms in existence. Plasma Lp(a) concentration is derived from the production of different amounts of apolipoprotein(a) by each allele. Genetic variants within the *LPA* gene region, hormones, inflammatory mediators, and other factors influence on Lp(a) concentrations. Reprinted with permission for Schmidt et al. (10). DNA = deoxyribonucleic acid; other abbreviations as in Figure 1.

Finally, drugs approved for homozygous familial hypercholesterolemia, such as mipomersen (24) and lomitapide (25), as well as several investigational agents such as CETP (cholesteryl ester transfer protein) inhibitors (26) and the thyromimetic eprotirome (27), also lower Lp(a) ~20% to 30%. Table 1 summarizes the pharmacologic effects of selected approaches on Lp(a) levels.

MECHANISMS OF RIBONUCLEIC ACID-TARGETING TECHNOLOGY TO LOWER Lp(a) LEVELS

ASOs are usually 16- to 20-nucleic-acid-long DNA fragments that are complementary to their messenger ribonucleic acid (mRNA) target. They

function as therapeutic agents due to a number of chemical modifications, principally in the phosphate backbone and the ribose moiety. To achieve a therapeutic effect, the ASO is injected subcutaneously; binds to a variety of plasma proteins, including albumin; and enters the extracellular space of the liver. The ASO enters the hepatocyte through a variety of mechanisms and interacts with mRNA in the cytoplasm and nucleus (Figure 3A). Concurrently, the *LPA* gene transcribes the 2 alleles of apolipoprotein(a) mRNA to which the ASO binds to generate an mRNA-ASO duplex. The key mechanism relevant to inhibiting translation of apolipoprotein(a) mRNA with antisense is that every cell contains the enzyme RNase H1 (ribonuclease H1), which recognizes this duplex as foreign and cleaves the sense strand.

TABLE 1 Selected Clinically Available Agents or Procedures Affecting Lp(a) Levels

Lp(a)-Lowering Therapy	Lp(a) Effect	Possible Mechanism of Lp(a) Lowering	Best Level of Evidence
Lipid apheresis	70% acute, 35% time-averaged reduction	Removal of Lp(a) and other lipoproteins using adsorption columns	Several longitudinal prospective trials (45)
Nicotinic acid	20% to 30% reduction	Inhibition of LPA promoter via cyclic AMP (46)	Randomized control trials (12)
PCSK9 inhibitors	14–30% reduction	Unknown, possibly due to decreased apo(a) secretion	Multiple, large, randomized trials (16,17,47)
Mipomersen	20% to 40% reduction	Inhibits synthesis of apoB-100	4 phase 3 randomized, placebo-controlled trials (24)
Lomitapide	17% reduction	Decrease in VLDL synthesis via microsomal triglyceride transfer protein inhibition	Small phase 2 and 3 randomized, placebo-controlled trials (48)
Statins	8% to 24% increase	Unknown, possibly due to increase in apo(a) secretion via PCSK9 (22)	Large meta-analysis and smaller single studies (22)
Ezetimibe/fibrates/bile acid sequestrants	? neutral	N/A	Small clinical studies, more data needed (49)

apo(a) = apolipoprotein(a); apoB = apolipoprotein B; Lp(a) = lipoprotein(a); N/A = not available; PCSK9 = proprotein convertase subtilisin kexin type 9; VLDL = very low-density lipoprotein.

Because the antisense strand is chemically modified, it is relatively resistant to RNase H1 cleavage and is free to then bind a second mRNA-ASO duplex. The resistance to nucleases also results in a long tissue half-life of antisense molecules, often in the 2- to 4-week range (28,29). This translates to flexibility in both dosing and frequency regimens to achieve optimal knockdown less frequent dosing for similar efficacy.

Medicinal chemistry advances in modifying naked DNA have led to a significant improvement in the potency of ASOs, as they allowed a higher affinity and stability of complementary binding to target mRNA and less proinflammatory effects and improved tolerability. These modifications have occurred by replacing some of the phosphodiester moieties with phosphorothioate in the backbone, by a variety of modifications in the 2' position of the ribose ring including the use of 2'-methoethyl and 2'-constrained ethyl chemistry, and by the addition of N-acetylgalactosamine (GalNAc) ligand to the 5' end of the molecule to allow targeting to hepatocyte asialoglycoprotein receptors (ASGPRs) that allow internalization of the ASO. Each iteration of advances in medicinal chemistry has improved the potency of the molecules by ~10-fold. Generation 2+ ASOs with the addition of GalNAc allows dosing at 10 to 40 mg/week or ~80 mg/month (25), and generation 2.5 (constrained ethyl chemistry) with GalNAc allows dosing at 1 to 5 mg/week or ~20 mg/month (Figure 3B).

The addition of GalNAc is particularly noteworthy for liver targets, as it allows specific targeting of the ASO to the hepatocyte, the site of inhibition where almost all of the apolipoprotein(a) is generated. The ASGPRs are present in 500,000 to 1 million copies per cell, and ASGPRs are present in all mammals and share their specificity for GalNAc-terminated oligosaccharides (26). Using GalNAc ligands covalently bound to antisense molecules has allowed 30-fold

higher potency and significantly lower doses for similar efficacy (30).

Small interfering RNAs also inhibit translation of target mRNA but differ with antisense in that they are double-stranded molecules that use the RNA-induced silencing complex to cleave the target mRNA to prevent protein synthesis. A detailed analysis of different RNA targeted approaches was recently published (31).

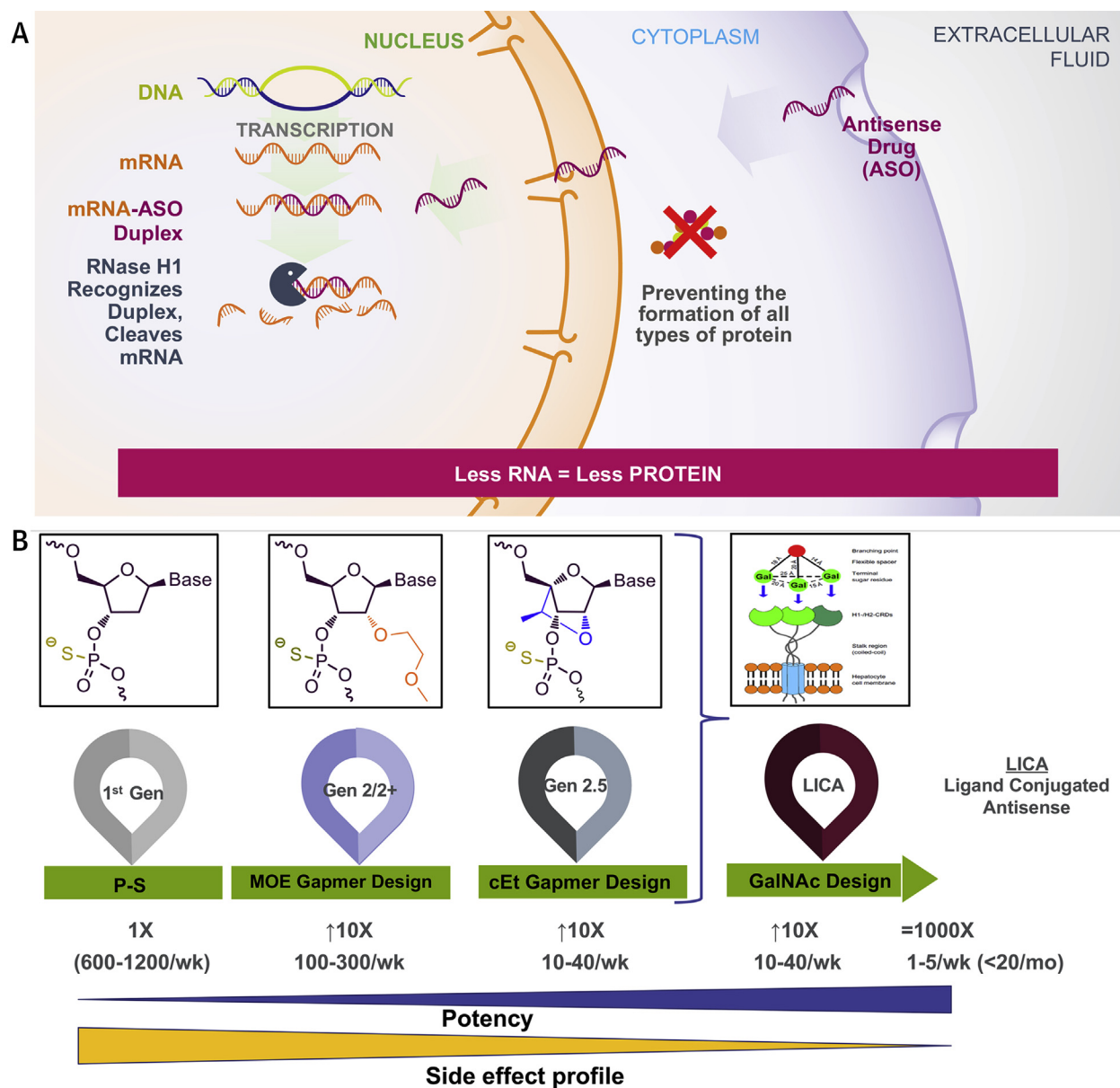
LOWERING Lp(a) WITH ANTISENSE TECHNOLOGY

The initial proof of concept using antisense technology to lower Lp(a) levels was reported in 2008 in fully Lp(a) transgenic mice expressing both human apoB-100 and a mini apolipoprotein(a) construct (32), that were treated with mipomersen, an ASO directed to human apoB-100 (33). Mipomersen significantly reduced plasma human apoB-100 levels in Lp(a)-transgenic and also significantly reduced Lp(a) levels by ~75% (Figure 4A). Mipomersen had no effect on apolipoprotein(a) levels or hepatic apolipoprotein(a) mRNA expression, so that the mechanism was likely related to preventing assembly of Lp(a) by limiting the amount of apoB-100 available (33). This approach was not ideal as the mice continued to make free apolipoprotein(a). A specific ASO was then generated to apolipoprotein(a) and studies reported in 2011 demonstrated significant reduction in apolipoprotein(a)/Lp(a) up to 86%, in 3 Lp(a)/apo(a)-transgenic models (Figure 4B) (34). Optimized ASOs then generated and proceeded into clinical development.

OPTIMIZATION OF APOLIPOPROTEIN(a) ASOS FOR CLINICAL TRIALS

The generation of ASOs directed to apolipoprotein(a) is challenging, as it requires not only unique complementary sequences to bind to mRNA at optimal 3-dimensional sites, but also that they cannot bind to

FIGURE 3 Mechanism of ASO Therapeutic Efficacy, Chemical Modifications, and Improvement in Potency

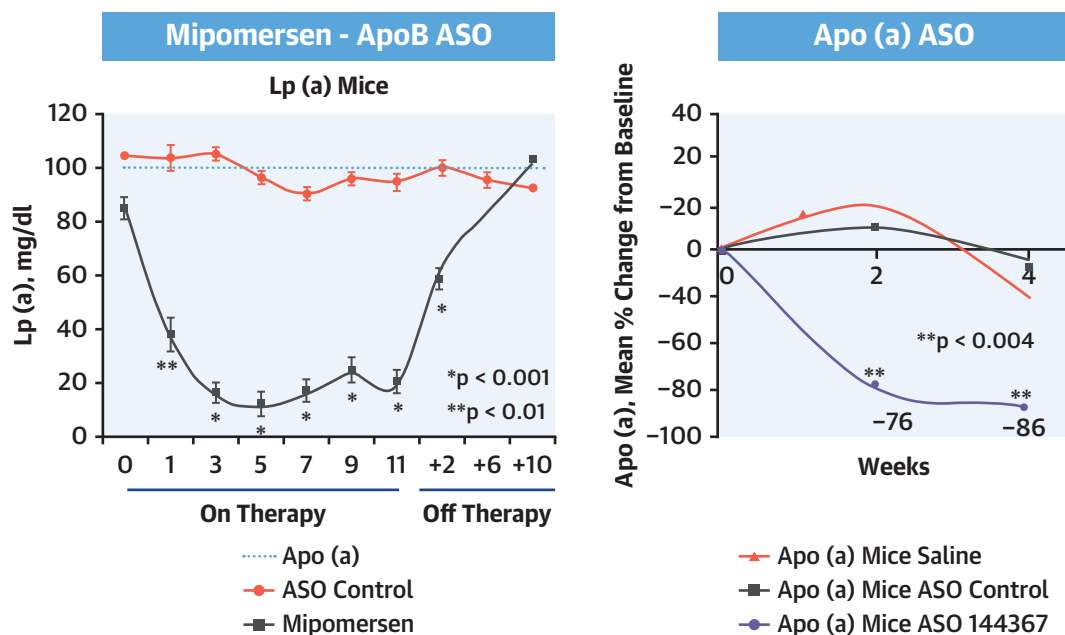


(A) A variety of cell surface proteins, including receptors, can interact with antisense oligonucleotide (ASOs), where they are internalized via clathrin- or caveolin-dependent endocytic pathways or via nonconventional endocytic pathways. ASOs enter cells via different endocytic pathways, including micropinocytosis, and traffic from early endosomes to late endosomes and to lysosomes, and then escape from endosomal organelles to reach the cytosol and nucleus and enter the nucleus and bind to their cognate mRNA and form a messenger ribonucleic acid (mRNA)-ASO duplex. Ribonuclease H1 (RNase H1) then cleaves the sense strand, allowing the antisense strand to bind another mRNA. Reduced mRNA leads to less protein translation. **(B)** A variety of modifications of ASO have been made to increase potency and stability and enhance binding, including modifications to the backbone phosphodiester linkages, sugar modifications, and base modifications. With advances in medicinal chemistry, the potency of ASOs has increased approximately 10-fold with each iteration. The addition of N-acetyl-galactosamine (GalNAc) for specific hepatocyte targeting in each iteration further increases potency ~10-fold. DNA = deoxyribonucleic acid; MOE = 2'-methoxyethyl; P-S = phosphorothioate.

plasminogen mRNA, which has 75% to 99% homology to apolipoprotein(a). An optimal ASO was identified that binds to the exon 24:25 splice site of the mature human apolipoprotein(a) transcript

(GenBank accession NM_005577.2) at position 3901 to 3920 with sequence CTTGTTCTGCTCCGTTGGTG. ISIS-APO(a)_{Rx} was designed to perfectly match only the exon 24:25 splice site present in all isoforms of

FIGURE 4 Effect of Mipomersen and ISIS 144367 on Lp(a) and Apo(a) Plasma Levels



(A) Mean percentage change in Lp(a) in 8K-Lp(a) transgenic mice in response to mipomersen targeting human apolipoprotein B-100 (apoB-100). **(B)** Mean percentage change in total apolipoprotein(a) levels in 12K-apolipoprotein(a) [apo(a)] mice in response to ISIS 144367, an early version of an antisense molecule used in mouse models. The p values represent differences compared with baseline values. Reprinted with permission for Merki et al. (33,34). ASO = antisense oligonucleotide; Lp(a) = lipoprotein(a).

apolipoprotein(a). This site also lacked any known single nucleotide polymorphisms that might limit efficacy in specific individuals with these genetic variations (35). Because the DNA bases are variable at this region, but identical at the KIV₂ protein level, this ASO recognizes all known human isoforms (35).

CLINICAL TRIALS OF Lp(a) LOWERING WITH ASOs

Table 2 summarizes the 4 trials conducted with ASOs to apolipoprotein(a) (30,36,37). The first 2 trials used a non-GalNac version of ISIS-APO_{Rx} and recruited healthy volunteers with elevated Lp(a) in a phase 1 study, or subjects with CVD and elevated Lp(a) of plasma levels (30,37) in a phase 2 study. In the phase 1 multiple-dose cohort, ISIS-APO(a)_{Rx} resulted in dose-dependent, mean percentage decreases in plasma Lp(a) concentration of 40% to 78% (absolute from 34 to 95 nmol/l or from ~14 to 38 mg/dl), along with significant reductions in oxidized phospholipids

carried by Lp(a). The phase 2 study recruited 2 groups of patients with elevated Lp(a), cohort A with Lp(a) 125 to 437 nmol/l and cohort B with Lp(a) ≥438 nmol/l, representing the 99th percentile of population levels (38). Subjects were treated with the ASO, 100 mg subcutaneously weekly for 1 month, 200 mg weekly for 1 month, and 300 mg weekly for 1 month, for a total of 3 months, and then followed off drug for an additional ~4 months due to the long tissue half-life of the drug to assess the kinetics of Lp(a) rebound off drug. In both cohorts, similar percent reductions in Lp(a) were noted (**Figure 5A**), but the absolute reduction in Lp(a) was higher in cohort B (183 vs. 305 nmol/l or 73 vs. 122 mg/dl) (**Table 2**). The plasma clearance of IONIS-APO(a)_{Rx} is very short (<4 h); however, the tissue half-life is approximately 3 weeks (28), and thus levels of these analytes remained suppressed for 3 months after the last dose. Significant reductions were also noted in oxidized phospholipids on apolipoprotein B-100 (OxPL-apoB) and oxidized phospholipids on apolipoprotein(a) [OxPL-apo(a)] (**Figures 5B and 5C**), as well

TABLE 2 Competed Clinical Trials in Lowering Lp(a) With Antisense Oligonucleotides

First Author (Ref. #)	Year Published	Drug	N	Dose/Dose Regimen	Mean Baseline Lp(a) (nmol/l)	Mean Lp(a) Reduction (%)	Absolute Lp(a) Reduction (nmol/l)
Tsimikas et al. (37)	2015	ISIS-APO(a) _{Rx}	16	Single doses of 50, 100, 200, and 400 mg	8-66	No significant change	N/A
			31	100, 200, and 300 mg/week, 6 doses over 4 weeks	82-152	40-78	34-95
Viney et al. (30)	2016	IONIS-APO(a) _{Rx}	50 (cohort A)	100-300 mg/week for 13 weeks	252-254	67	183
			11 (cohort B)	100-300 mg/week for 13 weeks	445-488	72	305
Viney et al. (30)	2016	Pelacarsen	28	Single doses of 10, 20, 40, 80, and 120 mg	111-219	26-85	59-107
			30	Multiple doses 10, 20, and 40 mg/week for 4 weeks	143-165	66-92	86-141
Tsimikas et al. (36)	2020	Pelacarsen	286	20, 40, or 60 mg every 4 weeks; 20 mg every 2 weeks; or 20 mg every week for 6-12 months	205-247	35-80	96-188

Lp(a) molar concentration in nmol/l cannot be scientifically converted to mass units in mg/dl. However, a rough estimate is to divide nmol/l by 2.5 to approximate values in mg/dl, with the realization that significant error may occur depending on isoform size (50).
Abbreviations as in Table 1.

as LDL-C and apoB-100 in both cohorts (30). Importantly, a substudy was embedded in the overall trial to study the promigratory behavior of CD14⁺ monocytes derived from the study subjects on and off drug timed to peak reduction in Lp(a) and then return to baseline. It demonstrated that from baseline to day 85 when participants were on the drug binding to endothelial cells were significantly reduced in the ASO group compared with the placebo group. The monocytes regained their promigratory phenotype by day 190 after the drug was stopped at day 85 (Figure 5D).

The rapid advancement of medicinal chemistry technology resulted in the development of pelacarsen, a generation 2.0+ ASO variant of IONIS-APO(a)_{Rx}. It contains the same 20 nucleotide sequence, but 6 of the 19 phosphorothioate linkages are replaced with phosphodiester linkages at positions 2, 3, 4, 5, 16, and 17. Furthermore, the GalNAc complex is covalently attached with a proprietary linker to the 5' end, allowing for rapid and specific uptake within hepatocytes via the asialoglycoprotein receptor (30).

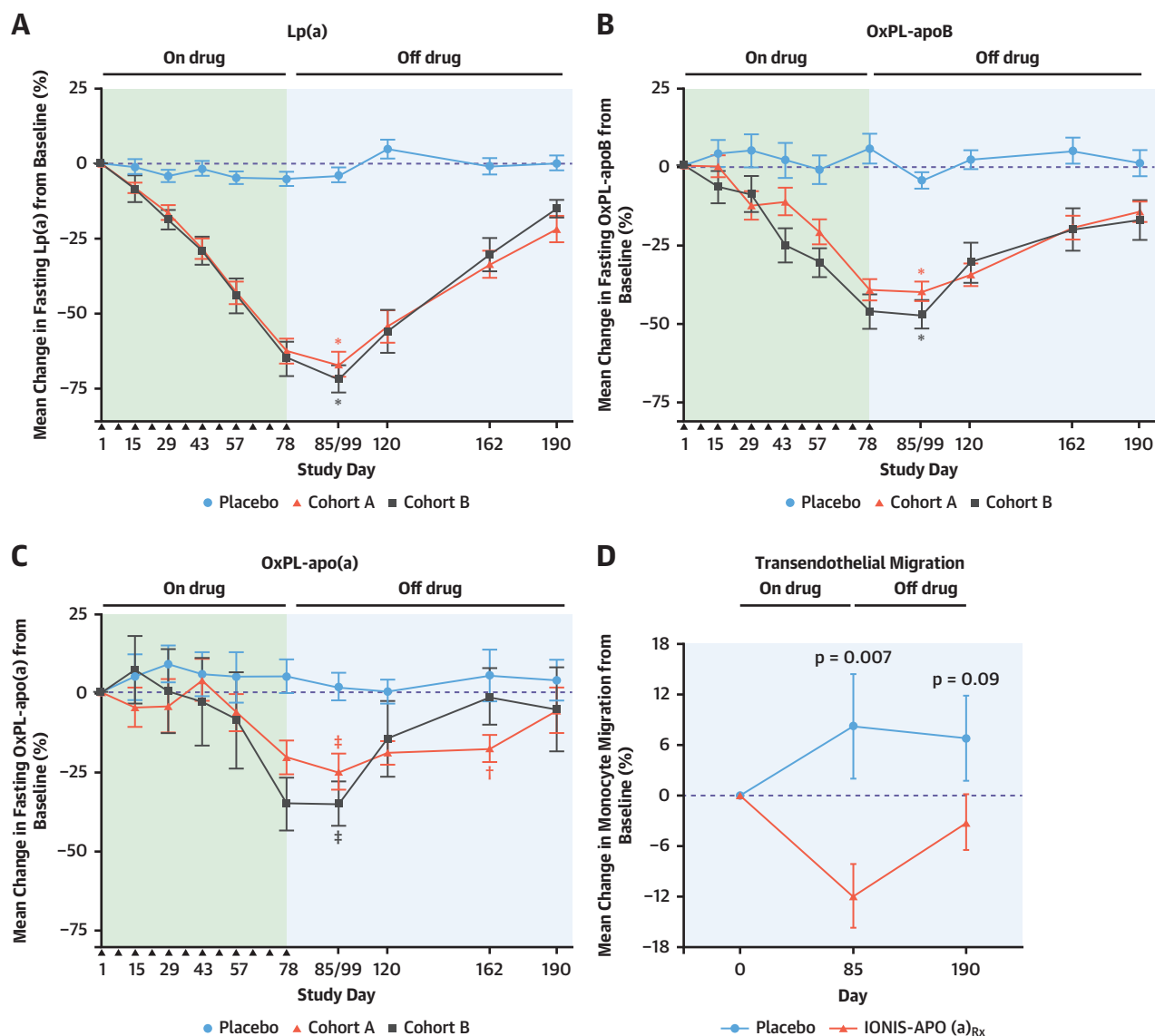
In a phase 1/2a trial, healthy volunteers [Lp(a) ≥75 nmol/l] were randomly assigned to receive single doses of 10, 20, 40, 80, and 120 mg or multiple doses of 10, 20, or 40 mg of pelacarsen. Significant dose-dependent reductions in mean Lp(a) concentrations were noted in all single-dose pelacarsen groups at day 30, ranging from 26.2% to 85.3% (from 59 to 107 nmol/l or from 23.6 to 42.8 mg/dl) (30). In the multidose groups, pelacarsen resulted in mean reductions in Lp(a) of 66% to 92% (from 86 to 141 nmol/l or from 34.4 to 56.4 mg/dl) along with significant reductions in OxPL-apoB, OxPL-apo(a), LDL-C, and apoB-100 levels (30).

Although the reductions in OxPL-apoB and OxPL-apo(a) were expected, the reductions in LDL-C and

apoB were not necessarily expected because pelacarsen does not affect apoB-100 transcription (35). A plausible mechanism might be that without apolipoprotein(a) covalently bound to apoB, LDL-apoB-100 particles may be cleared faster than Lp(a)-apoB particles. This is consistent with the reported slower fractional catabolic rate of Lp(a) versus LDL particles (30). Another potential mechanism might be decreased competition of LDL binding to hepatic LDL receptors by the lower plasma concentration of Lp(a). Irrespective of the mechanism(s), the extent of LDL-C reduction is robust and additive to baseline lipid-lowering therapies, and therefore might be postulated to provide additional benefit independent of Lp(a) lowering.

A phase 2b randomized, double-blind, placebo-controlled, dose-ranging trial was conducted in 286 patients with established cardiovascular disease and Lp(a) >60 mg per deciliter (150 nmol/l). Patients were randomized to pelacarsen to doses/dose regimens of 20, 40, or 60 mg every 4 weeks, 20 mg every 2 weeks, and 20 mg every week, or placebo subcutaneously for 6 to 12 months (36). The majority of patients were <65 years of age, and approximately one-half had premature coronary artery disease and prior myocardial infarction. LDL-C levels were well treated with 90% of patients on statins, 50% on ezetimibe and 20% on PCSK9i. The median baseline Lp(a) levels in the 6 groups ranged from 204.5 to 246.6 nmol/l. Administration of pelacarsen resulted in dose-dependent decreases in Lp(a) levels, with mean percent decreases of 35% to 80% (from 96 to 188 nmol/l or from 38.4 to 75.2 mg/dl), as compared with 6% reduction in the placebo group (p values for the comparison with placebo ranged from 0.003 to <0.001) (Figure 6A). The reduction in Lp(a) reached a nadir at ~14 weeks and was then sustained throughout the duration of treatment.

FIGURE 5 Effects of IONIS-APO(a)_{Rx} on Lp(a), Oxidized Phospholipids, and Monocyte Transendothelial Migration



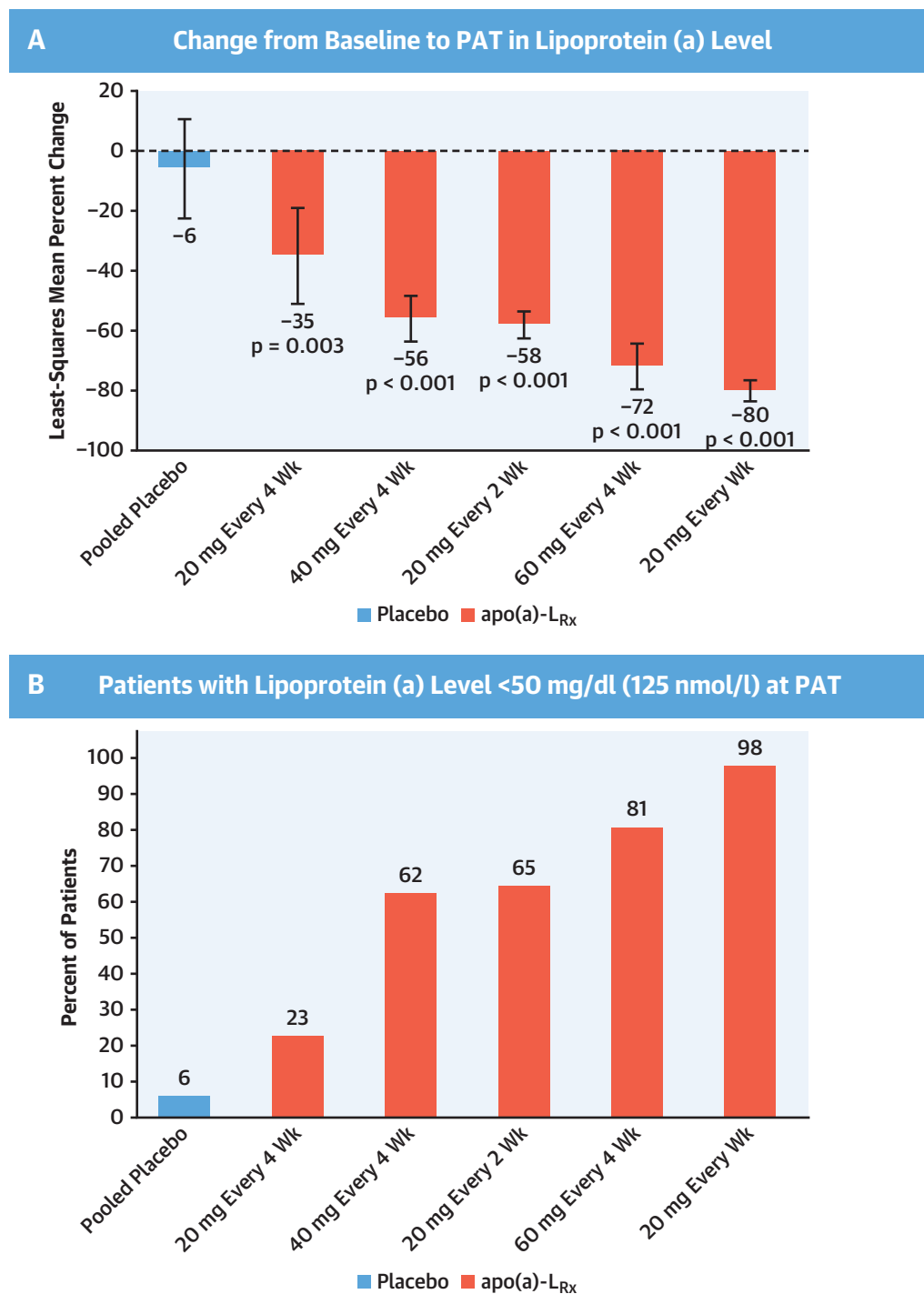
(A to C) The shaded area represents the dosing window and arrowheads indicate dosing every week. The p values show differences between treatment and pooled placebo at day 85/99. * $p \leq 0.0001$. * $p \leq 0.0001$. † $p = 0.0002$. ‡ $p = 0.0005$. Error bars are SEM. (D) The promigratory transendothelial migration of CD14⁺ monocytes, from baseline, at day 85, and day 190 (105 days after last drug administration) in subgroup of patients receiving IONIS-APO(a)_{Rx} (n = 17) and placebo (n = 13). Error bars are SEM. Reprinted with permission from Viney et al. (30). Lp(a) = lipoprotein(a); OxPL-apo(a) = oxidized phospholipids on apolipoprotein(a); OxPL-apoB = oxidized phospholipids on apolipoprotein B.

Importantly, 98% of participants reached <50 mg/dl (<125 nmol/l), a threshold associated with least cardiovascular risk in subjects on statin therapy (Figure 6B) (4,39). There were no significant differences between any pelacarsen dose or placebo with respect to platelet counts, liver and renal measures, or influenza-like symptoms.

CLINICAL TRIALS OF Lp(a) LOWERING WITH SMALL INTERFERING RNA

A clinical trial (NCT03626662) was reported at the American Heart Association Scientific Sessions 2020 evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of single doses (3 to 75 mg) of

FIGURE 6 Effect of Pelacarsen in Lowering Lp(a) Levels



(A) The least-squares mean percent changes from baseline to the primary analysis time point (PAT). **(B)** The percent of patients with Lp(a) levels of <50 mg/dl (125 nmol/l) in each group at the PAT. **Error bars** denote 95% confidence intervals. Reprinted with permission from Tsimikas et al (36). apo(a) = apolipoprotein(a); Lp(a) = lipoprotein(a).

TABLE 3 Estimated Lp(a)-Lowering Therapeutic Effect Size for Reduction in Coronary Heart Disease Outcomes Relative to 38.67-mg/dl Low-Density Lipoprotein Cholesterol Reduction

First Author (Ref. #)	Year Published	Study Design	N	Population Type	Estimated Lp(a) Reduction
Burgess et al. (40)	2018	Mendelian randomization	48,333	Primary prevention	101.5 mg/dl
Parish et al. (43)	2018	Clinical trial	3,978	Secondary prevention	80 nmol/l (~32 mg/dl)
Lamina et al. (41)	2019	Mendelian randomization	62,114	Primary prevention	65.7 mg/dl
Madsen et al. (42)	2020	Mendelian randomization	58,527	Primary prevention	50 mg/dl (105 nmol/l)
Szarek et al. (18)	2020	Clinical trial	18,924	Secondary prevention	40 mg/dl

Lp(a) = lipoprotein(a).

olpasiran (AMG890), a small interfering RNA to apolipoprotein(a), versus placebo in 7 cohorts of subjects with Lp(a) ≥ 70 to ≤ 199 nmol/l or ≥ 200 . In the Lp(a) ≥ 70 to ≤ 199 nmol/l group, olpasiran reduced mean Lp(a) levels from baseline by 71% to 96% at day 43, and by 80% to 94% at day 113 (cohorts 2 to 5). In the Lp(a) ≥ 200 group, olpasiran reduced mean Lp(a) levels from baseline by 75% to 89% at day 43 and by 61% to 80% at day 113. The effect of single doses of 225 and 625 mg olpasiran on Lp(a) levels were not reported. No safety concerns were identified.

ANTICIPATED EXTENT OF Lp(a) LOWERING NEEDED TO ACHIEVE A SIMILAR REDUCTION AS LOWERING LDL-C BY 38.67 mg/dl

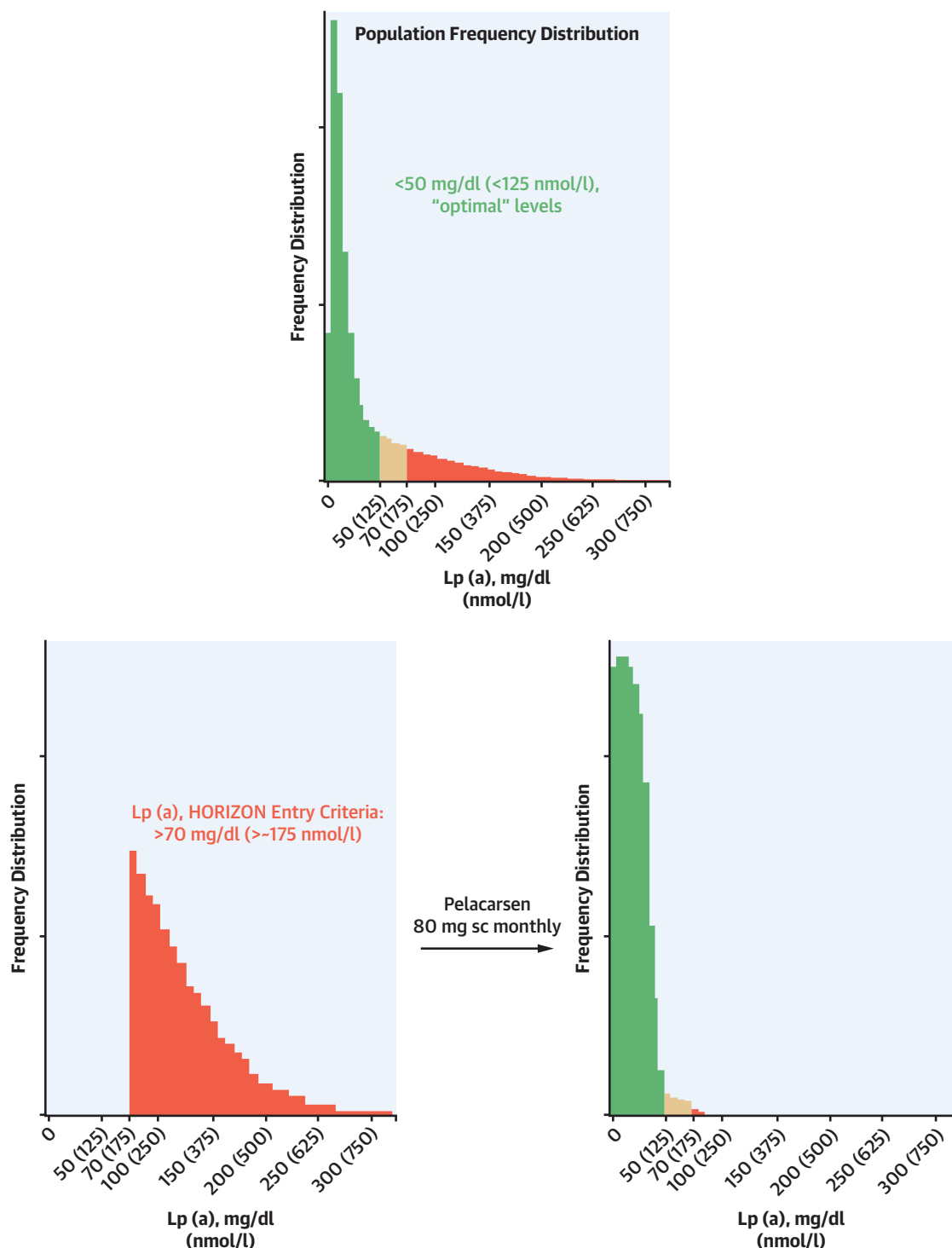
Several studies have used Mendelian randomization or trial data to estimate the extent of absolute Lp(a) lowering needed to achieve a relative risk reduction (20%) similar to a reduction of LDL-C by 38.67 mg/dl. Burgess et al. (40) suggested that a 101.5-mg/dl change (95% confidence interval: 71.0 to 137.0) in Lp(a) concentration would lead to an equivalent reduction in coronary heart disease risk as LDL-C. However, a subsequent analysis of similar methodology that included many of the same studies showed that the effect size was 65.7 mg/dl, with the discrepancy in effect size potentially explained by the skewed distributions of very high levels of Lp(a) in the former study leading to overestimation of effect size (41). A third Mendelian randomization analysis from the Copenhagen cohorts suggested the effect size is a 50 mg/dl reduction, or 105 nmol/l, with the estimate derived from 2 different assay methods (42). Finally, 2 clinical trials also provided effect size estimates: the HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events) trial estimated an 80-nmol/l (~32-mg/dl) reduction (43), and in the ODYSSEY OUTCOMES trial, a 5-mg/dl reduction was associated with a 2.5% relative risk reduction. Extrapolating this to 20% relative risk reduction translates to a 40 mg/dl absolute Lp(a) reduction. **Table 3** summarizes these data.

In view of the previous disparities, it is important to note that the 3 Mendelian randomization studies evaluated populations in the “primary prevention” sphere, and therefore their relevance to outcome trials of secondary prevention is questionable. The HPS2-THRIVE and ODYSSEY OUTCOMES trials are more likely to reflect the absolute change required to achieve a similar benefit to LDL-C with the caveat that niacin and PCSK9i have different mechanisms of Lp(a) lowering. Finally, these analyses cannot easily capture the non-LDL-C pathophysiology of Lp(a), namely the potential antifibrinolytic effects of apolipoprotein(a) and the proinflammatory content of oxidized phospholipids.

FUTURE DIRECTIONS

The phase 3 Lp(a)HORIZON (Assessing the Impact of Lipoprotein (a) Lowering With TQJ230 on Major Cardiovascular Events in Patients With CVD) trial (NCT04023552) is enrolling up to 7,680 patients with established history of myocardial infarction 3 months to 10 years from randomization, ischemic stroke and symptomatic peripheral arterial disease on background, guideline-recommended LDL-C-lowering therapy, and Lp(a) >70 mg/dl (>175 nmol/l) randomized to pelacarsen 80 mg subcutaneously monthly versus placebo (**Central Illustration**). There will be 2 co-primary outcome measures, either of which will be considered a positive trial if statistical significance is achieved: 1) time to the first occurrence of MACE, consisting of the combined endpoints of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and urgent coronary revascularization requiring hospitalization) in patients with Lp(a) ≥ 70 mg/dl; and 2) time to MACE in subjects with baseline Lp(a) ≥ 90 mg/dl. It is anticipated that the drug will lead to an 80% reduction in Lp(a) levels that will result in mean on-treatment Lp(a) <20 mg/dl (<50 nmol/l). The trial will be approximately 4.25 years in duration, during which 993 primary endpoint events are expected to accumulate and will read out in 2024.

CENTRAL ILLUSTRATION Anticipated Frequency Distribution of Baseline and On-Treatment Lipoprotein(a) Levels Following Pelacarsen in Lp(a)HORIZON Trial



Tsimikas, S. et al. J Am Coll Cardiol. 2021;77(12):1576-89.

The **top panel** represents the typical frequency distribution of Lp(a) levels. Optimal levels are defined as <50 mg/dl. The **light brown area** represents levels between 50 to 70 mg/dl and the **red area** levels >70 mg/dl. In the **lower panels**, the **red shaded area** represents the lipoprotein(a) [Lp(a)] inclusion threshold of >70/mg/dl in the Lp(a)HORIZON (Assessing the Impact of Lipoprotein (a) Lowering With TQJ230 on Major Cardiovascular Events in Patients With CVD) trial. Based on phase 2B data, treatment with pelacarsen is anticipated to shift the frequency distribution to the left and that most patients will reach <50 mg/dl (<~125 nmol/l).

A phase 2 trial (A Double-blind, Randomized, Placebo-controlled Phase 2 Study to Evaluate Efficacy, Safety, and Tolerability of AMG 890 [a GalNAc-conjugated Small Interfering in Subjects With Elevated Lipoprotein(a)]; [NCT04270760](#)) in 240 subjects with Lp(a) >150 nmol/l and established CVD is currently enrolling subjects with an estimated completion date April 2023. The trial includes 4 dose groups (dose and regimen not disclosed) and a placebo group with the primary endpoint being the percent change in Lp(a) at week 36. A third phase 1 trial (Study to Investigate Safety, Tolerability, PK and PD Response of SLN360 in Subjects With Elevated Lipoprotein(a); [NCT04606602](#)) is being initiated, with an estimated completion of November 2022. It will include single and multiple ascending doses in 88 healthy volunteers with Lp(a) >150 nmol/l, with doses ranging from 100 to 900 mg.

CONCLUSIONS

When Lp(a) was first shown to be an independent CVD risk factor, it has been anticipated that therapeutics would be developed to treat elevated Lp(a) levels. However, owing to the difficulties of targeting apolipoprotein(a), this hope could only emerge in conjunction with the parallel development of a whole new approach to therapeutics, namely inhibiting apolipoprotein(a) mRNA in hepatocytes (44). The ongoing trials provide hope to patients and

physicians that Lp(a)-mediated risk of atherosclerotic CVD and aortic stenosis can be rationally addressed to minimize future events.

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ADDRESS FOR CORRESPONDENCE: Dr. Sotirios Tsimikas, Vascular Medicine Program, Sulpizio Cardiovascular Center, University of California-San Diego, 9500 Gilman Drive, BSB 1080, La Jolla, California 92093-0682, USA. E-mail: stsimikas@ucsd.edu.

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