

ORIGINAL ARTICLE

Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease

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ABSTRACT

BACKGROUND

Lipoprotein(a) is a presumed risk factor for atherosclerotic cardiovascular disease. Olpasiran is a small interfering RNA that reduces lipoprotein(a) synthesis in the liver.

METHODS

We conducted a randomized, double-blind, placebo-controlled, dose-finding trial involving patients with established atherosclerotic cardiovascular disease and a lipoprotein(a) concentration of more than 150 nmol per liter. Patients were randomly assigned to receive one of four doses of olpasiran (10 mg every 12 weeks, 75 mg every 12 weeks, 225 mg every 12 weeks, or 225 mg every 24 weeks) or matching placebo, administered subcutaneously. The primary end point was the percent change in the lipoprotein(a) concentration from baseline to week 36 (reported as the placebo-adjusted mean percent change). Safety was also assessed.

RESULTS

Among the 281 enrolled patients, the median concentration of lipoprotein(a) at baseline was 260.3 nmol per liter, and the median concentration of low-density lipoprotein cholesterol was 67.5 mg per deciliter. At baseline, 88% of the patients were taking statin therapy, 52% were taking ezetimibe, and 23% were taking a proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor. At 36 weeks, the lipoprotein(a) concentration had increased by a mean of 3.6% in the placebo group, whereas olpasiran therapy had significantly and substantially reduced the lipoprotein(a) concentration in a dose-dependent manner, resulting in placebo-adjusted mean percent changes of –70.5% with the 10-mg dose, –97.4% with the 75-mg dose, –101.1% with the 225-mg dose administered every 12 weeks, and –100.5% with the 225-mg dose administered every 24 weeks ($P < 0.001$ for all comparisons with baseline). The overall incidence of adverse events was similar across the trial groups. The most common olpasiran-related adverse events were injection-site reactions, primarily pain.

CONCLUSIONS

Olpasiran therapy significantly reduced lipoprotein(a) concentrations in patients with established atherosclerotic cardiovascular disease. Longer and larger trials will be necessary to determine the effect of olpasiran therapy on cardiovascular disease. (Funded by Amgen; OCEAN[a]-DOSE ClinicalTrials.gov number, NCT04270760.)

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LIPOPROTEIN(A) CONSISTS OF AN APOLIPOPROTEIN B–containing lipoprotein that is covalently bound to apolipoprotein(a). Numerous epidemiologic studies over the past three decades have shown an association between higher circulating lipoprotein(a) concentrations and an increased risk of atherosclerotic cardiovascular disease.^{1,2} Moreover, a growing number of genomewide association and mendelian randomization studies also support a causal role for lipoprotein(a) in atherosclerosis^{3–5} and calcific valvular aortic stenosis.⁶

Although lipoprotein(a) is presumed, on the basis of genetic data, to be a causal risk factor for atherosclerotic cardiovascular disease, no currently available pharmacologic therapies substantially reduce lipoprotein(a) concentrations or are indicated to treat patients with an elevated lipoprotein(a) concentration. The plasma concentration of lipoprotein(a) is primarily genetically determined (approximately 70 to ≥90%),² and its expression is controlled by the apolipoprotein(a) gene (*LPA*).⁷ Olpasiran is a small interfering RNA (siRNA) molecule that disrupts expression of *LPA*, degrading apolipoprotein(a) mRNA and thereby preventing assembly of the lipoprotein(a) particle in the hepatocyte. In phase 1 testing, a single dose of olpasiran reduced the lipoprotein(a) concentration in a dose-dependent manner, with doses of 9 mg or higher reducing the circulating lipoprotein(a) concentration by more than 90% in persons with an elevated lipoprotein(a) concentration, with an effect that persisted for 3 to 6 months.⁸ The phase 2 OCEAN(a)-DOSE trial (Olpasiran Trials of Cardiovascular Events and Lipoprotein[a] Reduction–Dose Finding Study) was designed to evaluate the efficacy and safety of repeated administration of several different doses of olpasiran.⁹

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this multicenter, randomized, double-blind, placebo-controlled, dose-finding trial of olpasiran at 34 participating sites in seven countries.⁹ The trial was designed by the sponsor, Amgen, in collaboration with the Thrombolysis in Myocardial Infarction (TIMI) Study Group at Brigham and Women's Hospital and Harvard Medical School. The trial protocol (available with the full text of this article at NEJM.org) and

amendments were approved by the relevant ethics committees at each participating site. The raw database was provided to the TIMI Study Group, which conducted data analyses independently of the sponsor. The first author wrote the first draft of the manuscript, and all the authors participated in subsequent revisions. The academic authors made the decision to submit the manuscript for publication. The authors who had access to the data vouch for the accuracy and completeness of the data, and all the authors vouch for the fidelity of the trial to the protocol.

TRIAL POPULATION

Adults 18 to 80 years of age were considered to be eligible for trial participation if they had a serum lipoprotein(a) concentration of more than 150 nmol per liter (approximately 70 mg per deciliter) at the time of screening and a history of atherosclerotic cardiovascular disease, including established coronary heart disease, peripheral artery disease, or atherosclerotic cerebrovascular disease. Key exclusion criteria were severe renal dysfunction (estimated glomerular filtration rate, <30 ml per minute per 1.73 m² of body-surface area) or a history or clinical evidence of active liver disease. (A full list of the inclusion and exclusion criteria is provided in the Supplementary Appendix, available at NEJM.org.) Written informed consent was obtained from all the patients.

RANDOMIZATION

Eligible patients were randomly assigned in a 1:1:1:1 ratio to receive one of four doses of olpasiran (10 mg every 12 weeks, 75 mg every 12 weeks, 225 mg every 12 weeks, or 225 mg every 24 weeks) or matching placebo, administered subcutaneously. The trial treatment period was 48 weeks, after which the patients were followed for an extended safety follow-up without further administration of olpasiran or placebo for a minimum of 24 weeks. Randomization was performed by means of a central computerized system, with stratification according to the lipoprotein(a) concentration at screening (≤200 vs. >200 nmol per liter) and geographic region or country (Japan vs. other).

TRIAL PROCEDURES AND END POINTS

Enrolled patients had in-person trial visits on days 1 and 2, during week 4, and then every 4 weeks

during the 48-week treatment period. At each visit, adverse events, concomitant medications, fasting lipids, and lipoprotein(a) concentration were assessed. Olpasiran or matching placebo was given at randomization and at week 12, week 24, and week 36.

The primary end point was the percent change in the lipoprotein(a) concentration from baseline to week 36 in the modified intention-to-treat population and was reported as the placebo-adjusted mean percent change. The modified intention-to-treat population included all the patients who had undergone randomization and received at least one dose of olpasiran or placebo, regardless of whether they stopped receiving olpasiran or placebo during follow-up. The secondary end points were the percent change from baseline in the lipoprotein(a) concentration at week 48, the percent change from baseline in the low-density lipoprotein (LDL) cholesterol concentration at weeks 36 and 48, and the percent change from baseline in the apolipoprotein B concentration at weeks 36 and 48. A prespecified exploratory end point was the percentage of patients with a lipoprotein(a) concentration of less than 125 nmol per liter (approximately 50 to 60 mg per deciliter) at 36 weeks.

Safety was assessed by means of the collection of data on adverse events and safety laboratory values that were assessed by a central laboratory every 12 weeks during the treatment period. Safety analyses were conducted according to the actual receipt of olpasiran or placebo. Adverse events that occurred during the treatment period are reported. A clinical-events committee, which was led by the TIMI Study Group and in which the members were unaware of the trial-group assignments, adjudicated cause of death and cardiovascular events of interest (cardiac ischemic events, cerebrovascular events, coronary and noncoronary revascularization, and acute limb ischemia). Definitions of the end points are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Assuming a standard deviation of 30% and withdrawal by 5% of the patients, and with Bonferroni multiplicity adjustment to control the family-wise type I error for the primary end point at 0.05, we calculated that a minimum of 48 patients per group would be necessary for the trial to have at

least 90% power to detect a relative treatment difference of 25% between the olpasiran groups and the placebo group in the primary end-point analysis. All the efficacy analyses were conducted in the modified intention-to-treat analysis population. No imputations were made for missing values. The primary analysis of the percent change from baseline in the lipoprotein(a) concentration was assessed with a repeated-measures, linear mixed-effects model that included terms for trial group, stratification factors, scheduled visit, and the interaction of trial group with scheduled visit.

Because the statistical analysis plan did not include a provision for correction for multiplicity in tests for secondary end points, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used in place of a hypothesis test. All the analyses were conducted by the TIMI Study Group on a complete, independently held database with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

TRIAL PATIENTS

From July 28, 2020, to April 26, 2021, a total of 281 patients were randomly assigned to receive olpasiran (227 patients) or placebo (54 patients) (Fig. S1 in the Supplementary Appendix). The baseline characteristics of the patients were well matched across the trial groups (Table 1). Overall, the median baseline lipoprotein(a) concentration was 260.3 nmol per liter (interquartile range, 198.1 to 352.4), and the median LDL cholesterol concentration was 67.5 mg per deciliter (1.75 mmol per liter; interquartile range, 50.5 to 83.5 mg per deciliter [1.30 to 2.15 mmol per liter]). The mean (\pm SD) age of the patients was 61.9 \pm 9.5 years, and 32% of the patients were women. With respect to race and ethnic group, the trial population was generally representative of established populations with atherosclerotic cardiovascular disease in the countries participating in the trial (Table S2). At baseline, 88% of the patients were taking statin therapy (including 61% taking high-intensity statin therapy), 52% ezetimibe, and 23% a proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo		Olpasiran		
	Every 12 Wk (N=54)	10 mg, Every 12 Wk (N=58)	75 mg, Every 12 Wk (N=58)	225 mg, Every 12 Wk (N=56)	225 mg, Every 24 Wk (N=55)
Age — yr	63.4±8.9	63.4±9.5	61.3±9.2	59.7±10.1	61.8±9.4
Male sex — no. (%)	36 (67)	46 (79)	35 (60)	41 (73)	33 (60)
Race — no. (%)†					
White	48 (89)	52 (90)	52 (90)	47 (84)	49 (89)
Black	2 (4)	0	1 (2)	2 (4)	1 (2)
Asian	3 (6)	6 (10)	5 (9)	5 (9)	5 (9)
Other	1 (2)	0	0	2 (4)	0
Hispanic or Latino ethnic group — no. (%)†	2 (4)	2 (3)	0	0	2 (4)
Geographic region or country — no. (%)					
North America	37 (69)	34 (59)	34 (59)	27 (48)	36 (65)
Europe	9 (17)	7 (12)	12 (21)	15 (27)	8 (15)
Australia	6 (11)	12 (21)	7 (12)	10 (18)	8 (15)
Japan	2 (4)	5 (9)	5 (9)	4 (7)	3 (5)
Coronary artery disease — no. (%)	50 (93)	55 (95)	49 (84)	52 (93)	50 (91)
Myocardial infarction — no. (%)	20 (37)	15 (26)	13 (22)	21 (38)	12 (22)
Peripheral artery disease — no. (%)	3 (6)	9 (16)	6 (10)	6 (11)	6 (11)
Cerebrovascular disease — no. (%)	12 (22)	9 (16)	13 (22)	10 (18)	13 (24)
Familial hypercholesterolemia — no. (%)	9 (17)	9 (16)	11 (19)	5 (9)	15 (27)
Hypertension — no. (%)	38 (70)	37 (64)	38 (66)	39 (70)	32 (58)
Type 2 diabetes mellitus — no. (%)	12 (22)	8 (14)	14 (24)	9 (16)	7 (13)
Paroxysmal atrial fibrillation or flutter — no. (%)	5 (9)	4 (7)	3 (5)	2 (4)	2 (4)
Heart failure — no. (%)	3 (6)	2 (3)	3 (5)	2 (4)	3 (5)
Selected lipid-lowering therapies — no. (%)					
Statin	45 (83)	52 (90)	50 (86)	51 (91)	49 (89)
Ezetimibe	22 (41)	32 (55)	31 (53)	26 (46)	36 (65)
PCSK9 inhibitor	12 (22)	15 (26)	11 (19)	16 (29)	12 (22)
Fibrate	2 (4)	2 (3)	3 (5)	1 (2)	1 (2)
Median laboratory values (IQR)					
Lipoprotein(a) — nmol/liter	246.1 (199.9–343.3)	304.0 (194.2–397.6)	227.5 (188.4–304.2)	265.4 (200.6–342.2)	283.4 (204.6–389.2)
LDL cholesterol — mg/dl	64.8 (47.5–81.0)	69.0 (52.0–83.5)	75.0 (53.5–90.0)	62.3 (48.5–80.5)	66.0 (50.5–79.5)
Apolipoprotein B — mg/dl	62.5 (48.5–76.0)	66.8 (51.5–81.5)	74.0 (59.5–85.0)	65.8 (49.5–80.8)	64.0 (56.5–79.0)

* Plus-minus values are means ±SD. Percentages may not total 100 because of rounding. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. IQR denotes interquartile range, LDL low-density lipoprotein, and PCSK9 proprotein convertase subtilisin-kexin type 9.

† Race and ethnic group were reported by the patient.

PERCENT CHANGE IN LIPOPROTEIN(A) AND LIPID CONCENTRATIONS

At 36 weeks, the mean percent change in the lipoprotein(a) concentration in the placebo group

was an increase of 3.6% (95% confidence interval [CI], –0.1 to 7.3). In contrast, there were significant and substantial reductions in the lipoprotein(a) concentration in all the olpasiran

Table 2. Percent Change in Concentrations of Lipoprotein(a), LDL Cholesterol, and Apolipoprotein B from Baseline to Week 36.*

End Point	Placebo		Olpasiran			
	Every 12 Wk (N=51)	10 mg, Every 12 Wk (N=57)	75 mg, Every 12 Wk (N=57)	225 mg, Every 12 Wk (N=53)	225 mg, Every 24 Wk (N=53)	
Percent change in lipoprotein(a) concentration (95% CI)	3.6 (-0.1 to 7.3)	-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)	
Placebo-adjusted percent change in lipoprotein(a) concentration (95% CI)	NA	-70.5 (-75.1 to -65.9)	-97.4 (-102.0 to -92.8)	-101.1 (-105.8 to -96.5)	-100.5 (-105.2 to -95.8)	
Percent change in LDL cholesterol concentration (95% CI)	6.3 (-2.6 to 15.2)	-17.4 (-25.8 to -9.1)	-16.3 (-24.6 to -7.9)	-16.8 (-25.4 to -8.1)	-18.5 (-27.1 to -9.8)	
Placebo-adjusted percent change in LDL cholesterol concentration (95% CI)	NA	-23.7 (-35.3 to -12.2)	-22.6 (-34.1 to -11.0)	-23.1 (-34.8 to -11.4)	-24.8 (-36.5 to -13.0)	
Percent change in apolipoprotein B concentration (95% CI)	7.4 (1.4 to 13.4)	-11.5 (-17.2 to -5.8)	-9.3 (-15.0 to -3.6)	-10.2 (-16.0 to -4.4)	-11.4 (-17.3 to -5.5)	
Placebo-adjusted percent change in apolipoprotein B concentration (95% CI)	NA	-18.9 (-26.3 to -11.5)	-16.7 (-24.1 to -9.3)	-17.6 (-25.1 to -10.1)	-18.8 (-26.3 to -11.2)	

* All the efficacy analyses were conducted in the modified intention-to-treat analysis population, which included all the patients who had undergone randomization and received at least one dose of olpasiran or placebo. Values are the least-squares estimate and 95% confidence interval. P<0.001 for all comparisons with baseline in the analysis of the primary end point (the percent change in the lipoprotein[a] concentration to week 36 and reported as the placebo-adjusted mean percent change). Since the widths of the confidence intervals for secondary end points have not been adjusted for multiplicity, the intervals should not be used in place of a hypothesis test. NA denotes not applicable.

groups. The placebo-adjusted mean percent change in the lipoprotein(a) concentration was -70.5% (95% CI, -75.1 to -65.9) with the 10-mg dose every 12 weeks, -97.4% (95% CI, -102.0 to -92.8) with the 75-mg dose every 12 weeks, -101.1% (95% CI, -105.8 to -96.5) with the 225-mg dose every 12 weeks, and -100.5% (95% CI, -105.2 to -95.8) with the 225-mg dose every 24 weeks (P<0.001 for all comparisons with baseline) (Table 2 and Fig. 1). There was limited interpatient variability in the pharmacodynamic response with the higher doses (Fig. 2). The percent of lowering of the lipoprotein(a) concentration was consistent across prespecified subgroups, including those defined according to the median lipoprotein(a) and LDL cholesterol concentrations (Fig. S2).

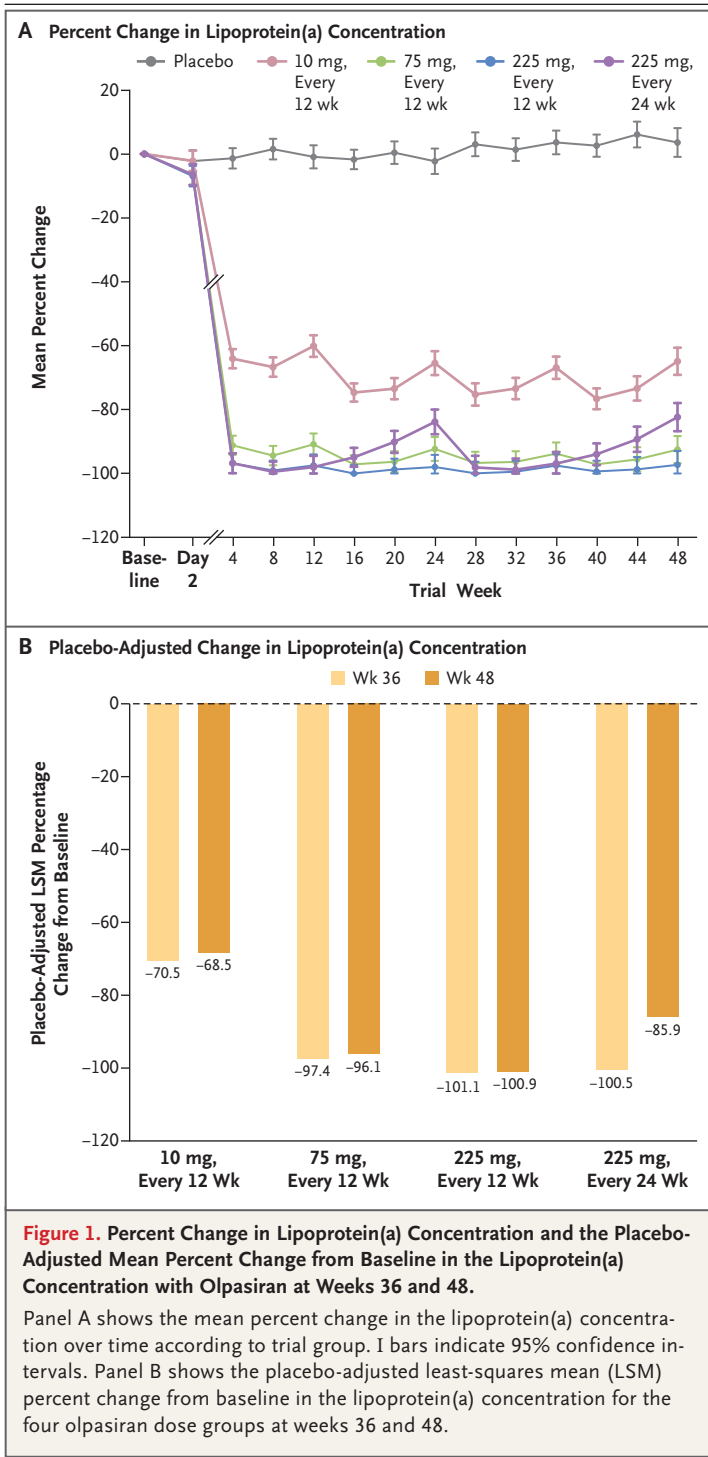
Regarding the effects of olpasiran on other lipids, the placebo-adjusted mean percent change in the LDL cholesterol concentration at 36 weeks ranged from -22.6% to -24.8% across the olpasiran dose levels (Table 2). The placebo-adjusted mean percent change in the apolipoprotein B concentration ranged from -16.7% to -18.9% across the olpasiran dose levels (Table 2, Table S1, and Fig. S3).

At 48 weeks, the placebo-adjusted mean per-

cent change in the lipoprotein(a) concentration with olpasiran was -68.5% (95% CI, -74.3 to -62.7) with the 10-mg dose every 12 weeks, -96.1% (95% CI, -101.9 to -90.3) with the 75-mg dose every 12 weeks, -100.9% (95% CI, -106.7 to -95.0) with the 225-mg dose every 12 weeks, and -85.9% (95% CI, -91.8 to -80.1) with the 225-mg dose every 24 weeks (Fig. 1). The percentage of patients with a lipoprotein(a) concentration of less than 125 nmol per liter (approximately 50 to 60 mg per deciliter) at 36 weeks (a prespecified exploratory end point) was 67% in the group that received the 10-mg dose every 12 weeks, 100% in the group that received the 75-mg dose every 12 weeks, 100% in the group that received the 225-mg dose every 12 weeks, and 98% in the group that received the 225-mg dose every 24 weeks (Fig. S4).

SAFETY

The overall incidence of adverse events and serious adverse events was similar among patients who were treated with olpasiran and those who received placebo. The incidence of adverse events leading to the discontinuation of olpasiran or placebo was similar across the trial groups (2% in each group).



The incidences of hyperglycemia or new-onset or worsening diabetes mellitus (in 7% of the patients overall) and of myalgias (in 6% overall) were similar with olpasiran and with placebo (Table 3). Liver-

related adverse events, kidney-related adverse events, thrombocytopenia, and peripheral neuropathy were all infrequent (overall incidence, $\leq 3\%$), and the incidences were similar with olpasiran and with placebo (Table 3). There were no cases that met the criteria for Hy's law or clinically important changes in safety laboratory evaluations (including any imbalances among the trial groups with respect to liver-function abnormalities [aspartate aminotransferase or alanine aminotransferase levels >3 times the upper limit of the normal range] or thrombocytopenia) on central laboratory testing.

Higher percentages of patients reported hypersensitivity and injection-site reactions with higher doses (≥ 75 mg) of olpasiran than with placebo (Table 3). A review of hypersensitivity events identified all the reports as involving local, cutaneous reactions. The majority of hypersensitivity and injection-site events were mild in severity and were reported as isolated events that resolved within 48 hours after onset, without treatment. The most common olpasiran-related adverse event was injection-site pain. Injection-site reactions led to the discontinuation of olpasiran in three patients; none of the events was considered by the investigators to be severe, and all the affected patients had preexisting dermatologic conditions.

CARDIOVASCULAR EVENTS

Three patients (6%) in the placebo group had an adjudicated cardiovascular event, including one patient who had an ischemic stroke, one who was hospitalized for unstable angina, and one who underwent coronary-artery bypass graft surgery. Two patients (1%) who received olpasiran (one at 10 mg every 12 weeks and one at 225 mg every 24 weeks) had a cardiovascular event, both of whom underwent percutaneous coronary intervention. No patients died from cardiovascular causes during the trial; one patient in the placebo group died from noncardiovascular causes.

DISCUSSION

Olpasiran is an siRNA drug that is administered subcutaneously and directed to the liver by means of its *N*-acetylgalactosamine moiety. Once inside the hepatocyte, the antisense strand of olpasiran is loaded into an RNA-induced silencing complex (RISC) and then binds to apolipoprotein(a)

mRNA, leading to its degradation. Subsequently, the RISC can target additional mRNA, thereby allowing for a prolonged duration of effect.¹⁰

The findings of this trial show that olpasiran treatment markedly reduced the concentration of lipoprotein(a) in a dose-dependent manner and appeared to be safe. At higher doses, olpasiran therapy reduced the lipoprotein(a) concentration by more than 95%, as compared with placebo, with nearly all patients who received olpasiran having a lipoprotein(a) concentration of less than 125 nmol per liter. Moreover, the pharmacody-

amic effects of olpasiran were maintained throughout the administration interval when the drug was administered every 12 weeks.

Although multiple pathways of investigation indicate a causal role for lipoprotein(a) in atherosclerotic cardiovascular disease,² large-scale clinical trials will be needed to show a clinical benefit of lipoprotein(a) lowering.^{11,12} Although several medical professional societies now recommend the measurement of lipoprotein(a) in all adults at least once,¹³⁻¹⁵ lipoprotein(a) currently remains infrequently measured in routine clinical practice.

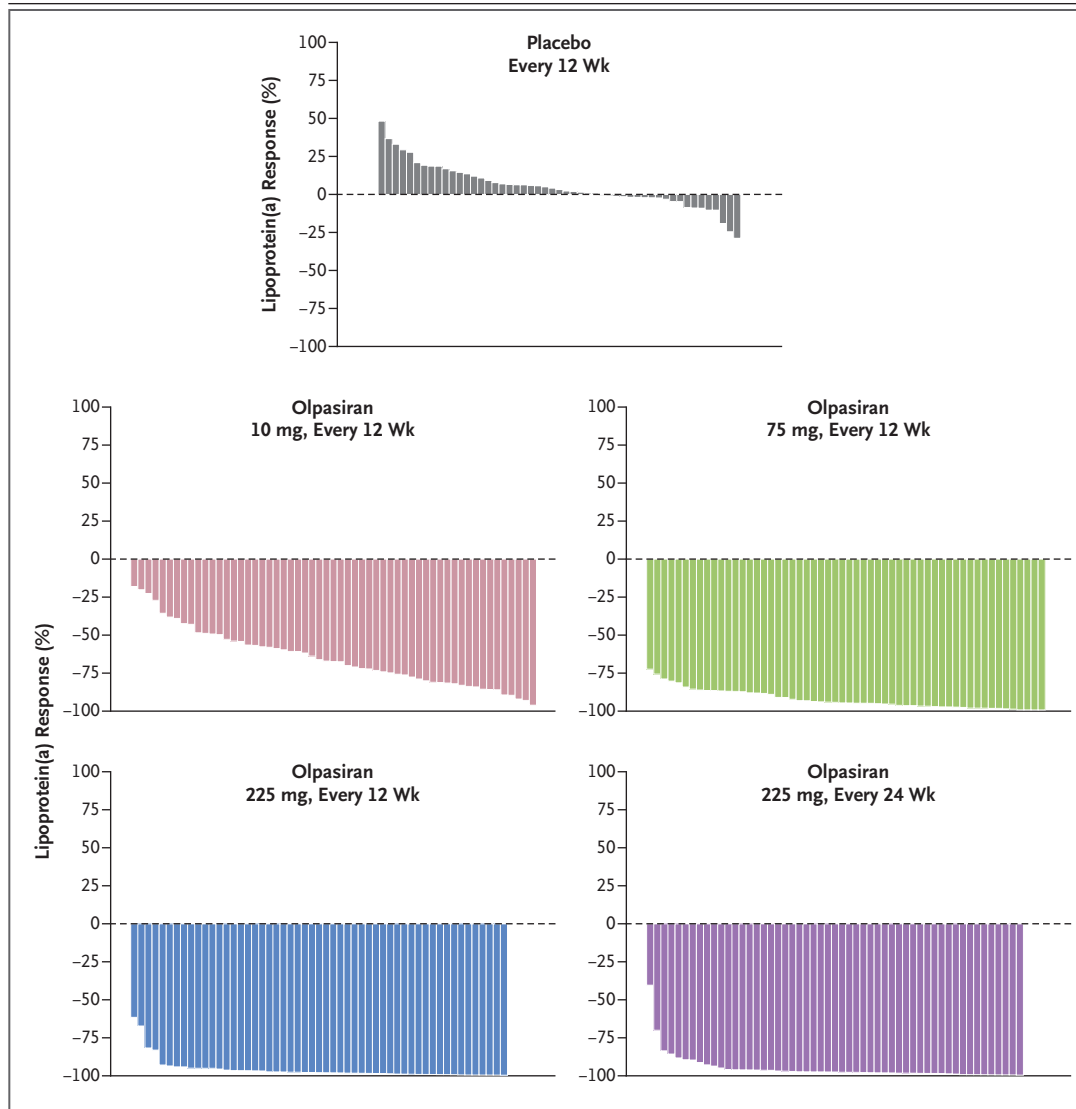


Figure 2. Distribution in Lipoprotein(a) Response at 36 weeks.

The waterfall plots show the distribution in the lipoprotein(a) response (percentage increase or decrease), according to trial group, in individual patients at 36 weeks.

Table 3. Adverse Events.

Event	Placebo		Olpasiran			Overall (N=227)
	Every 12 Wk (N=54)	10 mg, Every 12 Wk (N=58)	75 mg, Every 12 Wk (N=58)	225 mg, Every 12 Wk (N=56)	225 mg, Every 24 Wk (N=55)	
	<i>number of patients (percent)</i>					
Any adverse event during trial period	45 (83)	45 (78)	46 (79)	47 (84)	47 (85)	185 (81)
Serious adverse event	8 (15)	3 (5)	3 (5)	6 (11)	4 (7)	16 (7)
Adverse event reported as being related to placebo or olpasiran	11 (20)	7 (12)	13 (22)	16 (29)	14 (25)	50 (22)
Adverse event leading to discontinuation of placebo or olpasiran	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	4 (2)
Fatal adverse event	1 (2)	0	0	0	0	0
Myalgia	4 (7)	3 (5)	1 (2)	4 (7)	4 (7)	12 (5)
Peripheral neuropathy	0	1 (2)	2 (3)	0	1 (2)	4 (2)
Liver-related adverse event	2 (4)	1 (2)	2 (3)	1 (2)	1 (2)	5 (2)
Kidney-related adverse event	1 (2)	0	1 (2)	0	0	1 (<1)
Hyperglycemia or new-onset or worsening diabetes mellitus	3 (6)	5 (9)	3 (5)	5 (9)	3 (5)	16 (7)
Coagulopathy or bleeding diatheses, excluding thrombocytopenia	0	1 (2)	1 (2)	2 (4)	0	4 (2)
Thrombocytopenia	1 (2)	0	0	0	0	0
Injection-site reaction	6 (11)	3 (5)	11 (19)	12 (21)	13 (24)	39 (17)
Hypersensitivity reaction	1 (2)	1 (2)	4 (7)	3 (5)	5 (9)	13 (6)

In part, this situation relates to the lack of evidence to support a specific therapeutic strategy to help mitigate the cardiovascular risks associated with high lipoprotein(a) concentrations.

Moreover, there remains disagreement regarding the appropriate threshold for defining an abnormal lipoprotein(a) concentration.^{13,14,16-18} The relationship between lipoprotein(a) and risk of atherosclerotic cardiovascular disease appears to be broadly continuous and log-linear, thereby challenging the concept of a clear threshold for patient risk.¹ Although some consensus documents define an abnormal value as being above 50 mg per deciliter (approximately 125 nmol per liter), this threshold was identified as representing the 80th percentile in a Northern European population.⁷ Because lipoprotein(a) concentration is primarily genetically driven, there exists marked variation in its distribution according to patient race and ancestry,¹⁹ as well as according to sex.¹⁵ Despite this observed variation, the lipoprotein(a) concentration continues to consistently predict coronary heart disease risk in a log-linear manner

regardless of race or ethnic group.¹⁵ Contributing to the confusion, substantial differences also exist between diagnostic assays, including both molar concentration and mass-based assays without the ability to directly convert units.²

With respect to lipoprotein(a) as a therapeutic target, it remains unclear how much of a reduction in the lipoprotein(a) concentration would be necessary to translate into a meaningful reduction in the risk of cardiovascular events. Mendelian randomization studies suggest that an absolute reduction of 60 to 100 mg per deciliter (approximately 125 to 215 nmol per liter) in the lipoprotein(a) concentration may be necessary to derive a clinical benefit similar to a reduction of 38.7 mg per deciliter (1 mmol per liter) in the LDL cholesterol concentration.^{20,21} However, to date, no available pharmacologic therapies can consistently achieve this magnitude of reduction in lipoprotein(a) concentration. Statins do not lower, and in some instances may increase, lipoprotein(a) concentrations.²

In the current trial, olpasiran reduced the

lipoprotein(a) concentration in a dose-dependent manner, with a reduction of more than a 95% when the drug was administered every 12 weeks at a dose of 75 mg or 225 mg. Given the baseline median lipoprotein(a) concentration in this trial population, the higher doses of olpasiran led to a mean absolute reduction of approximately 250 nmol per liter. There also was limited interpatient variability in terms of the pharmacodynamic response; at higher doses of olpasiran, nearly all the patients had a lipoprotein(a) concentration of less than 125 nmol per liter at 36 weeks. Although the pharmacodynamic effects of olpasiran were maintained at 12 weeks, its effects toward maintaining suppression of lipoprotein(a) synthesis were attenuated when the frequency of administration was reduced to every 24 weeks. The observed reductions in the concentrations of LDL cholesterol and apolipoprotein B might be reasonably expected to be due to reductions in concentrations of those lipids and proteins on lipoprotein(a) particles, but whether this is indeed the case will require dedicated investigation. Regarding safety, olpasiran therapy led to a higher incidence of injection-site and hypersensitivity reactions than placebo; these effects were primarily transient and localized and infrequently led to the discontinuation of olpasiran.

Other new therapeutic agents that directly target lipoprotein(a) are in clinical development. Pelacarsen is an antisense oligonucleotide that binds to the mRNA transcript of the *LPA* gene by means of base-pairing, which thereby leads to reduced apolipoprotein(a) synthesis and to reduced lipoprotein(a) concentrations. In a phase 2 trial, subcutaneous administration of pelacarsen reduced lipoprotein(a) concentrations by 72% at a dose of 60 mg once monthly and by 80% at a dose of 20 mg once weekly in patients with established cardiovascular disease and a screening lipoprotein(a) concentration of at least 60 mg per deciliter (approximately 150 nmol per liter).²² A pelacarsen dose of 80 mg once monthly is now being evaluated in a phase 3 trial (ClinicalTrials

.gov number, NCT04023552) involving patients with elevated lipoprotein(a) concentrations and a history of cardiovascular disease. Aside from olpasiran, another siRNA that interferes with lipoprotein(a) production is in clinical development (SLN-360) and has been evaluated in a phase 1 trial.²³ The reductions in the concentrations of LDL cholesterol and apolipoprotein B that have been noted with these two lipoprotein(a)-lowering therapies are similar to those that have been observed with olpasiran.

A limitation of our trial is that the treatment period was limited to 48 weeks, which included 12 weeks of safety follow-up after the last administered dose. Although an extended safety follow-up phase was implemented as part of the current trial, a larger and longer trial is necessary for the evaluation of the long-term efficacy and safety of olpasiran. In addition, all the patients in the trial had an elevated lipoprotein(a) concentration at baseline; it remains unknown whether similar pharmacodynamic effects of olpasiran therapy would be observed in patients with lower baseline concentrations. Furthermore, approximately 2% of the patients identified as being Hispanic or Latino. Greater representation of Black and Hispanic or Latino patients will be important in future randomized trials, because higher concentrations of lipoprotein(a) have been described in these persons.¹⁹

In this trial, the siRNA olpasiran led to a profound and sustained reduction in the lipoprotein(a) concentration when administered every 12 weeks. In the context of this short-term trial of moderate size, the drug appeared to be safe. These findings provide the foundation for a large-scale evaluation that will be necessary to confirm a causal role for lipoprotein(a) in atherosclerotic cardiovascular disease.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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