ORIGINAL ARTICLE

Zodasiran, an RNAi Therapeutic Targeting ANGPTL3, for Mixed Hyperlipidemia

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ABSTRACT

BACKGROUND

Angiopoietin-like 3 (ANGPTL3) inhibits lipoprotein and endothelial lipases and hepatic uptake of triglyceride-rich lipoprotein remnants. *ANGPTL3* loss-of-function carriers have lower levels of triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and non-HDL cholesterol and a lower risk of atherosclerotic cardiovascular disease than noncarriers. Zodasiran is an RNA interference (RNAi) therapy targeting expression of *ANGPTL3* in the liver.

METHODS

We conducted a double-blind, placebo-controlled, dose-ranging phase 2b trial to evaluate the safety and efficacy of zodasiran in adults with mixed hyperlipidemia (fasting triglyceride level of 150 to 499 mg per deciliter and either an LDL cholesterol level of ≥70 mg per deciliter or a non-HDL cholesterol level of ≥100 mg per deciliter). Eligible patients were randomly assigned in a 3:1 ratio to receive subcutaneous injections of zodasiran (50, 100, or 200 mg) or placebo on day 1 and week 12 and were followed through week 36. The primary end point was the percent change in the triglyceride level from baseline to week 24.

RESULTS

A total of 204 patients underwent randomization. At week 24, substantial mean dose-dependent decreases from baseline in ANGPTL3 levels were observed with zodasiran (difference in change vs. placebo, –54 percentage points with 50 mg, –70 percentage points with 100 mg, and –74 percentage points with 200 mg), and significant dose-dependent decreases in triglyceride levels were observed (difference in change vs. placebo, –51 percentage points, –57 percentage points, and –63 percentage points, respectively) (P<0.001 for all comparisons). Other differences in change from baseline as compared with placebo included the following: for non-HDL cholesterol level, –29 percentage points with 50 mg, –29 percentage points with 100 mg, and –36 percentage points with 200 mg; for apolipoprotein B level, –19 percentage points, –15 percentage points, and –22 percentage points, respectively; and for LDL cholesterol level, –16 percentage points, –14 percentage points, and –20 percentage points, respectively. We observed a transient elevation in glycated hemoglobin levels in patients with preexisting diabetes who received the highest dose of zodasiran.

CONCLUSIONS

In patients with mixed hyperlipidemia, zodasiran was associated with significant decreases in triglyceride levels at 24 weeks. (Funded by Arrowhead Pharmaceuticals; ARCHES-2 ClinicalTrials.gov number, NCT04832971.)

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Mixed hyperlipidemia is characterized by elevated plasma levels of low-density and triglyceride-rich lipoproteins. Elevated plasma triglyceride levels reflect the total levels of triglyceride-rich lipoproteins, including chylomicrons, very-low-density lipoproteins (VLDLs), and their respective remnants[1]; remnants contain up to four times as much cholesterol per particle as low-density lipoprotein (LDL).[2,3] Cholesterol that is carried in remnants (i.e., triglyceride-rich lipoprotein cholesterol) penetrates the arterial subendothelial space and binds to proteoglycans, initiating cholesterol deposition and foam-cell formation, with progression of atherosclerotic cardiovascular disease (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[4,5]

Despite the effectiveness of LDL cholesterol–lowering therapies, there remains residual risk of atherosclerotic cardiovascular disease associated with elevated levels of remnant cholesterol.[2,6] Multiple observational studies have shown an association between elevated levels of remnant cholesterol and an increased risk of atherosclerotic cardiovascular disease.[2,3] Support for the causal role of remnant cholesterol in atherosclerotic cardiovascular disease has emerged in genetic and mendelian randomization studies.[2,7-9] However, triglyceride-targeted therapies have failed to reduce atherosclerotic cardiovascular disease events in patients who receive statins.[9]

Angiopoietin-like 3 (ANGPTL3) regulates lipid and lipoprotein metabolism, including the metabolism of triglycerides and non–high-density lipoprotein (HDL) cholesterol, through reversible inhibition of lipoprotein lipase, endothelial lipase, and LDL receptor–independent hepatic lipoprotein uptake.[10-20] *ANGPTL3* loss-of-function variants lead to enhanced lipoprotein lipase and endothelial lipase activity, resulting in lower levels of most plasma lipoproteins, including triglyceride-rich lipoproteins (e.g, chlyomicrons, remnants, VLDL, and intermediate-density lipoprotein), LDL, HDL, lipoprotein(a), and their cholesterol content. Moreover, persons who are heterozygous for *ANGPTL3* loss-of-function variants with reduced levels of triglyceride-rich lipoproteins and LDL cholesterol have an approximately 40% lower risk of atherosclerotic cardiovascular disease events than noncarriers and have no known adverse clinical phenotypes.[10,21] Because *ANGPTL3* is hepatically expressed, its messenger RNA (mRNA) is an appropriate target for gene-silencing therapies. Small interfering RNAs (siRNAs) have high specificity, potent activity, and reversibility; are generally safe; and can effect durable gene silencing with infrequent dose administration. Zodasiran (ARO-ANG3) is an siRNA molecule that disrupts expression of *ANGPTL3* by degrading its mRNA and thereby inhibiting the hepatic synthesis and secretion of ANGPTL3. On the basis of the findings of a phase 1 study,[19] we carried out a phase 2b trial (ARCHES-2) to evaluate the efficacy and safety of different doses of zodasiran in adults with mixed hyperlipidemia.

Methods

Trial Oversight

The ARCHES-2 trial was conducted at 25 sites across four countries from June 28, 2021, to August 31, 2022, in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. The sponsor, Arrowhead Pharmaceuticals, funded the trial, designed the trial protocol, and selected the trial sites. The sponsor was responsible for the design and conduct of the trial; the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication. The trial protocol (available at NEJM.org) and amendments were approved by institutional review boards or ethics committees at individual sites. The first author and last two authors had full access to all the data in the trial and vouch for the completeness and accuracy of the data and, along with the sponsor, for the fidelity of the trial to the protocol. All the patients provided written informed consent before trial initiation.

Trial Design and Patients

This phase 2b, double-blind, randomized, placebo-controlled clinical trial tested zodasiran in the treatment of adult patients with mixed hyperlipidemia, defined as a fasting triglyceride level of 150 to 499 mg per deciliter (1.69 to 5.63 mmol per liter) and either an LDL cholesterol level of at least 70 mg per deciliter (1.81 mmol per liter) or a non-HDL cholesterol level of at least 100 mg per deciliter (2.59 mmol per liter). Patients had been

following a stable diet for at least 2 weeks, receiving a stable statin regimen (unless they were unable to take statins owing to unacceptable side effects) for at least 4 weeks, and receiving stable background medications (Tables S1 and S2). To reduce unplanned interventions during the trial, investigators were instructed to limit changes to baseline medications. Eligible patients were randomly assigned in a 3:1 ratio with the use of a block randomization algorithm to receive one of three doses of zodasiran (50, 100, or 200 mg) or placebo, with all groups enrolled in parallel. Investigational products were administered according to the randomized sequence generated by an interactive Web-response system. During the double-blind treatment period, each patient received (volume-matched) subcutaneous injections on day 1 and at week 12 and was followed through week 36 (Fig. S2).

END POINTS

The primary end point was the percent change from baseline to week 24 in fasting plasma triglyceride levels, representing the trough effect with quarterly dose administration. We calculated the difference in means between each zodisiran group and the placebo group. Secondary end points included the percent change in fasting triglyceride levels through week 36 and the percent change from baseline to week 24 and through week 36 in levels of fasting non-HDL cholesterol, apolipoprotein B, LDL cholesterol, ANGPTL3, and HDL cholesterol. Safety end points included the incidence and severity of adverse events that emerged or worsened after the first administration of zodasiran or placebo. Exploratory efficacy end points included the change from baseline over time in fasting levels of remnant cholesterol and lipoprotein(a). Remnant cholesterol was calculated as total cholesterol minus HDL cholesterol and LDL cholesterol (ultracentrifugation). Exploratory safety end points included the change from baseline to week 24 in liver fat content as measured by the magnetic resonance imaging protein density fat fraction (MRI-PDFF) in a subgroup of patients with liver steatosis (MRI-PDFF ≥8%) at baseline and the emergence of anti-zodasiran antibodies.

STATISTICAL ANALYSIS

An analysis of covariance (ANCOVA) model with repeated-measures approaches was used for statistical modeling. With an assumption of a 35 to 60% reduction in fasting triglyceride levels with zodasiran and none with placebo and 180 randomly assigned patients, we estimated that the trial would have more than 98% power to detect a significant difference between at least one zodasiran dose group and the placebo group and more than 95% power to detect significant differences between all zodasiran dose groups and the placebo group, using a two-sided test with a 5% level of significance, with adjustment for multiple testing. The primary analysis used the mean of two triglyceride values, when available, obtained during week 24. The ANCOVA with repeated-measures model is likelihood based, and missing observations are assumed to be missing at random. Holm's step-down procedure was used for control of multiplicity. (Table S3 shows the P values and significance thresholds for the test procedure.) Although the significance tests are adjusted for multiplicity, the 95% confidence intervals corresponding to between-group differences are not and therefore should not be used to infer treatment effect. The ANCOVA model was used in a subgroup of patients who completed the week 24 assessment of liver fat content with the use of the MRI-PDFF. The ANCOVA model includes covariates for trial group, randomization stratification factor, and baseline value (Table S4). Safety analyses were performed on data from all randomly assigned patients who received at least one dose of zodasiran or placebo; patients were classified according to the dose received if that differed from the assigned dose. Efficacy analyses were performed on data from all randomly assigned patients who received at least one dose of zodasiran or placebo; patients were classified according to the assigned dose. Missing values were not imputed except for missing or partial dates with respect to adverse events, concomitant medications, and procedures and when a complete date was required for calculations.

RESULTS

PATIENTS

Of 204 adults with mixed hyperlipidemia who underwent randomization, 191 (94%) completed the double-blind treatment period (Fig. S3). The baseline characteristics of the patients were generally balanced across the trial groups, with the exception of ANGPTL3 levels, which appeared to

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=51)	Zodasiran, 50 mg (N=51)	Zodasiran, 100 mg (N=51)	Zodasiran, 200 mg (N=51)
Age — yr	60.2±11.3	60.4±12.7	60.0±9.9	61.5±12.5
Sex — no. (%)				
Female	24 (47)	25 (49)	22 (43)	24 (47)
Male	27 (53)	26 (51)	29 (57)	27 (53)
White race — no. (%)†	48 (94)	49 (96)	49 (96)	49 (96)
Body-mass index	33.0±6.8	33.3±4.7	32.5±5.5	31.6±5.5
ANGPTL3 — μg/liter	93.2±29.0	98.6±35.7	93.2±27.4	101.2±36.2
Triglycerides — mg/dl				
Mean	235.2±86.1	242.5±79.9	246.7±98.0	260.0±93.3
Median (IQR)	219.9 (181.2–266.8)	223.3 (178.6–303.3)	228.4 (190.5–265.4)	234.1 (183.5–329.1)
Remnant cholesterol — mg/dl‡	44.9±34.3	48.5±19.2	48.6±31.4	51.2±27.5
Non-HDL cholesterol — mg/dl	138.6±41.6	151.3±36.2	149.8±47.2	143.3±39.6
Apolipoprotein B — mg/dl	95.6±24.4	105.0±24.1	100.1±25.8	94.1±25.0
HDL cholesterol — mg/dl	41.6±11.9	43.1±13.2	39.8±10.5	42.3±13.6
LDL cholesterol — mg/dl	93.7±31.2	102.8±29.4	101.2±45.3	92.1±34.1
Lipid-lowering therapy — no. (%)				
Any statin	46 (90)	50 (98)	50 (98)	50 (98)
High-intensity statin	22 (43)	17 (33)	23 (45)	14 (27)
Fibrate	9 (18)	13 (25)	11 (22)	10 (20)
N–3 fatty acids	3 (6)	3 (6)	4 (8)	2 (4)
Icosapent ethyl	2 (4)	3 (6)	3 (6)	0
PCSK9 inhibitor	0	0	0	2 (4)
GLP-1 receptor agonist — no. (%)	3 (6)	2 (4)	3 (6)	4 (8)
Type 2 diabetes — no. (%)	20 (39)	19 (37)	22 (43)	25 (49)
10-Yr risk of coronary heart disease >20% — no. (%)	5 (10)	6 (12)	8 (16)	9 (18)
Tobacco use — no. (%)	10 (20)	6 (12)	16 (31)	9 (18)
Chronic kidney disease — no. (%)	4 (8)	5 (10)	2 (4)	6 (12)

* Plus–minus values are means ±SD. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. ANGPTL3 denotes angiopoietin-like 3, GLP-1 glucagon-like peptide 1, HDL high-density lipoprotein, IQR interquartile range, LDL low-density lipoprotein, and PCSK9 proprotein convertase subtilisin–kexin type 9.
† Race was reported by the patient.
‡ Remnant cholesterol was calculated as total cholesterol minus HDL cholesterol and LDL cholesterol.

be higher in patients assigned to the zodasiran 200-mg group (Table 1). The mean age of the patients was 61 years, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 33. A total of 20% of the patients were smokers, 8% had chronic kidney disease, and 14% had a 10-year risk of coronary heart disease of more than 20%. The mean triglyceride level was 246 mg per deciliter (2.78 mmol per liter); the mean remnant cholesterol and non-HDL cholesterol levels were 48 mg per deciliter (1.24 mmol per liter) and 146 mg per deciliter (3.78 mmol per liter), respectively; the mean LDL cholesterol level was 97 mg per deciliter (2.51 mmol per liter); and 20% of the patients had LDL cholesterol levels of less

than 70 mg per deciliter. Nearly all the patients (96%) were receiving statin therapy (37% high-intensity), 1% were receiving inhibitors of proprotein convertase subtilisin–kexin type 9, and 21% were receiving fibrates. A total of 42% of the patients had type 2 diabetes, and 6% were receiving glucagon-like peptide-1 receptor agonists. The representativeness of the trial population is shown in Table S5.

EFFICACY ANALYSES AT WEEK 24 AND WEEK 36

At week 24, zodasiran treatment was associated with significant and dose-dependent least-squares mean differences in triglyceride levels as compared with placebo. The difference in change from baseline as compared with placebo was −51 percentage points (95% confidence interval [CI], −62 to −41) with 50 mg, −57 percentage points (95% CI, −67 to −46) with 100 mg, and −63 percentage points (95% CI, −74 to −53) with 200 mg ($P<0.001$ for all comparisons). Differences were maintained at 36 weeks, at which point the difference in change as compared with placebo was −34 percentage points (95% CI, −45 to −24), −38 percentage points (95% CI, −49 to −27), and −51 percentage points (95% CI, −62 to −41), respectively (Table 2, Fig. 1, Fig. S4, and Table S6). We also observed commensurate dose-dependent reductions in mean ANGPTL3 levels (difference in change vs. placebo, −54 percentage points [95% CI, −62 to −46] with 50 mg, −70 percentage points [95% CI, −78 to −62] with 100 mg, and −74 percentage points [95% CI, −81 to −66] with 200 mg), which were strongly correlated with triglyceride levels (Pearson correlation coefficient, 0.69) (Fig. S5, nonprespecified exploratory analysis). Dose-dependent reductions in mean ANGPTL3 levels seemed to be maintained to the end of the trial (36 weeks; i.e., 24 weeks since the last dose), with a difference in change as compared with placebo of −45 percentage points (95% CI, −54 to −37), −57 percentage points (95% CI, −66 to −48), and −64 percentage points (95% CI, −72 to −55), respectively.

As with ANGPTL3 levels, changes in remnant cholesterol levels seemed to parallel changes in triglyceride levels. The mean relative change from baseline to week 24 in the remnant cholesterol level (exploratory end point) was −32.2 mg per deciliter (−0.83 mmol per liter) in the zodasiran 200-mg group and 2.2 mg per deciliter (0.06 mmol per liter) in the placebo group (difference in change, −34.4 mg per deciliter [−0.89 mmol per liter]). The absolute difference in change from baseline in mean remnant cholesterol levels with zodasiran as compared with placebo was −73 percentage points (95% CI, −94 to −51) with 50 mg, −76 percentage points (95% CI, −98 to −54) with 100 mg, and −82 percentage points (95% CI, −103 to −61) with 200 mg at 24 weeks and −43 percentage points (95% CI, −58 to −28), −45 percentage points (95% CI, −60 to −30), and −58 percentage points (95% CI, −73 to −43), respectively, at 36 weeks (Table 2). The extent of change in remnant cholesterol levels was correlated with the extent of change in triglyceride levels (Pearson correlation coefficient, 0.87) (Table S7 and Fig. S6, nonprespecified exploratory analysis).

We also observed changes in levels of other atherogenic lipoproteins (Table 2). Reductions in LDL cholesterol levels at 24 weeks were observed across all three doses of zodasiran (difference in change with 200-mg dose vs. placebo, −20 percentage points; 95% CI, −31 to −9), with parallel reductions in apolipoprotein B levels across doses (difference in change with 200-mg dose vs. placebo, −22 percentage points [95% CI, −30 to −14] at 24 weeks and −11 percentage points [95% CI, −19 to −3] at 36 weeks). Although reductions in LDL cholesterol levels were seen at all three doses, the effects were slightly attenuated at higher tertiles of baseline triglyceride levels, findings consistent with previous published results and rapid triglyceride hydrolysis that occurs at higher baseline levels. Similarly, non-HDL cholesterol levels decreased (difference in change with 200-mg dose vs. placebo, −36 percentage points [95% CI, −46 to −27] at 24 weeks and −23 percentage points [95% CI, −31 to −14] at 36 weeks). For HDL cholesterol levels, the greatest reductions were observed with the 200-mg dose at 24 weeks (difference in change vs. placebo, −25 percentage points; 95% CI, −33 to −17) and with the 100-mg dose at 36 weeks (difference in change vs. placebo, −20 percentage points; 95% CI, −28 to −12); for lipoprotein(a) levels (exploratory end point), the difference in change at 24 weeks with the 100-mg dose as compared with placebo was −20 percentage points (95% CI, −35 to −5). At 24 weeks, there were positive correlations between the extent of change in ANGPTL3 levels and the extent of change in non-HDL cholesterol levels (Pearson correlation coefficient, 0.61), between change in ANGPTL3 levels and change in remnant choles-

Table 2. Changes in Plasma Levels of ANGPTL3, Lipids, Apolipoprotein B, and Lipoprotein(a).*

End Point	Placebo (N=51)	Zodasiran, 50 mg (N=51)	Zodasiran, 100 mg (N=51)	Zodasiran, 200 mg (N=51)
Primary end point				
Triglycerides				
Mean at baseline — mg/dl	235.2±86.1	242.5±79.9	246.7±98.0	260.0±93.3
Least-squares mean difference in change vs. placebo at wk 24 (95% CI) — percentage points	—	−51.2 (−61.7 to −40.7)†	−56.6 (−67.1 to −46.0)†	−63.1 (−73.6 to −52.7)†
Least-squares mean difference in change vs. placebo at wk 36 (95% CI) — percentage points	—	−34.1 (−44.7 to −23.5)	−37.9 (−48.6 to −27.3)	−51.2 (−61.7 to −40.7)
Secondary end points				
ANGPTL3				
Mean at baseline — μg/liter	93.2±29.0	98.6±35.7	93.2±27.4	101.2±36.2
Least-squares mean difference in change vs. placebo at wk 24 (95% CI) — percentage points	—	−54.3 (−62.1 to −46.4)	−69.8 (−77.6 to −62.0)	−73.7 (−81.4 to −65.9)
Least-squares mean difference in change vs. placebo at wk 36 (95% CI) — percentage points	—	−45.4 (−54.2 to −36.7)	−57.2 (−65.9 to −48.4)	−63.6 (−72.2 to −55.0)
LDL cholesterol‡				
Mean at baseline — mg/dl	93.7±31.2	102.8±29.4	102.8±44.2	92.1±34.1
Least-squares mean difference in change vs. placebo at wk 24 (95% CI) — percentage points	—	−15.8 (−27.0 to −4.5)	−13.6 (−24.9 to −2.3)	−19.9 (−31.0 to −8.8)
Least-squares mean difference in change vs. placebo at wk 36 (95% CI) — percentage points	—	−12.0 (−23.9 to −0.1)	−7.0 (−19.0 to 5.0)	−7.3 (−19.0 to 4.5)
Non-HDL cholesterol				
Mean at baseline — mg/dl	138.6±41.6	151.3±36.2	149.8±47.2	143.3±39.6
Least-squares mean difference in change vs. placebo at wk 24 (95% CI) — percentage points	—	−29.2 (−38.5 to −20.0)	−28.7 (−37.9 to −19.5)	−36.4 (−45.5 to −27.2)
Least-squares mean difference in change vs. placebo at wk 36 (95% CI) — percentage points	—	−18.6 (−27.6 to −9.7)	−15.8 (−24.7 to −6.8)	−22.6 (−31.4 to −13.8)
Apolipoprotein B				
Mean at baseline — mg/dl	95.6±24.4	105.0±24.1	100.1±25.8	94.1±25.0
Least-squares mean difference in change vs. placebo at wk 24 (95% CI) — percentage points	—	−18.7 (−26.5 to −10.8)	−15.2 (−23.0 to −7.4)	−21.9 (−29.7 to −14.1)
Least-squares mean difference in change vs. placebo at wk 36 (95% CI) — percentage points	—	−10.6 (−18.3 to −2.8)	−6.8 (−14.5 to 1.0)	−10.9 (−18.6 to −3.2)
HDL cholesterol				
Mean at baseline — mg/dl	41.6±11.9	43.1±13.2	39.8±10.5	42.3±13.6
Least-squares mean difference in change vs. placebo at wk 24 (95% CI) — percentage points	—	−12.0 (−20.2 to −3.9)	−21.6 (−29.8 to −13.4)	−24.5 (−32.6 to −16.5)
Least-squares mean difference in change vs. placebo at wk 36 (95% CI) — percentage points	—	−7.8 (−15.6 to 0.0)	−20.1 (−27.9 to −12.2)	−15.8 (−23.5 to −8.1)
Exploratory end points				
Remnant cholesterol				
Mean at baseline — mg/dl	44.9±34.3	48.5±19.2	48.6±31.4	51.2±27.5
Least-squares mean difference in change vs. placebo at wk 24 (95% CI) — percentage points	—	−72.6 (−94.2 to −51.0)	−75.9 (−97.5 to −54.3)	−82.0 (−103.4 to −60.6)
Least-squares mean difference in change vs. placebo at wk 36 (95% CI) — percentage points	—	−42.7 (−57.6 to −27.7)	−44.7 (−59.7 to −29.7)	−58.0 (−72.8 to −43.2)

Table 2. (Continued.)

End Point	Placebo (N=51)	Zodasiran, 50 mg (N=51)	Zodasiran, 100 mg (N=51)	Zodasiran, 200 mg (N=51)
Lipoprotein(a)				
Mean at baseline — nmol/liter	97.0±187.3	64.0±111.0	91.3±118.8	63.3±95.5
Least-squares mean difference in change vs. placebo at wk 24 (95% CI) — percentage points	—	−7.3 (−22.3 to 7.6)	−20.0 (−34.9 to −5.2)	−17.1 (−31.9 to −2.3)
Least-squares mean difference in change vs. placebo at wk 36 (95% CI) — percentage points	—	−3.3 (−20.4 to 13.7)	−12.2 (−29.2 to 4.8)	−6.0 (−22.8 to 10.9)

* Plus–minus values are means ±SD. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.
† P<0.001.
‡ One patient in the zodasiran 100-mg group with an LDL cholesterol level of 17 mg per deciliter (0.44 mmol per liter) at baseline was removed from the analysis.

terol levels (Pearson correlation coefficient, 0.52), and between change in ANGPTL3 levels and change in LDL cholesterol levels (Pearson correlation coefficient, 0.40).

At week 24, normalization of fasting triglyceride levels (<150 mg per deciliter) was achieved in 43 of 49 patients (88%) receiving the 200-mg dose of zodasiran (Fig. 2). With respect to high-sensitivity C-reactive protein levels, no substantial differences were observed between any zodasiran dose group and the placebo group at week 24 or week 36 (Fig. S7).

SAFETY

Overall adverse events and adverse events that were considered by the investigator to be related to zodasiran or placebo were generally balanced between the zodasiran dose groups and the placebo group, with only two patients discontinuing the trial regimen because of adverse events (one patient in the placebo group and one in the 100-mg zodasiran group). All serious adverse events in the zodasiran groups resolved; one fatal serious adverse event occurred in the placebo group (Table 3).

There were no liver-related adverse events. In a subgroup of patients who had liver steatosis (MRI-PDFF ≥8%) at baseline and underwent MRI of the liver at week 24, dose-dependent changes in liver fat content were observed, reaching −28% with the 200-mg dose, as compared with −2% with placebo. In general, there were no substantial differences at baseline in levels of lipids or lipoproteins between patients who had liver steatosis at baseline and those who did not. However, in the zodasiran 200-mg group, the prevalence of diabetes at baseline was higher among patients who had liver steatosis at baseline than among those who did not (73% vs. 47%) (Table S8). There were no clinically meaningful differences among groups in laboratory safety evaluations, including with respect to levels of alanine aminotransferase and aspartate aminotransferase and the platelet count (Table 3).

Increases in glycated hemoglobin levels were seen primarily in patients with preexisting diabetes, with a mean (±SD) change from baseline to week 24 of 0.38±0.66% with the 200-mg zodasiran dose and −0.03±0.88% with placebo, whereas the mean change from baseline to week 24 in patients without diabetes was 0.12±0.19% with the 200-mg dose and −0.03±0.19% with placebo. Worsened glycemic control was reported more frequently in the 200-mg zodasiran group (Table 3).

There was no change in the homeostasis model assessment of insulin resistance for any dose of zodasiran or placebo (Table 3 and Fig. S8). These findings indicate that insulin sensitivity had not changed.

We assessed the effects of zodasiran and placebo in patients meeting American Diabetes Association criteria at trial entry for normoglycemia (glycated hemoglobin level, <5.7%), prediabetes (glycated hemoglobin level, 5.7 to <6.5%), and diabetes (glycated hemoglobin level, ≥6.5%). Results for mean glycated hemoglobin levels over time are shown in Table 3; the numbers of patients who had glycated hemoglobin levels in the diabetic range and who had new antidiabetic drugs added

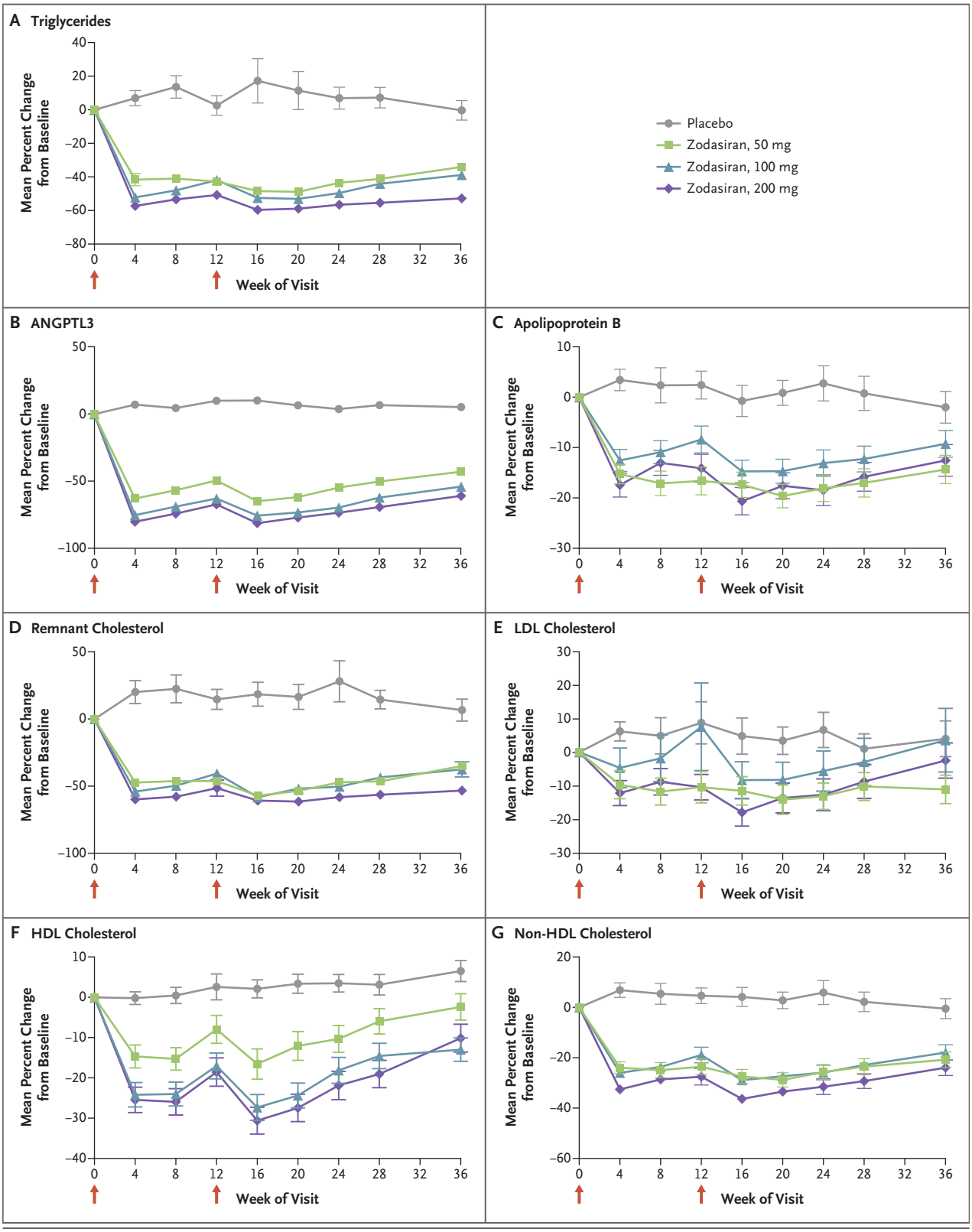
A Triglycerides
Mean Percent Change from Baseline
40
20
0
−20
−40
−60
−80
0 4 8 12 16 20 24 28 32 36
Week of Visit
Placebo
Zodasiran, 50 mg
Zodasiran, 100 mg
Zodasiran, 200 mg
B ANGPTL3
Mean Percent Change from Baseline
50
0
−50
−100
0 4 8 12 16 20 24 28 32 36
Week of Visit
C Apolipoprotein B
Mean Percent Change from Baseline
10
0
−10
−20
−30
0 4 8 12 16 20 24 28 32 36
Week of Visit
D Remnant Cholesterol
Mean Percent Change from Baseline
50
0
−50
−100
0 4 8 12 16 20 24 28 32 36
Week of Visit
E LDL Cholesterol
Mean Percent Change from Baseline
30
20
10
0
−10
−20
−30
0 4 8 12 16 20 24 28 32 36
Week of Visit
F HDL Cholesterol
Mean Percent Change from Baseline
10
0
−10
−20
−30
−40
0 4 8 12 16 20 24 28 32 36
Week of Visit
G Non-HDL Cholesterol
Mean Percent Change from Baseline
20
0
−20
−40
−60
0 4 8 12 16 20 24 28 32 36
Week of Visit

Figure 1 (facing page). Change from Baseline in Laboratory Measures.

The red arrows at week 0 (day 1) and week 12 indicate administration of zodasiran or placebo. Remnant cholesterol (exploratory end point) was calculated as total cholesterol minus HDL cholesterol and LDL cholesterol. I bars indicate the standard error of the mean. ANGPTL3 denotes angiopoietin-like 3, HDL high-density lipoprotein, and LDL low-density lipoprotein.

to their regimen are provided in Table S9, and data on the level of variability in glycated hemoglobin in patients with diabetes as compared with those without diabetes at baseline are provided in Figure S9. Glycated hemoglobin levels showed variability across zodasiran dose groups, but with respect to reported adverse events involving worsened diabetic control, excursions of glycated hemoglobin levels into the diabetic range, or the addition of new antidiabetes therapies, the findings seemed similar in the placebo group, 50-mg group, and 100-mg group irrespective of baseline glycemic status. The 200-mg dose was associated with more adverse events related to glycemic control, excursions into the diabetic range, and use of additional therapies (Table 3). Patients with diabetes at baseline generally showed more variability at baseline and during therapy.

A higher incidence of urinary tract infections (UTIs) was observed in the 200-mg dose group (12%, vs. 4% in the placebo group, 6% in the 50-mg group, and 6% in the 100-mg group), and all cases of UTIs across cohorts occurred in patients with a history of diabetes at baseline. These events were not related to the development of new diabetes. Some of the UTIs were reported before the administration of zodasiran or placebo, so the causal relationship is unclear — infections, including UTIs, can exacerbate glycemic control, and poorly controlled diabetes can, in turn, predispose patients to infection (Table 3 and Table S10).

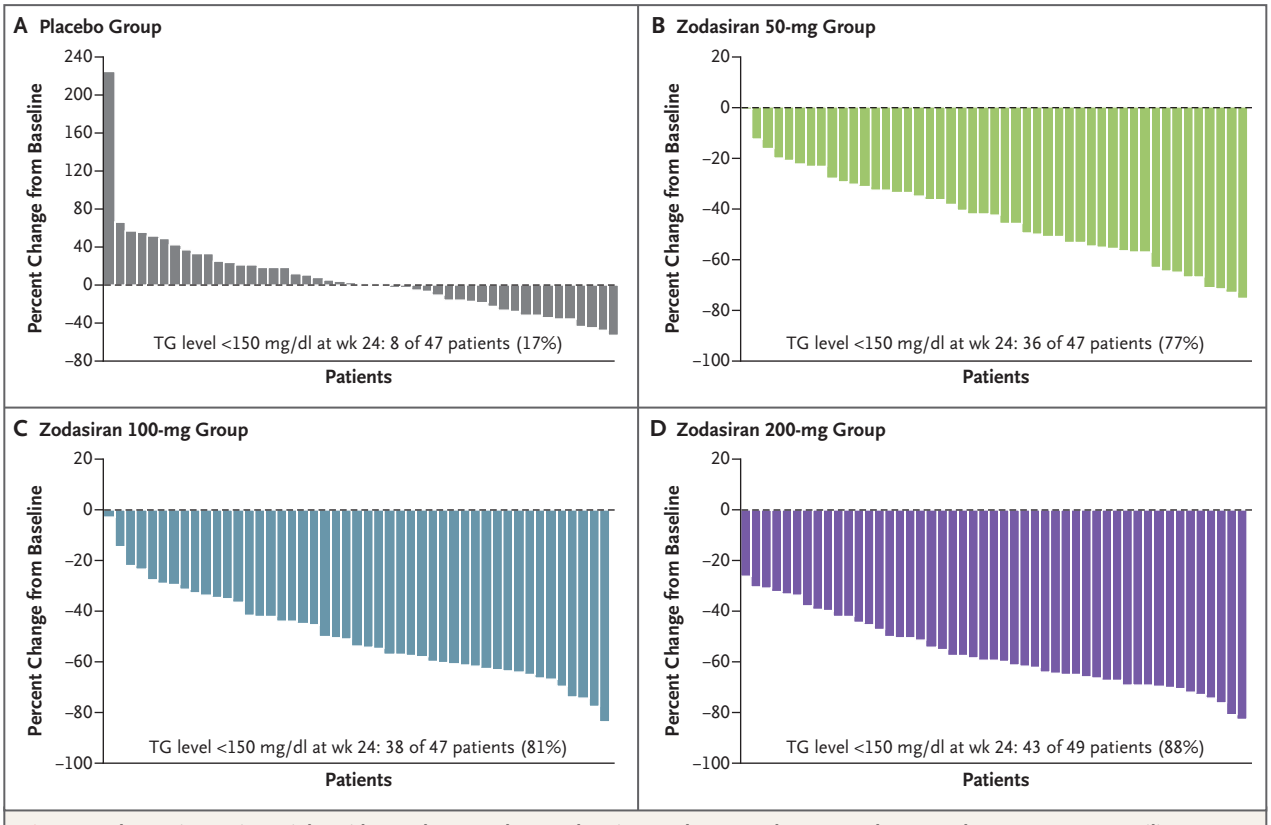

Figure 2. Change in Fasting Triglyceride Levels at Week 24 and Patients Whose Level Decreased to Less than 150 mg per Deciliter.

Each bar represents an individual patient. TG denotes triglyceride.

Table 3. Safety Results.*

Variable	Placebo (N=51)	Zodasiran, 50 mg (N=50)	Zodasiran, 100 mg (N=51)	Zodasiran, 200 mg (N=52)
Any adverse event — no. (%)	34 (67)	40 (80)	33 (65)	42 (81)
Adverse events affecting ≥10% of the patients in any group — no. (%)				
Covid-19	9 (18)	10 (20)	12 (24)	11 (21)
Upper respiratory tract infection	4 (8)	5 (10)	1 (2)	5 (10)
Headache	2 (4)	5 (10)	2 (4)	7 (13)
Urinary tract infection	2 (4)	3 (6)	3 (6)	6 (12)
Diabetes	2 (4)	2 (4)	2 (4)	7 (13)
Injection-site pain	0	5 (10)	4 (8)	2 (4)
Back pain	0	3 (6)	2 (4)	6 (12)
Adverse event considered by the investigator to be related to zodasiran or placebo — no. (%)	9 (18)	13 (26)	9 (18)	13 (25)
Serious adverse event — no. (%)	4 (8)	5 (10)	0	1 (2)
Adverse event leading to interruption or discontinuation of zodasiran or placebo or to withdrawal from the trial — no. (%)	1 (2)	0	1 (2)	0
Local injection-site reaction — no. (%)	1 (2)	0	3 (6)	2 (4)
Adverse event associated with death — no. (%)	1 (2)	0	0	0
Glycated hemoglobin — %				
All patients				
Mean at baseline	6.5±1.2	6.2±1.0	6.4±1.1	6.6±1.2
Mean at wk 24	6.4±1.0	6.4±1.0	6.4±1.1	6.8±1.4
Mean at wk 36	6.6±1.3	6.2±1.0	6.4±1.1	6.8±1.3
Patients without diabetes at baseline				
Mean at baseline	5.7±0.3	5.6±0.7	5.6±0.3	5.6±0.4
Mean at wk 24	5.7±0.3	5.8±0.6	5.6±0.3	5.7±0.4
Mean at wk 36	5.8±0.3	5.7±0.6	5.6±0.4	5.8±0.4
Patients with diabetes at baseline†				
Mean at baseline	7.3±1.2	6.8±1.0	7.2±1.0	7.4±1.0
Mean at wk 24	7.2±1.0	7.0±1.0	7.4±1.0	7.7±1.3
Mean at wk 36	7.4±1.3	6.8±1.0	7.3±0.7	7.6±1.2
Alanine aminotransferase — U/liter				
Mean at baseline	23.0±10.6	27.0±16.5	25.3±12.7	22.8±9.1
Mean change from baseline at wk 24	0.4±9.8	2.5±8.6	0.8±8.5	2.3±8.6
Mean change from baseline at wk 36	1.2±9.9	2.0±13.1	−0.6±8.5	0.4±9.1
Aspartate aminotransferase — U/liter				
Mean at baseline	19.6±6.7	21.4±9.0	19.4±7.9	19.7±7.6
Mean change from baseline at wk 24	1.0±7.7	1.9±5.5	−0.2±6.0	0.3±6.0
Mean change from baseline at wk 36	0.9±6.9	1.9±6.7	0.0±6.2	0.2±9.6
Platelet count — $\times 10^{-9}$/liter				
Mean at baseline	246.4±58.5	238.0±63.6	252.2±49.4	239.0±73.8
Mean change from baseline at wk 24	11.1±40.3	18.0±31.8	4.6±34.8	10.7±41.4
Mean change from baseline at wk 36	3.3±38.7	4.2±39.0	1.9±26.2	11.2±43.7

Table 3. (Continued.)

Variable	Placebo (N=51)	Zodasiran, 50 mg (N=50)	Zodasiran, 100 mg (N=51)	Zodasiran, 200 mg (N=52)
Liver fat content as measured by MRI-PDFF‡				
No. of patients evaluated	16	15	15	15
Mean at baseline — %	15.9±9.2	17.5±5.3	19.8±9.3	14.7±4.6
Least-squares mean change at wk 24 — %§	–1.6±9.5	–11.9±9.5	–17.9±9.6	–28.4±9.2
Least-squares mean difference in change vs. placebo (95% CI) — percentage points	—	–10.3 (–36.7 to 16.1)	–16.4 (–43.5 to 10.8)	–26.9 (–53.1 to –0.7)

* Plus–minus values are means ±SD unless otherwise noted. The adverse events shown are those that emerged or worsened after the first administration of zodasiran or placebo. One patient who was assigned to the 50-mg zodasiran group incorrectly received 200 mg of zodasiran on day 1 and at week 12; this patient was included in the 200-mg group for the safety analyses. Covid-19 denotes coronavirus disease 2019.
† Patients were considered to have diabetes if they had a glycated hemoglobin level of at least 6.5% or a fasting glucose level of at least 126 mg per deciliter (7.0 mmol per liter) or if they had a medical history of diabetes or were receiving diabetic medications at baseline.
‡ Shown are results among patients with hepatic steatosis (magnetic resonance imaging proton density fat fraction [MRI-PDFF] ≥8% at baseline). For between-group differences, the analysis of covariance model includes covariates for trial group, randomization stratification factor, and baseline value for liver fat.
§ Plus–minus values for this variable are means ±SE.

DISCUSSION

In this randomized clinical trial involving patients with mixed hyperlipidemia receiving statins, zodasiran reduced triglyceride levels, with commensurate changes in plasma levels of ANGPTL3 and remnant cholesterol. The reduction in remnant cholesterol levels was accompanied by lowering of levels of non-HDL cholesterol, LDL cholesterol, and apolipoprotein B. In the past several years, levels of non-HDL cholesterol and apolipoprotein B have been substantiated to be reliable predictors of the risk of coronary artery disease among patients receiving statins.[22,23] Historically, reductions in levels of both non-HDL cholesterol and apolipoprotein B, driven by decreases in LDL cholesterol levels, have translated into considerable clinical benefit. In contrast, among patients in our trial, almost all of whom were receiving statins, reductions in non-HDL cholesterol levels were due principally to large reductions in remnant cholesterol levels rather than reductions in LDL cholesterol levels.

With respect to the mean change from baseline to week 24 in the remnant cholesterol level, the difference between the highest dose of zodasiran and placebo was −34.4 mg per deciliter (−0.89 mmol per liter). On the basis of modeling from mendelian randomization studies, this reduction is predicted to translate into a 20% reduction in major adverse cardiac events.[6,7] Reductions across all lipid and lipoprotein end points with zodasiran were durable through 36 weeks, findings consistent with prolonged silencing of *ANGPTL3* mRNA and decreases in plasma ANGPTL3 levels. Of the patients who received the highest dose of zodasiran, 88% had triglyceride levels of less than 150 mg per deciliter at week 24.

An increase in glycated hemoglobin levels was observed in some patients with preexisting diabetes who received the highest dose of zodasiran: with treatment, glycated hemoglobin levels were similar to those at baseline by the end of the trial. Concern that the elevation in glycated hemoglobin levels is an on-target effect of zodasiran is mitigated by the findings that homozygotes with loss-of-function variants in *ANGPTL3* have increased insulin sensitivity[24] and that the incidence of diabetes is not increased among persons with chronically low levels of ANGPTL3.[25]

Whether dysglycemia with therapeutic inhibition of ANGPTL3 is related to alterations in the supply of free fatty acids to the liver remains unclear. Perhaps increased substrate delivery to the liver and a subsequent increase in hepatic gluconeogenesis due to enhanced metabolism of triglyceride-rich lipoproteins with zodasiran contributed to this observed effect.[24] This hypothesis would be consistent with rapid hydrolysis at higher tertiles of triglyceride levels, which appeared to attenuate the LDL cholesterol–lowering effects at the highest tertiles.[24] Dysglycemia has also been described with statins, and this diabetogenic effect appears to be accentuated by elevated tri-

glyceride levels; however, this effect can be clinically managed and is offset by the cardiovascular benefit of statins.[26,27] Mild dysglycemia with zodasiran can be readily managed with lifestyle changes, antiglycemic therapy, or both.

Unlike vupanorsen, an antisense oligonucleotide directed against *ANGPTL3* mRNA, zodasiran was not associated with an increase in liver fat content or increased levels of serum aminotransferases.[18,28] In addition, hepatic effects have not been observed with evinacumab,[17] which suggests that the toxicity of vupanorsen is not a class effect of ANGPTL3 inhibition. In fact, we observed an overall reduction in the MRI-PDFF in patients who received the highest dose of zodasiran. There were no substantial changes in mean platelet counts, findings consistent with those of previous reports that showed no concerns regarding thrombocytopenia, as has been reported with antisense oligonucleotides.

Also now reported in the *Journal* is the MUIR trial, which evaluated the effect of apolipoprotein C3 (APOC3) inhibition with another hepatically targeted siRNA, plozasiran.[29] APOC3 is a genetically validated regulator of triglyceride metabolism, and as with variation in *ANGPTL3*, variation in *APOC3* is associated with a risk of atherosclerotic cardiovascular disease in mendelian randomization studies. The MUIR trial showed reductions in levels of triglycerides and remnant cholesterol that were nearly equivalent to those observed in the ARCHES-2 trial, with additional pleiotropic HDL cholesterol–raising effects. Given their potent effects on triglyceride-rich lipoproteins and similar safety profiles, both zodasiran and plozasiran could potentially address the residual risk of atherosclerotic cardiovascular disease that persists among patients with mixed hyperlipidemia with elevated remnant cholesterol levels despite effective reductions in LDL cholesterol levels. In previous fibrate trials, the extent of triglyceride lowering was approximately 50% less than that observed in the ARCHES-2 trial. In the PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) trial of the selective perioxisome proliferator–activated receptor α modulator pemafibrate, triglyceride lowering did not lower the plasma level of atherogenic lipoproteins (non-HDL cholesterol and apolipoprotein B) and failed to reduce major adverse cardiovascular events.[30,31] The use of icosapent ethyl has been associated with a significantly reduced incidence of atherosclerotic cardiovascular disease events among high-risk patients with moderate hypertriglyceridemia (triglyceride level, ≥200 mg per deciliter [2.26 mmol per liter]),[32] but this clinical benefit appeared to be out of proportion to the triglyceride and non–HDL-cholesterol lowering observed, which was comparatively modest (and less than half of that in the present trial). The extent to which pleiotropic effects of icosapent ethyl and inhibitors of ANGPTL3 and APOC3 affect the risk of atherosclerotic cardiovascular disease is unclear.

The availability of two classes of agents — which act by ANGPTL3 inhibition and APOC3 inhibition through siRNA — that regulate triglyceride metabolism with near-equal triglyceride lowering permits the design of studies to determine whether large reductions in levels of triglyceride-rich lipoproteins will replicate the genetic data by reducing the risk of atherosclerotic cardiovascular disease. Other questions are whether the effects of zodasiran on levels of LDL cholesterol, remnant cholesterol, apolipoprotein B, and lipoprotein(a) will show additional benefit beyond that seen from triglyceride reduction alone and what effect, if any, will arise from the differences in HDL cholesterol levels produced by the two agents. To this end, the sponsor and investigators of this trial are planning a three-group cardiovascular outcomes trial comparing zodasiran (200 mg) and plozasiran (25 mg) with matching placebo.

A limitation of our trial pertains to the relatively short duration and administration of zodasiran at only two time points. Data from the ongoing 2-year open-label extension study will provide further information on longer-term safety and efficacy. Another limitation is that the patients were almost exclusively White, thus limiting the generalizability of our findings and warranting further trials involving persons of non-European ancestries.

In this trial involving patients with mixed hyperlipidemia, zodasiran use led to significant decreases in triglyceride levels at 24 weeks. It also led to robust and durable reductions in levels of triglyceride-rich lipoprotein remnants and total atherogenic lipoproteins, including LDL cholesterol, and phenocopied the effects of *ANGPTL3* loss-of-function mutations on levels of atherogenic lipoproteins. The overall safety and efficacy pro-

file of the 200-mg dose of zodasiran, administered quarterly, supports its use in further studies.

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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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