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*A list of the ORION-10 and ORION-11 investigators is provided in the Supplementary Appendix, available at NEJM.org.

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The binding of proprotein convertase subtilisin–kexin type 9 (PCSK9) in the circulation by monoclonal antibodies reduces both low-density lipoprotein (LDL) cholesterol levels and the incidence of cardiovascular events.[1,2] Inclisiran, a small interfering RNA (siRNA) therapeutic agent, reduces hepatic synthesis of PCSK9. In one trial, the LDL cholesterol level was lowered by 52.6% at 180 days after two doses of 284 mg of inclisiran (equivalent to 300 mg of inclisiran sodium) administered on day 1 and day 90.[3] Data from the same trial following the same patients over a period of 360 days suggested that inclisiran might provide sustained reductions in LDL cholesterol levels, with the potential for a dosing schedule of once every 6 months.[4]

Methods

Trial Design and Oversight

We conducted two randomized, double-blind, placebo-controlled, parallel-group, phase 3 trials. The objectives of the ORION-10 and ORION-11 trials were to assess the efficacy, safety, and adverse-event profile of inclisiran over a period of 18 months in patients at high risk for cardiovascular disease in whom LDL cholesterol levels were elevated despite receiving statin therapy at the maximum tolerated dose with or without additional lipid-lowering therapy. The maximum tolerated dose was defined as the maximum dose of a statin that could be taken by the patient on a regular basis without unacceptable adverse events. Inability to receive statins required documentation of historical adverse events that were attributable to more than one statin and that were recorded in source documents and the trial case-report form.

The trial protocols (available with the full text of this article at NEJM.org) were identical and were approved by an institutional review board or independent ethics committee at each participating institution. All the patients provided written informed consent. The first two authors and the steering committee in collaboration with the sponsor (the Medicines Company) designed each trial protocol (with subsequent review and approval by regulators) and selected participating countries and sites. Monitoring and site supervision were performed by a contract research organization (PPD) with oversight by the sponsor. The first two authors wrote the first draft of the manuscript. All the authors participated in its revision, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trials to the protocols.

Patients

The ORION-10 trial was conducted in the United States and included adults with atherosclerotic cardiovascular disease. Patients were eligible for enrollment if their LDL cholesterol levels at screening were 70 mg per deciliter (1.8 mmol per liter) or higher. The ORION-11 trial was conducted in Europe and South Africa and included adults with atherosclerotic cardiovascular disease or an atherosclerotic cardiovascular disease risk equivalent (type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event of ≥20% as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent). The LDL cholesterol eligibility criteria for patients with atherosclerotic cardiovascular disease were identical in the two trials, but in the ORION-11 trial, patients with an atherosclerotic cardiovascular disease risk equivalent were required to have an LDL cholesterol level of 100 mg per deciliter (2.6 mmol per liter) or higher.[5] Entry criteria required stable doses of background lipid-lowering therapies for at least 30 days before screening. Patients receiving treatment with monoclonal antibodies directed toward PCSK9 within 90 days before screening were excluded. Detailed inclusion and exclusion criteria for each trial are provided in the Supplementary Appendix, available at NEJM.org.

Trial Procedures

Randomization was stratified according to background use of statins in both trials and also according to country in the ORION-11 trial, with patients assigned (in a 1:1 ratio) to receive either inclisiran (284 mg) or matching placebo — both administered as a 1.5-ml subcutaneous injection under blinded conditions. Each patient received four injections of inclisiran or placebo. After the first injection (day 1), patients returned on day 90, day 270, and day 450 to receive subsequent doses of inclisiran or placebo (Fig. S1 in the Supplementary Appendix). Patients also attended the clinic on days 30, 150, 330, and 510 for follow-up and limited laboratory assessments. The end-of-trial visit was conducted on day 540.

END POINTS

The coprimary end points in each trial were the placebo-corrected percentage change in LDL cholesterol level from baseline to day 510 and the time-adjusted percentage change in LDL cholesterol level from baseline after day 90 and up to day 540. The latter end point is the mean percentage change in LDL cholesterol level from baseline over the period after day 90 and up to day 540 and takes into account peak and trough measurements within that time window (samples recorded on days 150, 270, 330, 450, 510, and 540). Key secondary end points for each trial were the absolute change in LDL cholesterol level from baseline to day 510, the time-adjusted absolute change in LDL cholesterol level from baseline after day 90 and up to day 540, and the percentage change from baseline to day 510 in levels of PCSK9, total cholesterol, apoliprotein B, and non–high-density lipoprotein (HDL) cholesterol. Full details of other prespecified secondary end points are listed in the Supplementary Appendix. Finally, the incidence of a *Medical Dictionary for Regulatory Activities* (MedDRA)–defined cardiovascular basket of nonadjudicated terms, including those classified within cardiac death, and any signs or symptoms of cardiac arrest, nonfatal myocardial infarction, or stroke was a prespecified exploratory end point.

We recorded adverse events and clinical laboratory values at all visits through the end-of-trial visit (day 540). Investigators classified adverse events according to organ class and as mild, moderate, or severe using standard MedDRA nomenclature. Antidrug antibodies were measured in plasma with the use of highly sensitive screening methods and, if needed, 5 (, i)-19 0 Td(-)Tj-0.01t

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	ORION-10 Trial		ORION-11 Trial	
	Inclisiran (N=781)	Placebo (N=780)	Inclisiran (N=810)	Placebo (N=807)
Age — yr	66.4±8.9	65.7±8.9	64.8±8.3	64.8±8.7
Male sex — no. (%)	535 (68.5)	548 (70.3)	579 (71.5)	581 (72.0)
White race — no. (%)†	653 (83.6)	685 (87.8)	791 (97.7)	796 (98.6)
Cardiovascular risk factors — no. (%)				
ASCVD	781 (100)	780 (100)	712 (87.9)	702 (87.0)
ASCVD risk equivalent‡	0	0	98 (12.1)	105 (13.0)
Current smoker§	123 (15.7)	111 (14.2)	160 (19.8)	132 (16.4)
Hypertension§	714 (91.4)	701 (89.9)	640 (79.0)	661 (81.9)
Diabetes§	371 (47.5)	331 (42.4)	296 (36.5)	272 (33.7)
Heterozygous familial hypercholesterolemia§	8 (1.0)	12 (1.5)	14 (1.7)	14 (1.7)
Concomitant lipid-modifying therapy — no. (%)				
Statin	701 (89.8)	692 (88.7)	766 (94.6)	766 (94.9)
High-intensity statin	525 (67.2)	537 (68.8)	640 (79.0)	631 (78.2)
Ezetimibe	80 (10.2)	74 (9.5)	52 (6.3)	62 (7.7)
Lipid measures — mg/dl				
LDL cholesterol	104.5±39.6	104.8±37.0	107.2±41.8	103.7±36.4
Total cholesterol	180.6±46.1	180.6±43.6	187.3±48.2	183.3±42.8
Non-HDL cholesterol	134.0±44.5	134.7±43.5	137.6±46.9	133.9±41.0
HDL cholesterol	46.6±14.3	45.9±14.4	49.7±15.5	49.3±13.8
Apolipoprotein B	94.1±25.6	94.6±25.1	97.1±28.0	95.1±5.2
Lipoprotein(a) — nmol/liter				
Median	57	56	42	35
IQR	18–181	20–189	18–178	18–181
Triglycerides — mg/dl				
Median	127	129	135	135
IQR	92–181	96–182	99–181	102–185
PCSK9 — μg/liter	422.1±176.9	414.9±145.7	355±98.9	353±97.4

* Plus–minus values are means ±SD. For the levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, triglycerides, and total cholesterol, the baseline value was defined as the mean of the values at screening and before receipt of the dose of inclisiran or placebo on day 1; for other variables, the baseline value was defined as the last value before the first dose of inclisiran or placebo. In a post hoc analysis to provide descriptive statistical comparisons, there were no significant differences between the two groups in the baseline characteristics. To convert values for cholesterol and apolipoprotein B to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. ASCVD denotes atherosclerotic cardiovascular disease, IQR interquartile range, and PCSK9 proprotein convertase subtilisin–kexin type 9.

† Race was reported by the patient.

‡ Patients in this category had type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event of 20% or greater as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent.

§ Percentages are reported as a proportion of the overall cohort, including patients in the risk-equivalent category.

patients with atherosclerotic cardiovascular disease, in the ORION-11 trial there were also 203 patients (12.6%) enrolled in the risk-equivalent category, of whom 132 (65.0%) had diabetes, 30 (14.8%) had heterozygous familial hypercholesterolemia, and 41 (20.2%) had a 10-year predicted risk of cardiovascular disease of 20% or greater.

The use of stable doses of statin treatment was high (89.2% in the ORION-10 trial and 94.7% in

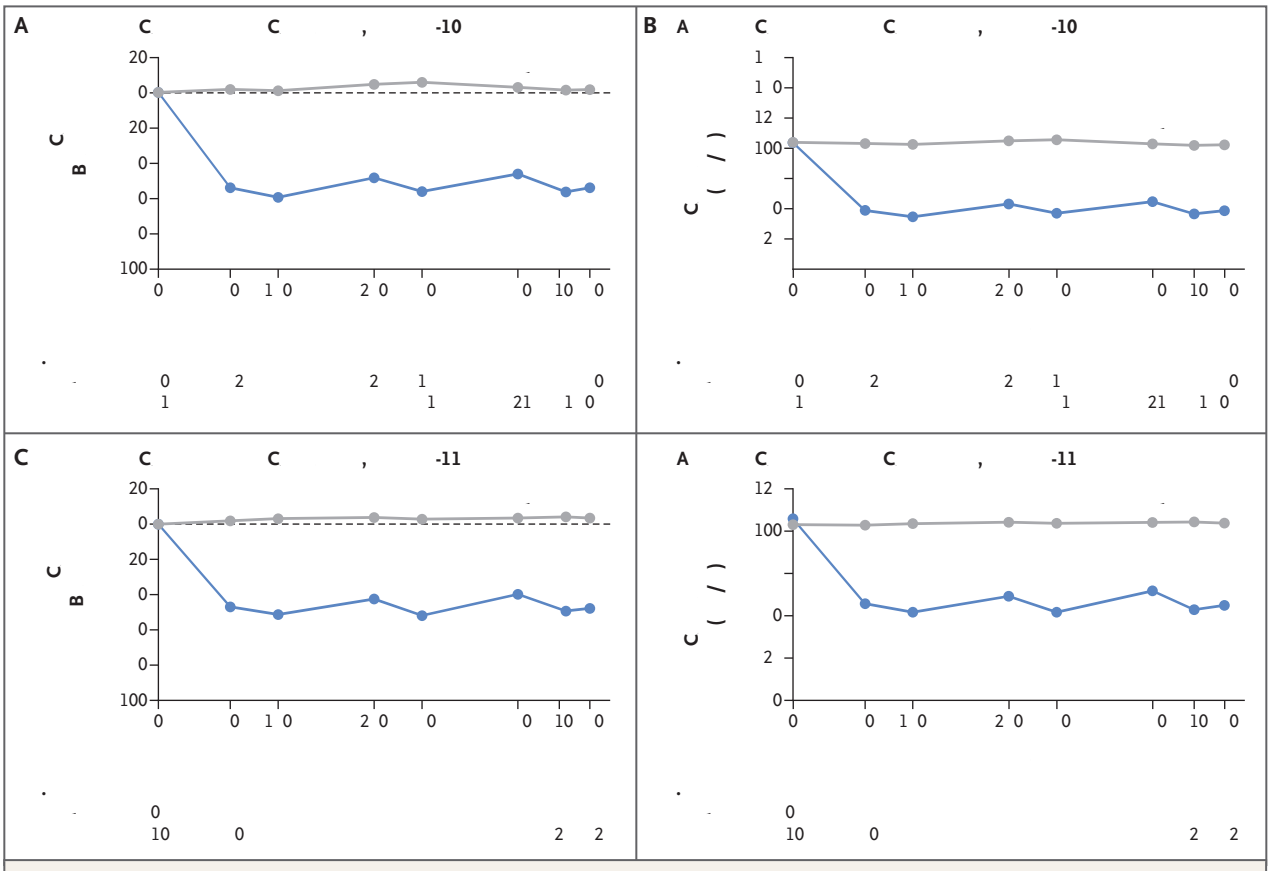

Figure 1. Efficacy of Inclisiran or Placebo in Lowering LDL Cholesterol over the 540-Day Trial Period (Intention-to-Treat Population).

The graphs use observed data. The numbers of patients with missing data at each time point are shown in Table S1 in the Supplementary Appendix. Least-squares means are shown for inclisiran and placebo over time. Panels A and B show the percentage change and the absolute change in low-density lipoprotein (LDL) cholesterol level over time in the ORION-10 trial. Panels C and D show the percentage change and the absolute change in LDL cholesterol level over time in the ORION-11 trial. The primary end point of percentage change in LDL cholesterol level from baseline to day 510 and a key secondary end point of absolute change at day 510 were analyzed with the use

the ORION-11 trial), with the majority of patients receiving high-intensity statins (68.0% and 78.6%, respectively). Use of ezetimibe either alone or in combination with statins was low (9.9% in the ORION-10 trial and 7.1% in the ORION-11 trial). The mean (±SD) LDL cholesterol level at baseline was 104.7±38.3 mg per deciliter (2.71±0.99 mmol per liter) and 105.5±39.1 mg per deciliter (2.73±1.01 mmol per liter) in the respective trials (Table 1).

EFFICACY

Primary End Points

The percentage and absolute changes in LDL cholesterol level from baseline with inclisiran or placebo in each trial are shown in Figure 1. In the ORION-10 trial, the percentage change in LDL cholesterol level at day 510 was 1.0% in the placebo group and −51.3% in the inclisiran group, resulting in a between-group difference of −52.3% (95% confidence interval [CI], −55.7 to −48.8; P<0.001). The time-adjusted change in LDL cholesterol level after day 90 and up to day 540 (coprimary end point) as compared with baseline was 2.5% with placebo and −51.3% with inclisiran, representing a between-group difference of −53.8% (95% CI, −56.2 to −51.3; P<0.001). In the ORION-11 trial, the corresponding percentage change in LDL cholesterol level at day 510 was 4.0% in the placebo group and −45.8% in the inclisiran group, resulting in a between-group difference of −49.9% (95%

CI, −53.1 to −46.6; P<0.001). The corresponding time-adjusted change in LDL cholesterol level was 3.4% with placebo and −45.8% with inclisiran, representing a between-group difference of −49.2% (95% CI, −51.6 to −46.8; P<0.001).

Key Secondary End Points

In the ORION-10 trial, the absolute change in LDL cholesterol level at day 510 was −2.1 mg per deciliter (−0.05 mmol per liter) in the placebo group and −56.2 mg per deciliter (−1.45 mmol per liter) in the inclisiran group, with a between-group difference of −54.1 mg per deciliter (−1.40 mmol per liter) (95% CI, −57.4 to −50.9 mg per deciliter [−1.48 to −1.32 mmol per liter]; P<0.001). The time-adjusted absolute change in LDL cholesterol level from day 90 to day 540 was −0.4 mg per deciliter (−0.01 mmol per liter) in the placebo group and −53.7 mg per deciliter (−1.39 mmol per liter) in the inclisiran group, with a difference of −53.3 mg per deciliter (−1.38 mmol per liter) (95% CI, −55.8 to −50.8 mg per deciliter [−1.44 to −1.31 mmol per liter]; P<0.001).

In the ORION-11 trial, the corresponding absolute change in LDL cholesterol level at day 510 was 1.0 mg per deciliter (0.03 mmol per liter) in the placebo group and −50.9 mg per deciliter (−1.32 mmol per liter) in the inclisiran group, with a between-group difference of −51.9 mg per deciliter (−1.34 mmol per liter) (95% CI, −55.0 to −48.7 mg per deciliter [−1.42 to −1.26 mmol per liter]; P<0.001). The time-adjusted absolute change in LDL cholesterol level from day 90 to day 540 was 0.3 mg per deciliter (0.01 mmol per liter) in the placebo group and −48.6 mg per deciliter (−1.26 mmol per liter) in the inclisiran group, with a difference of −48.9 mg per deciliter (−1.26 mmol per liter) (95% CI, −51.4 to −46.5 mg per deciliter [−1.33 to −1.20 mmol per liter]; P<0.001).

The percentage and absolute changes in PCSK9 levels from baseline with inclisiran or placebo in each trial are shown in Figure 2. In the ORION-10 trial, the percentage change at day 510 (key secondary end point) was 13.5% with placebo and −69.8% with inclisiran, representing a between-group difference of −83.3% (95% CI, −89.3 to −77.3; P<0.001). Similarly, in the ORION-11 trial, the percentage change at day 510 was 15.6% with placebo and −63.6% with inclisiran, representing a between-group difference of −79.3% (95% CI, −82.0 to −76.6; P<0.001). In each trial, inclisiran resulted in improvement in other key secondary end points at day 510 as compared with placebo, including lower levels of total cholesterol, non-HDL cholesterol, and apolipoprotein B (P<0.001 for all three comparisons) (Table S4A and S4B). The effect of inclisiran on LDL cholesterol levels at day 510 appeared consistent within each trial across a range of subgroups (Figs. 3 and 4).

Other End Points

Inclisiran lowered levels of triglycerides and lipoprotein(a) and increased HDL cholesterol levels at day 510 (Table S4A and S4B). In each trial, the proportion of patients likely to have a 50% reduction in LDL cholesterol level was higher in the inclisiran group than in the placebo group (Table S5), as were the proportions of patients in whom an LDL cholesterol level of less than 25, 50, 70, and 100 mg per deciliter (0.65, 1.3, 1.8, and 2.6 mmol per liter, respectively) was achieved. Although the placebo group showed considerable variation in changes in PCSK9 and LDL cholesterol levels at day 510, the inclisiran group showed very little (Fig. S3).

SAFETY

In the ORION-10 trial, 2 patients who were assigned to the placebo group did not receive placebo; therefore, the safety population comprises 781 patients in the inclisiran group and 778 patients in the placebo group. In the ORION-11 trial, 2 patients who were assigned to the placebo group did not receive placebo, and 1 patient who was assigned to placebo was given a dose of inclisiran in error and is included in the inclisiran group for safety reporting; therefore, the safety population of the latter trial comprises 811 patients exposed to inclisiran and 804 patients exposed to placebo.

The incidence of adverse events is shown in Table 2. Adverse events that occurred during the trial period, regardless of causality, were reported in 574 of 781 patients (73.5%) receiving inclisiran and 582 of 778 (74.8%) receiving placebo in the ORION-10 trial and in 671 of 811 patients (82.7%) receiving inclisiran and 655 of 804 (81.5%) receiving placebo in the ORION-11 trial. The majority of events in each trial were reported to be mild or moderate, with the most common adverse events occurring with similar frequency in the inclisiran and placebo groups. Laboratory results with respect to liver and kidney function, levels of creatine kinase and high-

Figure 2. Efficacy of Inclisiran or Placebo in Lowering PCSK9 Levels over the 540-Day Trial Period (Intention-to-Treat Population).
The graphs use observed data. The numbers of patients with missing data at each time point are shown in Table S2. Least-squares means are shown for inclisiran and placebo over time. Panels A and B show the percentage change and the absolute change in proprotein convertase subtilisin–kexin type 9 (PCSK9) level over time in the ORION-10 trial. Panels C and D show the percentage change and the absolute change in PCSK9 level over time in the ORION-11 trial. The key secondary end point of percentage change in PCSK9 level from baseline to day 510 and the secondary end point of absolute change at day 510 were analyzed with the use of separate mixed mod-

sensitivity C-reactive protein, and platelet count were also similar in the inclisiran and placebo groups in each trial (Table 2 and Tables S6, S7A, and S7B). Injection-site adverse events were more frequent with inclisiran than with placebo in both trials, with between-group differences of 1.7 percentage points in the ORION-10 trial and 4.2 percentage points in the ORION-11 trial; the majority of reactions were mild (between-group differences in mild reactions, 0.8 percentage points and 2.4 percentage points, respectively), with none being severe or persistent.

Antidrug antibodies were detected in 2.0% and 2.5% of the samples from inclisiran-treated patients in the ORION-10 and ORION-11 trials, respectively, findings consistent with assay specifications but not drug induction. The frequency of positive samples was similar in pretreatment and post-treatment samples. The presence of antidrug antibodies in post-treatment samples was low titer, often transient, and not associated with changes in any pharmacologic or clinical variables. In addition, there were no treatment-boosted antidrug antibodies.

Serious adverse events were reported in 175 patients (22.4%) receiving inclisiran and 205 (26.3%) receiving placebo in the ORION-10 trial and in 181 patients (22.3%) receiving inclisiran and 181 (22.5%) receiving placebo in the ORION-11 trial. These included 12 deaths (1.5%) in the inclisiran group and 11 (1.4%) in the placebo group in the ORION-10 trial and 14 deaths (1.7%) in

Figure 3. Subgroup Analysis of Placebo-Corrected Percentage Change in LDL Cholesterol from Baseline to Day 510 with Inclisiran in the ORION-10 Trial (Intention-to-Treat Population).

Data are least-squares mean differences and 95% confidence intervals. The difference in the percentage change from baseline between inclisiran and placebo was analyzed for each subgroup with the use of a mixed model for repeated measures. The model used observed case data and thus all data available on a patient, who could have data at day 510 missing but have data at earlier time points. The median body-mass index (the weight in kilograms divided by the square of the height in meters) was 30.8. High-intensity statins are defined in the Methods section in the Supplementary Appendix. Renal function was divided into normal (estimated glomerular filtration rate, ≥90 ml per minute per 1.73 m^2), mild impairment (60 to 89 ml per minute per 1.73 m^2), and moderate impairment (30 to 59 ml per minute per 1.73 m^2).

the inclisiran group and 15 (1.9%) in the placebo group in the ORION-11 trial. The incidences of cancer-related deaths and new, worsening, or recurrent cancer were low and were similar among patients receiving inclisiran and those receiving placebo.

EXPLORATORY ANALYSIS

The prespecified exploratory cardiovascular end point occurred in 58 patients (7.4%) in the inclisiran group and 79 (10.2%) in the placebo group in the ORION-10 trial and in 63 patients (7.8%) in the inclisiran group and 83 (10.3%) in the placebo group in the ORION-11 trial.

DISCUSSION

In our trials, a regimen of subcutaneous inclisiran injections on day 1, day 90, and then every 6 months reduced LDL cholesterol levels by

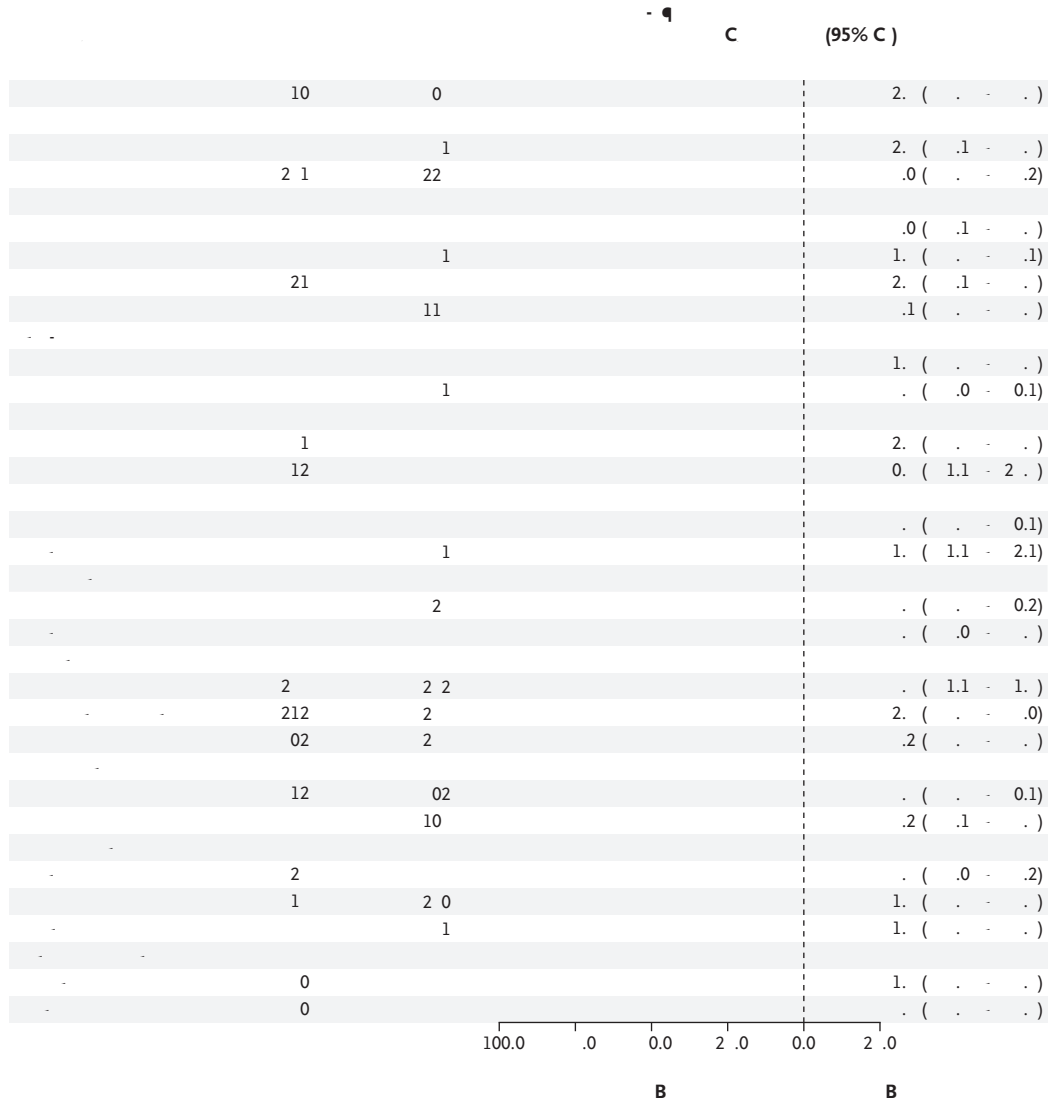

Figure 4. Subgroup Analysis of Placebo-Corrected Percentage Change in LDL Cholesterol from Baseline to Day 510 with Inclisiran in the ORION-11 Trial (Intention-to-Treat Population).

Data are least-squares mean differences and 95% confidence intervals. The difference in the percentage change from baseline between inclisiran and placebo was analyzed for each subgroup with the use of a mixed-effects model for repeated measures. The model used observed case data and thus all data available on a patient, who could have data at day 510 missing but have data at earlier time points. The median body-mass index was 29.4. Patients with an atherosclerotic cardiovascular disease (ASCVD) risk equivalent had type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event of 20% or greater as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent.

49.9% to 52.2% at month 17 and lowered time-adjusted LDL cholesterol levels between months 3 and 18 by 49.2% to 53.8% as compared with placebo in two separate populations at high risk for cardiovascular disease. These reductions were achieved on top of maximum tolerated, guideline-recommended statin treatment. The results for the percentage change in LDL cholesterol levels at month 17 were consistent across subgroups. Among patients given placebo, PCSK9 levels generally increased, whereas PCSK9 levels decreased in nearly all the patients given inclisiran.

Peak plasma levels of inclisiran occur approximately 4 hours after dosing, and most is excreted through the kidney.[8] Triantennary N-acetylgalactosamine (GalNAc) modification of the double-stranded inclisiran molecule ensures rapid hepatic uptake through the asialoglycoprotein receptors expressed exclusively on liver cells; after uptake, inclisiran is bound to the RNA-induced silencing complex in liver-cell cytoplasm.[9,10] Inclisiran is no longer detectable in plasma within 24 to 48 hours after dosing.[9,10] A theoretical concern for therapies with a long duration of action is the potential for irreversible adverse events. Without further injections, the

Table 2. Adverse Events and Key Safety Laboratory Findings.*

Variable	ORION-10 Trial			ORION-11 Trial		
	Inclisiran (N=781)	Placebo (N=778)	Risk Ratio (95% CI)	Inclisiran (N=811)	Placebo (N=804)	Risk Ratio (95% CI)
	no. of patients (%)			*no. of patients (%)*		
Adverse events						
≥1 Adverse event	574 (73.5)	582 (74.8)	1.0 (0.9–1.0)	671 (82.7)	655 (81.5)	1.0 (0.9–1.1)
≥1 Event leading to discontinuation of inclisiran or placebo	19 (2.4)	17 (2.2)	1.1 (0.6–2.1)	23 (2.8)	18 (2.2)	1.3 (0.7–2.3)
Serious adverse events						
≥1 Serious adverse event	175 (22.4)	205 (26.3)	0.9 (0.7–1.0)	181 (22.3)	181 (22.5)	1.0 (0.8–1.2)
Death	12 (1.5)	11 (1.4)	1.1 (0.5–2.4)	14 (1.7)	15 (1.9)	0.9 (0.4–1.9)
Death from cardiovascular causes	7 (0.9)	5 (0.6)	1.4 (0.4–4.4)	9 (1.1)	10 (1.2)	0.9 (0.4–2.2)
Cancer-related death	1 (0.1)	3 (0.4)	0.3 (0.0–3.2)	3 (0.4)	3 (0.4)	1.0 (0.2–4.9)
New, worsening, or recurrent cancer	26 (3.3)	26 (3.3)	1.0 (0.6–1.7)	16 (2.0)	20 (2.5)	0.8 (0.1–1.5)
Other cardiovascular adverse events						
Prespecified exploratory cardiovascular end point†	58 (7.4)	79 (10.2)	0.7 (0.5–1.0)	63 (7.8)	83 (10.3)	0.8 (0.6–1.0)
Fatal or nonfatal myocardial infarction	20 (2.6)	18 (2.3)	1.1 (0.6–2.1)	10 (1.2)	22 (2.7)	0.5 (0.2–0.9)
Fatal or nonfatal stroke	11 (1.4)	7 (0.9)	1.6 (0.6–4.0)	2 (0.2)	8 (1.0)	0.2 (0.1–1.2)
Injection-site adverse events‡						
Any reaction	20 (2.6)	7 (0.9)	2.9 (1.2–6.7)	38 (4.7)	4 (0.5)	9.4 (3.4–26.3)
Mild	13 (1.7)	7 (0.9)	1.9 (0.7–4.6)	23 (2.8)	3 (0.4)	7.6 (2.3–25.2)
Moderate	7 (0.9)	0	—	15 (1.8)	1 (0.1)	14.9 (2.0–112.3)
Severe	0	0	—	0	0	—
Persistent	0	0	—	0	0	—
Frequent adverse events§						
Diabetes mellitus	120 (15.4)	108 (13.9)	1.1 (0.9–1.4)	88 (10.9)	94 (11.7)	0.9 (0.7–1.2)
Nasopharyngitis	—	—	—	91 (11.2)	90 (11.2)	1.0 (0.8–1.3)
Bronchitis	46 (5.9)	30 (3.9)	1.5 (1.0–2.4)	—	—	—
Dyspnea	39 (5.0)	33 (4.2)	1.2 (0.7–1.9)	—	—	—
Hypertension	42 (5.4)	42 (5.4)	1.0 (0.7–1.5)	53 (6.5)	54 (6.7)	1.0 (0.7–1.4)
Upper respiratory tract infection	39 (5.0)	33 (4.2)	1.2 (0.7–1.9)	52 (6.4)	49 (6.1)	1.1 (0.7–1.5)
Arthralgia	—	—	—	47 (5.8)	32 (4.0)	1.5 (0.9–2.3)
Osteoarthritis	—	—	—	32 (3.9)	40 (5.0)	0.8 (0.5–1.2)
Back pain	39 (5.0)	39 (5.0)	1.0 (0.6–1.5)	—	—	—

LDL cholesterol–lowering effects of inclisiran are reversed at the rate of approximately 2% per month,[3,4] which means that these effects can

favorable reductions in LDL cholesterol levels and in turn a higher risk of cardiovascular events as compared with good adherence.[18,19] Furthermore, at a population level, poor adherence attenuates the benefit of LDL cholesterol reduction that is achievable through proper adherence.[18] Our trials suggest that sustained reductions in LDL cholesterol levels are achievable with an infrequent dosing schedule of inclisiran. Complete adherence might be feasible if this therapy were administered by a health care professional,[20] thus potentially helping address an existing challenge to contemporary prevention strategies — namely, how to maintain reductions to adverse exposures such as LDL cholesterol over the long term.

We found that a regimen of inclisiran every 6 months was feasible and significantly reduced LDL cholesterol levels by approximately 50%. More injection-site adverse events occurred with inclisiran than with placebo.

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