ORIGINAL ARTICLE

Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol

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ABSTRACT

BACKGROUND

Inclisiran inhibits hepatic synthesis of proprotein convertase subtilisin–kexin type 9. Previous studies suggest that inclisiran might provide sustained reductions in low-density lipoprotein (LDL) cholesterol levels with infrequent dosing.

METHODS

We enrolled patients with atherosclerotic cardiovascular disease (ORION-10 trial) and patients with atherosclerotic cardiovascular disease or an atherosclerotic cardiovascular disease risk equivalent (ORION-11 trial) who had elevated LDL cholesterol levels despite receiving statin therapy at the maximum tolerated dose. Patients were randomly assigned in a 1:1 ratio to receive either inclisiran (284 mg) or placebo, administered by subcutaneous injection on day 1, day 90, and every 6 months thereafter over a period of 540 days. 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.

RESULTS

A total of 1561 and 1617 patients underwent randomization in the ORION-10 and ORION-11 trials, respectively. Mean (±SD) LDL cholesterol levels at baseline were 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), respectively. At day 510, inclisiran reduced LDL cholesterol levels by 52.3% (95% confidence interval [CI], 48.8 to 55.7) in the ORION-10 trial and by 49.9% (95% CI, 46.6 to 53.1) in the ORION-11 trial, with corresponding time-adjusted reductions of 53.8% (95% CI, 51.3 to 56.2) and 49.2% (95% CI, 46.8 to 51.6) ($P<0.001$ for all comparisons vs. placebo). Adverse events were generally similar in the inclisiran and placebo groups in each trial, although injection-site adverse events were more frequent with inclisiran than with placebo (2.6% vs. 0.9% in the ORION-10 trial and 4.7% vs. 0.5% in the ORION-11 trial); such reactions were generally mild, and none were severe or persistent.

CONCLUSIONS

Reductions in LDL cholesterol levels of approximately 50% were obtained with inclisiran, administered subcutaneously every 6 months. More injection-site adverse events occurred with inclisiran than with placebo. (Funded by the Medicines Company; ORION-10 and ORION-11 ClinicalTrials.gov numbers, NCT03399370 and NCT03400800.)

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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.

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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, confirmatory assays in accordance with the most recent regulatory guidance, developed and validated to minimize the risk of false negative results.[6,7]

STATISTICAL ANALYSIS

The detailed statistical analysis plans for both trials are available with the protocols at NEJM.org. In brief, under the assumption of a 5% dropout rate, a mean reduction in LDL cholesterol level of no less than 30 mg per deciliter (0.8 mmol per liter), and a standard deviation of 20 mg per deciliter (0.5 mmol per liter), a sample of approximately 1425 patients who could be evaluated would provide more than 90% power to detect a 30% lower level of LDL cholesterol in the inclisiran group than in the placebo group with a two-sided significance level of 0.05 in each trial.

In each trial, the first primary efficacy end point was analyzed with the use of an analysis-of-covariance model, and the second primary efficacy end point was analyzed with the use of a mixed model for repeated measures, both with multiple imputation of data. A nested procedure was specified for the two primary end points, with the requirement that significance must be shown for the first primary end point before the second primary end point could be tested. For the key secondary end points, there were six different tests (two absolute-change measures and four percentage-change measures). With an alpha of 0.05 overall, the Hochberg procedure was applied, in which the highest P value was tested at $0.05 \div 1$, the next one was tested at $0.05 \div 2$, and continuing until the final (lowest) P value was tested at $0.05 \div 6$ (0.008). All primary and secondary end points used multiple imputation to account for missing data (see the Supplementary Appendix). The planned sample size of approximately 1425 in each trial was also expected to contribute safety data from more than 6000 injections per trial. Analyses were performed with the use of SAS software, version 9.2 or higher (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PATIENTS

The ORION-10 and ORION-11 trials screened 2329 and 2381 patients, respectively, with 1561 and 1617 subsequently undergoing randomization. The intention-to-treat populations comprised 781 patients assigned to inclisiran and 780 to placebo in the ORION 10 trial and 810 assigned to inclisiran and 807 to placebo in the ORION 11 trial. A large majority of those enrolled completed the trial activities (90.6% and 95.2%, respectively) through the end-of-trial visit on day 540 (Fig. S2). Thus, these two trials provide 2166 person-years of exposure to inclisiran.

The characteristics of the populations in each trial were similar with respect to age and the proportion of men enrolled (Table 1), but there were differences between the trials, with the ORION-10 trial enrolling fewer white patients but a higher proportion of patients with diabetes, hypertension, and heterozygous familial hypercholesterolemia. Although both trials enrolled

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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

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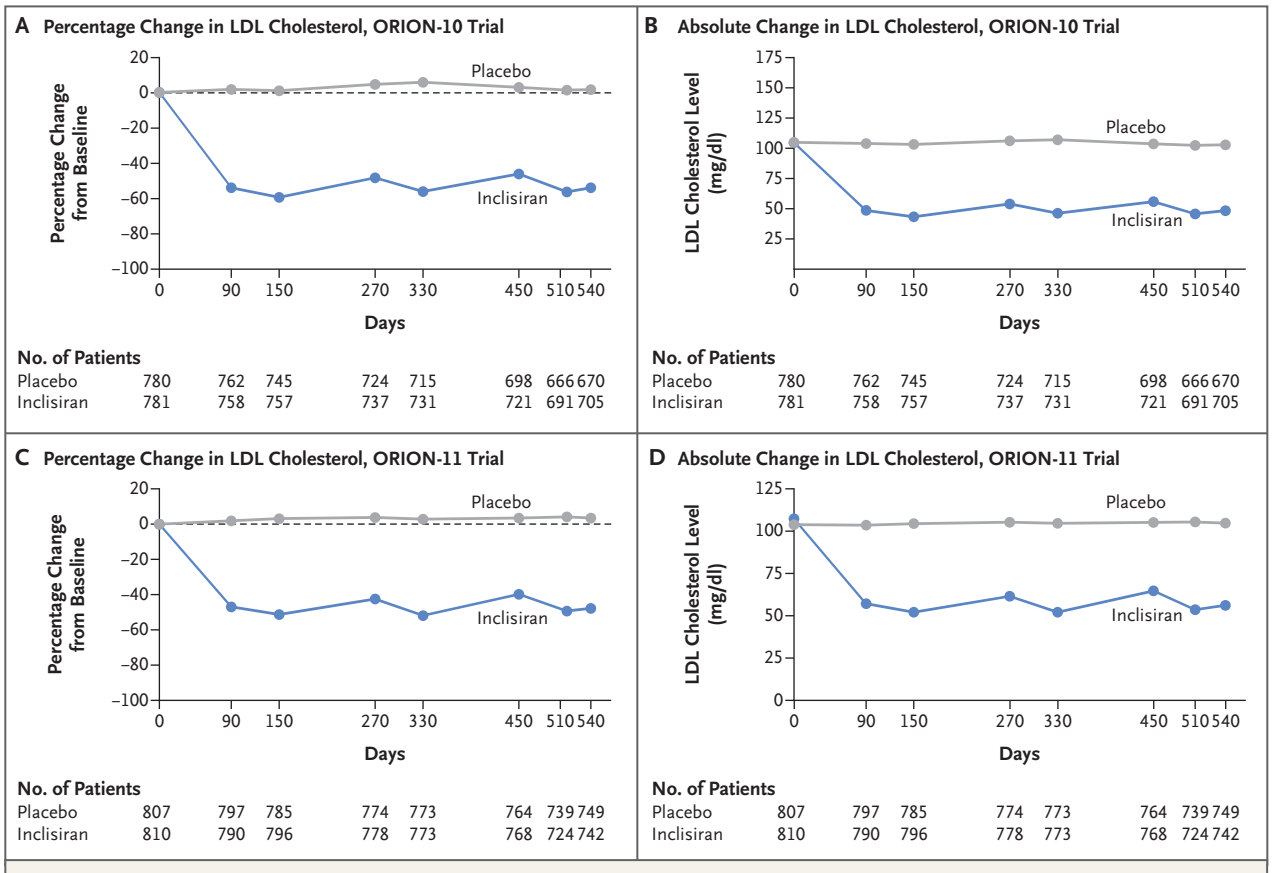

Figure 1. Efficacy of Inclisiran or Placebo in Lowering LDL Cholesterol over the 540-Day Trial Period (Intention-to-Treat Population).

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 of an analysis-of-covariance model and a mixed model for repeated measures, respectively, with multiple imputation for missing values. P values for the comparison of inclisiran with placebo for the percentage and absolute change from baseline were less than 0.001 for all four comparisons at day 510.

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%

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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-

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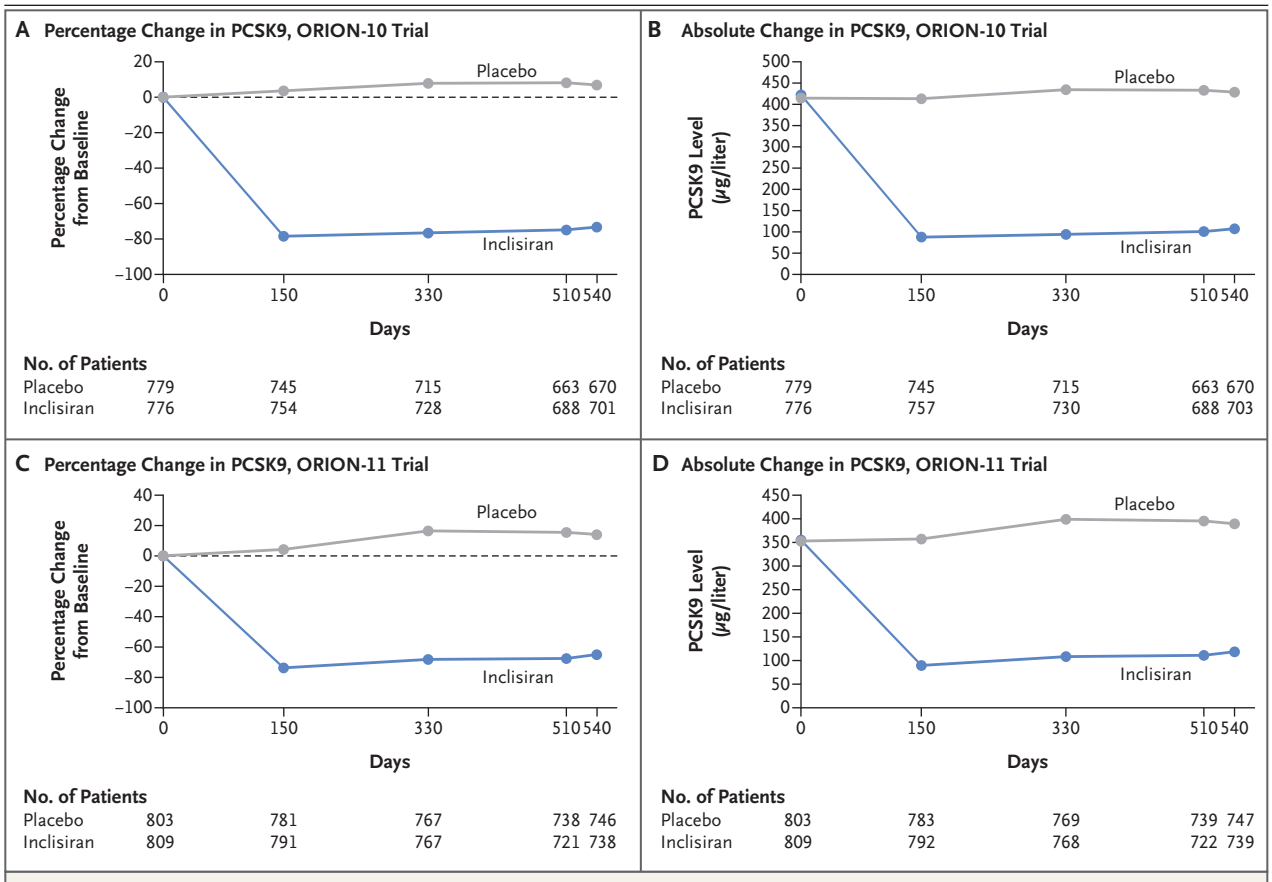

Figure 2. Efficacy of Inclisiran or Placebo in Lowering PCSK9 Levels over the 540-Day Trial Period (Intention-to-Treat Population).

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 models for repeated measures, with multiple imputation for missing values. P values for the comparison of inclisiran with placebo for the percentage and absolute change from baseline were less than 0.001 for all four comparisons at day 510.

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

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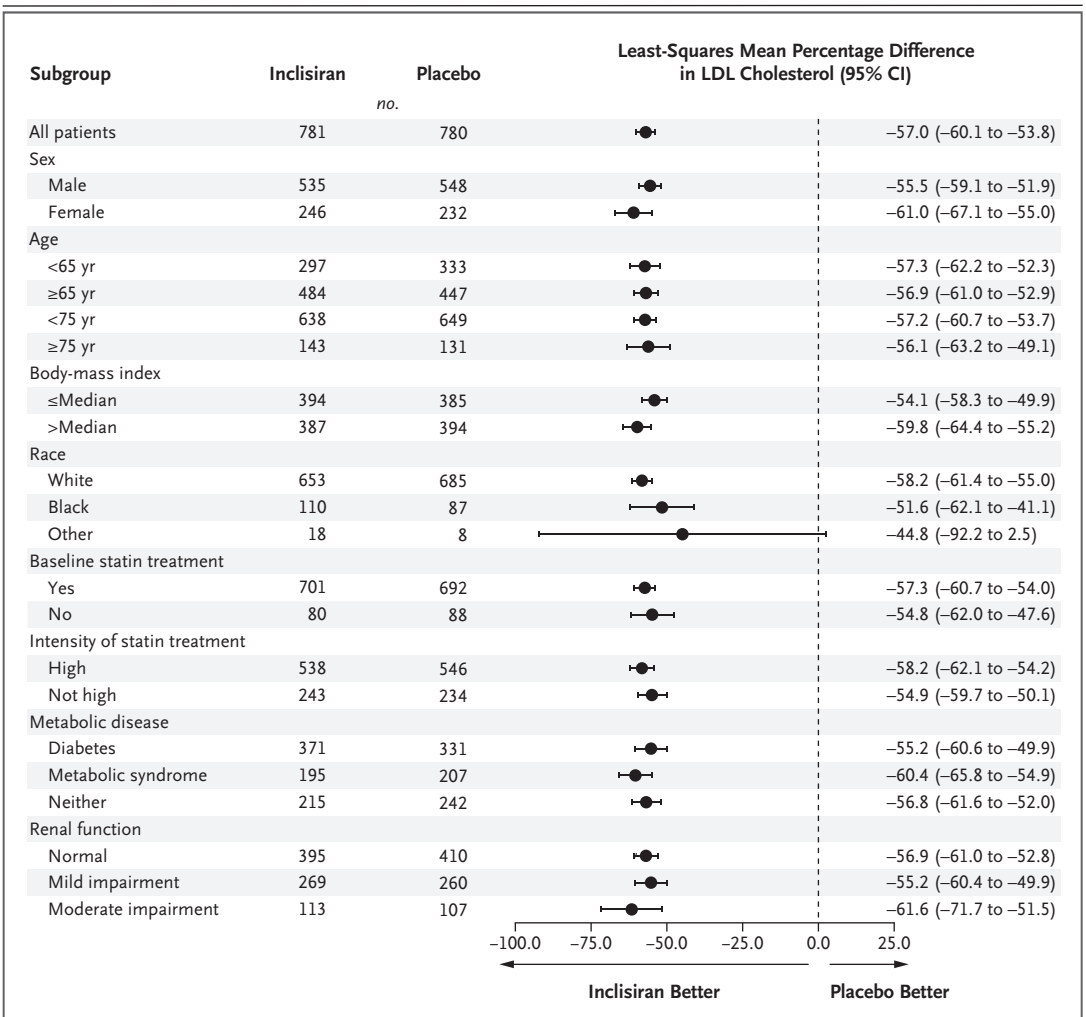

Figure 3. Subgroup Analysis of Placebo-Corrected Percentage Change in LDL Cholesterol from Baseline to Day 510 with Inclisiran in the ORION-10 Trial (Intention-to-Treat Population).

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

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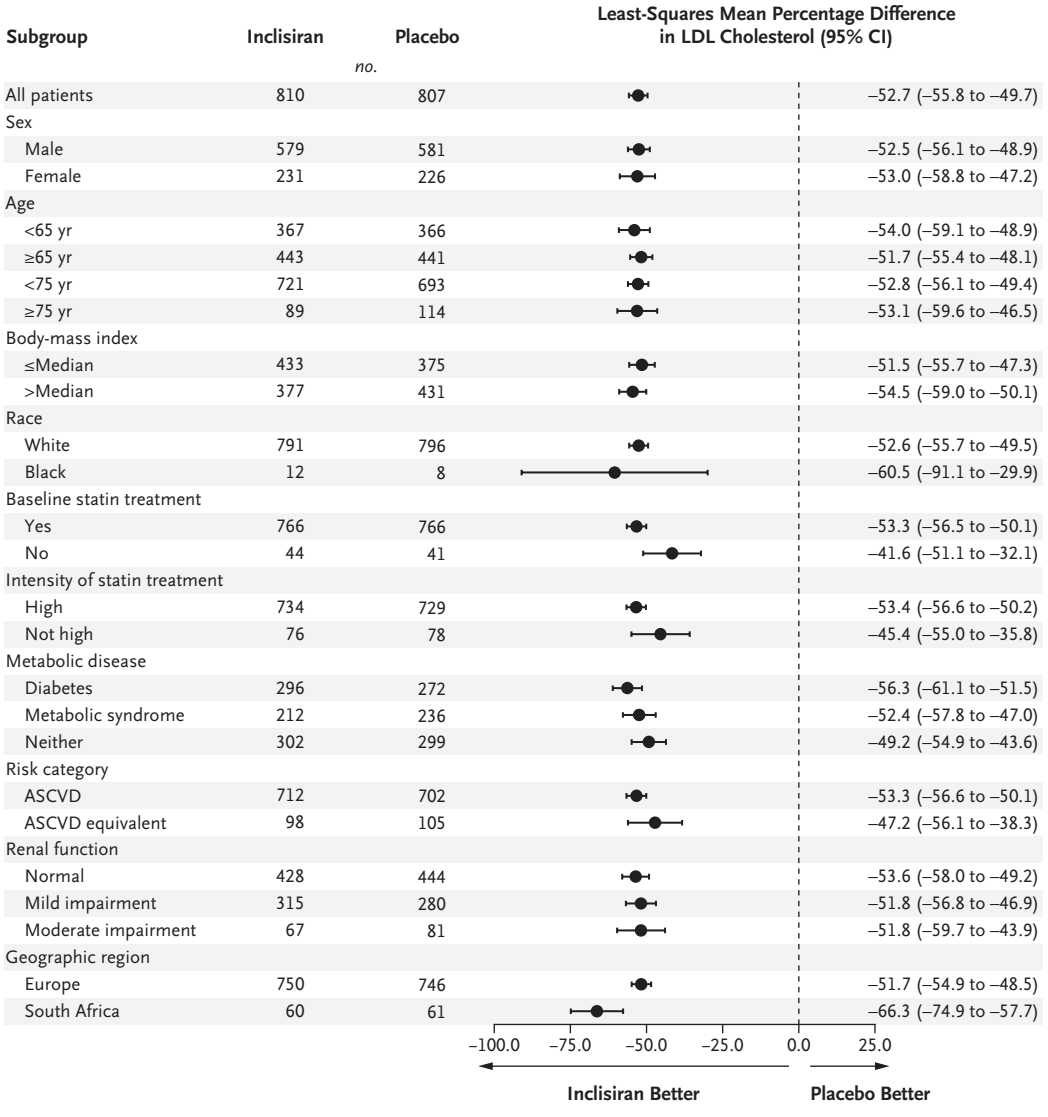

Figure 4. Subgroup Analysis of Placebo-Corrected Percentage Change in LDL Cholesterol from Baseline to Day 510 with Inclisiran in the ORION-11 Trial (Intention-to-Treat Population).

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.

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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)	—	—	—

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Table 2. (Continued.)

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 (%)*		
Laboratory results						
Liver function						
Alanine aminotransferase >3× ULN	2 (0.3)	2 (0.3)	1.0 (0.1–7.1)	4 (0.5)	4 (0.5)	1.0 (0.2–4.0)
Aspartate aminotransferase >3× ULN	4 (0.5)	5 (0.6)	0.8 (0.2–3.0)	2 (0.2)	4 (0.5)	0.5 (0.1–2.7)
Alkaline phosphatase >3× ULN	5 (0.6)	3 (0.4)	1.7 (0.4–6.9)	1 (0.1)	2 (0.2)	0.5 (0.0–5.5)
Bilirubin >2× ULN	4 (0.5)	3 (0.4)	1.3 (0.3–5.9)	6 (0.7)	8 (1.0)	0.7 (0.3–2.1)
Kidney function: creatinine >2 mg/dl	30 (3.8)	30 (3.9)	1.0 (0.6–1.6)	5 (0.6)	11 (1.4)	0.5 (0.2–1.3)
Muscle: creatine kinase >5× ULN	10 (1.3)	8 (1.0)	1.2 (0.5–3.1)	10 (1.2)	9 (1.1)	1.1 (0.5–2.7)
Hematology: platelet count <75×10^9/liter	1 (0.1)	0	—	0	1 (0.1)	—

* The safety population included all the patients who received at least one dose of inclisiran or placebo. Adverse events were recorded over the trial period of 540 days. ULN denotes the upper limit of the normal range.

† The exploratory cardiovascular end point comprised a *Medical Dictionary for Regulatory Activities*–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.

‡ Injection-site adverse events included the preferred terms injection-site erythema, injection-site hypersensitivity, injection-site pruritus, injection-site rash, and injection-site reaction.

§ Shown are events occurring with a frequency of 5% or more in either the inclisiran group or the placebo group in each trial. Some events occurred with a frequency of less than 5% in one trial but not the other; a dash indicates that the frequency was less than 5% in that trial.

LDL cholesterol–lowering effects of inclisiran are reversed at the rate of approximately 2% per month,[3,4] which means that these effects can persist for up to approximately 2 years. It is therefore reassuring that in the present trials with 6075 injections of inclisiran and 2166 person-years of exposure, the adverse-event profile of inclisiran was similar to that of placebo. Injection-site adverse events were more frequent with inclisiran than with placebo, but most were mild or moderate, did not require intervention, and were not persistent. Ongoing open-label extension studies will provide additional longer-term safety follow-up information.[8]

Overall deaths were similar in the inclisiran and placebo groups in each trial. The prespecified cardiovascular composite end point was reported with lower frequency in the inclisiran group (7.4 to 7.8%, as compared with 10.2 to 10.3% in the placebo group). However, the total number of nonadjudicated cardiovascular events observed was too small to draw meaningful conclusions about any potential benefits of inclisiran on cardiovascular outcomes, a question that is being tested in an ongoing cardiovascular outcomes trial.[8]

The potential for siRNA-based therapies has already reached fruition in rare-disease areas such as transthyretin amyloidosis and porphyria.[11,12] This therapeutic approach harnesses the intrinsic natural and highly conserved process of RNA interference present in all mammalian cells. Therapies that are based on RNAi seem to require less frequent dosing than other RNA-based therapies, such as antisense oligonucleotides.[13] The results of our trials have the potential to move RNAi-based therapies from the realm of rare to common diseases.[10]

The aim of any cholesterol-lowering therapeutic regimen is to maintain consistent, long-term reductions in the exposure to LDL cholesterol and to do so safely. Statins are first-line pharmacotherapy for LDL cholesterol lowering, but many patients require additional LDL cholesterol lowering.[14,15] The convenience of a treatment regimen and the medication burden that is placed on the patient may influence long-term adherence.[16,17] Poor adherence to statins is associated with less

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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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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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

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REFERENCES

1. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713-22.
2. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097-107.
3. Ray KK, Landmesser U, Leiter LA, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. N Engl J Med 2017;376:1430-40.
4. Ray KK, Stoekenbroek RM, Kallend D, et al. Effect of 1 or 2 doses of inclisiran on low-density lipoprotein cholesterol levels: one-year follow-up of the ORION-1 randomized clinical trial. JAMA Cardiol 2019 September 25 (Epub ahead of print).
5. 2016 ESC/EAS guidelines for the management of dyslipidaemias: the Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis 2016;253:281-344.
6. Immunogenicity testing of therapeutic protein products — developing and validating assays for anti-drug antibody detection. Silver Spring, MD: Food and Drug Administration, 2019 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/immunogenicity-testing-therapeutic-protein-products-developing-and-validating-assays-anti-drug).
7. Guideline on immunogenicity assessment of therapeutic proteins. London: European Medicines Agency, 2017 (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-immunogenicity-assessment-therapeutic-proteins-revision-1_en.pdf).
8. Stoekenbroek RM, Kallend D, Wijngaard PL, Kastelein JJ. Inclisiran for the treatment of cardiovascular disease: the ORION clinical development program. Future Cardiol 2018;14:433-42.
9. Khvorova A. Oligonucleotide therapeutics — a new class of cholesterol-lowering drugs. N Engl J Med 2017;376:4-7.
10. Levin AA. Targeting therapeutic oligonucleotides. N Engl J Med 2017;376:86-8.
11. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med 2018;379:11-21.

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12. Sardh E, Harper P, Balwani M, et al. Phase 1 trial of an RNA interference therapy for acute intermittent porphyria. N Engl J Med 2019;380:549-58.
13. Ray KK, Corral P, Morales E, Nicholls SJ. Pharmacological lipid-modification therapies for prevention of ischaemic heart disease: current and future options. Lancet 2019;394:697-708.
14. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73(24):e285-e350.
15. Mach F, Baigent C, Catapano AL, et al. ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41:111-88.
16. Choudhry NK, Fischer MA, Avorn J, et al. The implications of therapeutic complexity on adherence to cardiovascular medications. Arch Intern Med 2011;171:814-22.
17. Danese MD, Gleeson M, Kutikova L, et al. Estimating the economic burden of cardiovascular events in patients receiving lipid-modifying therapy in the UK. BMJ Open 2016;6(8):e011805.
18. Khunti K, Danese MD, Kutikova L, et al. Association of a combined measure of adherence and treatment intensity with cardiovascular outcomes in patients with atherosclerosis or other cardiovascular risk factors treated with statins and/or ezetimibe. JAMA Netw Open 2018;1(8):e185554.
19. Rodriguez F, Maron DJ, Knowles JW, Virani SS, Lin S, Heidenreich PA. Association of statin adherence with mortality in patients with atherosclerotic cardiovascular disease. JAMA Cardiol 2019;4:206-13.
20. Brookhart MA, Patrick AR, Schneeweiss S, et al. Physician follow-up and provider continuity are associated with long-term medication adherence: a study of the dynamics of statin use. Arch Intern Med 2007;167:847-52.
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