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Effects of Inclisiran in Patients With Atherosclerotic Cardiovascular Disease A pooled Analysis of the ORION10 and ORION11 Randomized Trials

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Effects of Inclisiran in Patients With Atherosclerotic Cardiovascular Disease: A Pooled Analysis of the ORION-10 and ORION-11 Randomized Trials

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Abstract

Objective: To evaluate the efficacy, safety, and tolerability of inclisiran in participants with atherosclerotic cardiovascular disease (ASCVD) from ORION-10 and ORION-11 stratified by key patient characteristics.

Patients and Methods: Participants were randomized 1:1 to receive 300 mg inclisiran sodium (284 mg inclisiran) or placebo on Days 1, 90, 270, and 450, alongside background lipid-lowering therapy. This pooled, post hoc analysis stratified participants with ASCVD by sex, age, race, kidney function, body mass index, and glycemic status. Co-primary endpoints were percentage changes in low-density lipoprotein cholesterol (LDL-C) from baseline to Day 510, and after Day 90 and up to Day 540 (time-adjusted). LDL-C goal attainment and safety were also assessed.

Results: This analysis of 2975 participants included: female, n=827; Black, n=213; 75 years of age or older, n=458; obese, n=1474; diabetes, n=1182; and moderate-to-severe chronic kidney disease, n=538. Mean baseline LDL-C levels in the total ASCVD population were balanced between treatment arms (inclisiran, 103.4 mg/dL; placebo, 102.0 mg/dL). With inclisiran, mean placebo-corrected percentage changes in LDL-C from baseline were −51.5% (95% CI, −54.0 to −49.0) and −52.1% (95% CI, −53.9 to −50.4) to Day 510 and Day 540 (time-adjusted), respectively; this was consistent across subgroups. LDL-C less than 55 mg/dL at one or more visits was reached by 87.6% of participants receiving inclisiran. The inclisiran safety profile was consistent across subgroups.

Conclusion: Twice-yearly inclisiran (after initial and 3-month doses) was well tolerated and provided significant, consistent LDL-C reductions for up to 18 months in participants with ASCVD independent of key patient characteristics (ORION-10; NCT03399370 and ORION-11; NCT03400800).

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For editorial comment, see page 1204

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Patients with clinical atherosclerotic cardiovascular disease (ASCVD) and elevated low-density lipoprotein cholesterol (LDL-C), despite statin therapy, are at very high risk of recurrent ASCVD events.[1,2] This risk is further compounded by the presence of other ASCVD risk factors, including diabetes, chronic kidney disease (CKD), and elevated lipoprotein(a) [Lp(a)].[1,3-6] Consequently, when patients do not meet guideline-directed LDL-C goals with maximally tolerated statins alone, intensive LDL-C lowering with the addition of non-statin lipid-lowering therapy (LLT) is recommended.[1,3,5-7]

In clinical trials in patients with ASCVD, the addition of ezetimibe or anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies to statin therapy has been shown to reduce the risk of major adverse cardiac events by 6.4% and 15%,

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respectively, vs statins alone.[8-10] Additionally, bempedoic acid has been shown to reduce the risk of major adverse cardiac events in statin-intolerant patients by 13% compared with placebo.[11] Nonetheless, registry studies suggest that, despite the availability of non-statin LLT, up to 80% of patients with ASCVD are not at guideline-recommended LDL-C goals,[12-14] indicating a need to optimize LLT for patients at the highest risk of ASCVD events. Further, there are disparities in the management of elevated LDL-C between patients of different ages, sexes, races, and ethnicities.[15-17]

Inclisiran, a small-interfering RNA that prevents hepatic PCSK9 synthesis,[18] has been shown to produce substantial and sustained reductions in LDL-C and other atherogenic lipoproteins with twice-yearly subcutaneous dosing (after initial doses at baseline and 3 months).[19-21] Therefore, inclisiran may be a convenient and effective therapy for the management of patients with clinical ASCVD. This post hoc analysis evaluated the efficacy, safety, and tolerability of inclisiran in a subset of participants with clinical ASCVD from the ORION-10 (NCT03399370) and ORION-11 (NCT03400800) clinical trials stratified by key demographic and clinical characteristics.

PATIENTS AND METHODS

Study Design and Participants

This was a post hoc, exploratory analysis of pooled data from the randomized, double-blind, placebo-controlled, phase III ORION-10 and ORION-11 trials conducted between December 21, 2017, and September 09, 2019, and November 01, 2017, and July 31, 2019, respectively. The methodology and results of both trials have been published previously (corresponding protocols are available at NEJM.org).[21] The study protocols for both trials were identical and were approved by an institutional review board or independent ethics committee at each participating institution.

In brief, both studies were 18 months in duration; participants were randomized 1:1 to receive 300 mg inclisiran sodium (equivalent to 284 mg of inclisiran) or placebo at Days 1, 90, 270, and 450 in combination with background maximally tolerated statin therapy and/or other oral LLT (Figure 1A). ORION-10 and ORION-11 included adult participants (≥18 years of age) with a history of ASCVD (coronary heart disease, cerebrovascular disease, or peripheral artery disease) and LDL-C greater than or equal to 70 mg/dL (to convert values to mmol/L, multiply by 0.0259). If taking statin therapy or other LLT, the dosage must have been stable for 30 days or longer before screening, with no planned changes. ORION-11 also included adult participants with LDL-C 100 mg/dL or more and an ASCVD 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). Written informed consent was obtained from all participants.

This post hoc analysis included the subset of participants with ASCVD only (the total ASCVD population). Participants were stratified by sex (male, female), age (18 to <65 years, ≥65 to <75 years, ≥75 years), race (White, Black, or "other" [American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander]), kidney function (based on estimated glomerular filtration rate [eGFR]; no CKD, eGFR ≥90 mL/min per 1.73 m^2; mild CKD, eGFR ≥60 to <90 mL/min per 1.73 m^2; moderate-to-severe CKD, eGFR <60 mL/min per 1.73 m^2), body mass index (BMI) (normal weight, BMI <25 kg/m^2; overweight, BMI ≥25 to <30 kg/m^2; obese, BMI ≥30 kg/m^2),[22] and glycemic status (normoglycemia, prediabetes, diabetes; see Supplemental Material for definitions [available online at http://www.mayoclinicproceedings.org]).

Endpoints

The first co-primary endpoint was the percentage change in LDL-C from baseline to Day 510. To assess the effect of inclisiran on LDL-C at a steady state, the second co-primary endpoint was the mean percentage change in LDL-C from baseline after Day 90 and up to Day 540 (time-adjusted percentage

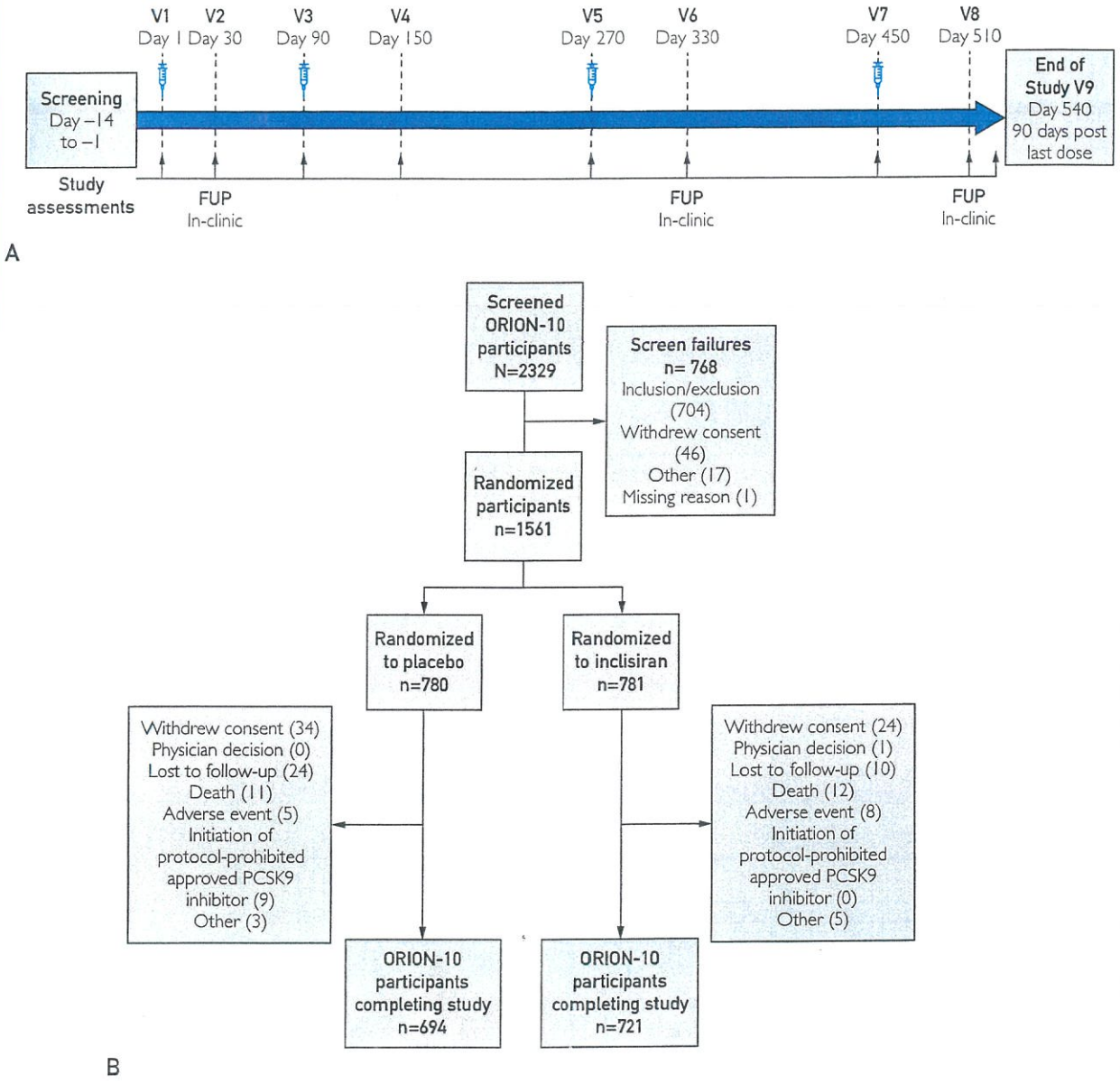


FIGURE 1. Study design (A) and participant disposition of the ORION-10 (B) and ORION-11 (C) studies. ASCVD, atherosclerotic cardiovascular disease; FUP, follow-up; PCSK9, proprotein convertase subtilisin/kexin type 9; V, visit.

change). Key secondary endpoints are listed in the Supplemental Material.

For this post hoc analysis, the proportion of participants reaching the LDL-C goals of less than 40 mg/dL and less than 55 mg/dL at one or more visits were evaluated as exploratory analyses based on the 2019 European Society of Cardiology/European Atherosclerosis Society lipid management guidelines and the 2022 American College of Cardiology Expert Consensus Decision Pathway published following the finalization of the study protocols.[1,7] The proportion of participants reaching a greater than or equal to 50% reduction in LDL-C (from their statin-treated baseline) in addition to the

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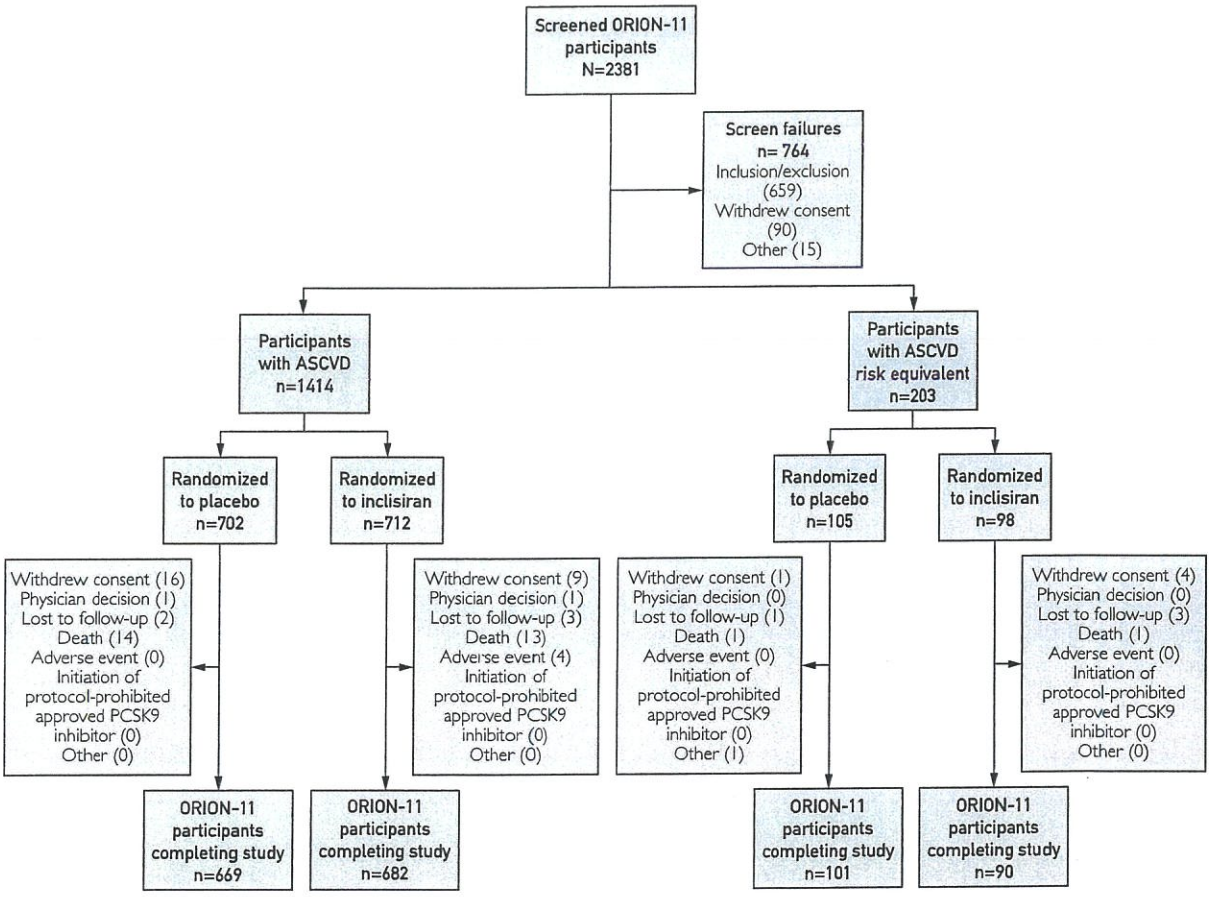


FIGURE 1. *(continued).*

goals of less than 70 mg/dL, less than 55 mg/dL, or less than 40 mg/dL at one or more visits was also evaluated.

Statistical Analysis

The statistical analyses used have been described previously; detailed statistical analysis plans for both trials are available at NEJM.org.[21] For this analysis, all randomized participants were included in efficacy analyses unless otherwise specified. All participants who received one or more doses of study drug were included in safety analyses, with treatment classification based on actual treatment received.

The percentage change (first co-primary endpoint) and absolute change in LDL-C from baseline to Day 510 were analyzed using an analysis of covariance (ANCOVA). The second co-primary endpoint (time-adjusted percentage change) was analyzed using a mixed-effects model for repeated measures (MMRM). Further details of individual analyses can be found in the Supplemental Material.

For continuous variables, two-sided 95% CIs for least squares means, or 95% CIs for median values, were calculated. For binary variables, 95% CIs for proportions were calculated. The nominal *P* values and 95% CIs provided are considered descriptive measures for the strength of association between treatment arms and endpoints and are not formal criteria to claim statistical

significance. For treatment-emergent adverse events (TEAEs), risk ratios (RRs) and 95% CIs were calculated. Analyses were performed using SAS software, version 9.4 or higher (SAS Institute Inc).

RESULTS

Participants

This post hoc, pooled analysis included 2975 participants with ASCVD (93.6% of all 3178 ORION-10 and ORION-11 randomized participants, excluding n=203 participants without ASCVD). Of included participants, 827 (27.8%) were female, 213 (7.2%) were Black, 32 (1.1%) were included in the "other" race category, 458 (15.4%) were 75 years of age or older, 1474 (49.5%) were obese, 1182 (39.7%) had diabetes, and 538 (18.1%) had moderate-to-severe CKD (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). Overall, 1493 participants with ASCVD were randomized to inclisiran and 1482 to placebo; most completed ORION-10 (inclisiran, 92.3%; placebo, 89.0%) (Figure 1B) or ORION-11 (inclisiran, 95.8%; placebo, 95.3%) (Figure 1C).

Baseline characteristics were generally balanced between treatment arms within each key demographic and clinical characteristic subgroup, although there was some variation (Supplemental Tables 1-4, available online at http://www.mayoclinicproceedings.org). Median baseline Lp(a) levels varied across subgroups, although this was generally balanced between treatment arms except for the Black (inclisiran, 129.0 nmol/L; placebo, 169.0 nmol/L; $P=.02$) and overweight (inclisiran, 53.5 nmol/L; placebo, 43.0 nmol/L; $P=.03$) subgroups (Supplemental Table 4). Median baseline Lp(a) levels were greater than or equal to 2.0-fold higher in female vs male participants (inclisiran, 84.0 nmol/L and 38.5 nmol/L; placebo, 80.0 nmol/L and 40.0 nmol/L, respectively), and were greater than or equal to 3.1-fold higher in Black vs White participants (inclisiran, 129.0 nmol/L and 41.0 nmol/L; placebo, 169.0 nmol/L and 41.0 nmol/L, respectively) (Supplemental Table 4).

Efficacy

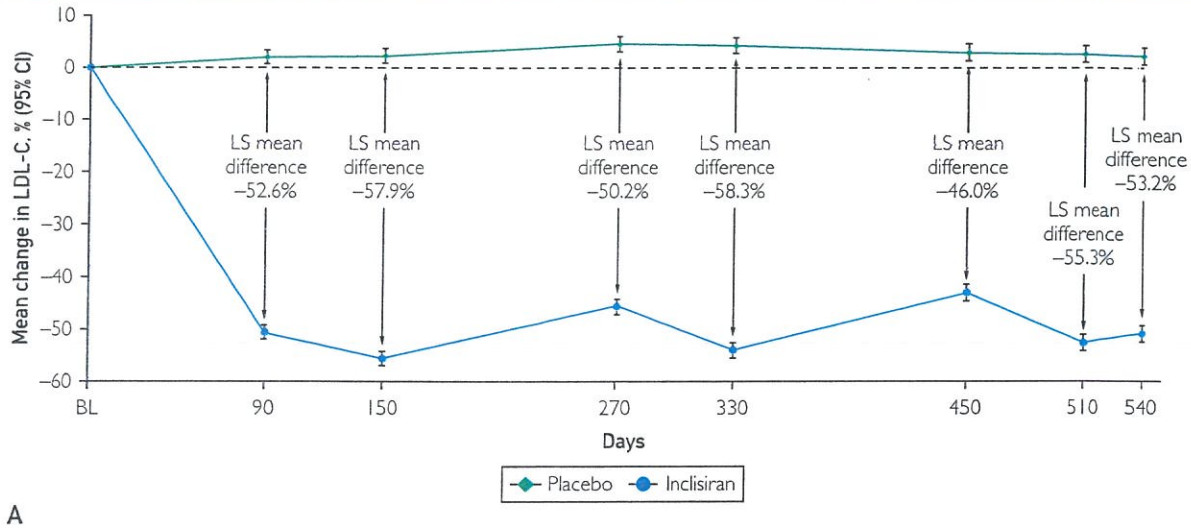
Figure 2A summarizes the percentage change in LDL-C from baseline in the total ASCVD population. With inclisiran, mean overall placebo-corrected percentage change in LDL-C from baseline to Day 510 (co-primary endpoint) was −51.5% (95% CI, −54.0 to −49.0; $P<.001$), and LDL-C lowering was consistent across subgroups (−53.7% to −45.2%) (Figure 2B). Mean absolute change in LDL-C from baseline to Day 510 was −50.8 mg/dL (95% CI, −52.6 to −49.0) with inclisiran vs −0.4 mg/dL (95% CI, −2.1 to 1.3) with placebo; this was consistent across all subgroups ($P<.001$ for inclisiran vs placebo) (Supplemental Table 5, available online at http://www.mayoclinicproceedings.org).

With inclisiran, the mean placebo-corrected, time-adjusted percentage change (co-primary endpoint) and absolute change in LDL-C from baseline after Day 90 and up to Day 540 was −52.1% (95% CI, −53.9 to −50.4) and −52.3 mg/dL (95% CI, −54.0 to −50.6) respectively (Figures 3A and 3B). There was minimal variation across subgroups (mean percentage change, −54.4% to −48.3%; mean absolute change, −59.7 mg/dL to −48.7 mg/dL) (Figures 3A and 3B and Supplemental Table 6 [available online at http://www.mayoclinicproceedings.org]).

Overall, inclisiran treatment reduced PCSK9 levels from baseline by 71.6% (95% CI, −73.2 to −69.9) at Day 510 compared with an increase of 12.1% (95% CI, 10.4 to 13.7) with placebo. The decrease in PCSK9 from baseline to Day 510 with inclisiran was consistent across subgroups (Supplemental Table 7, available online at http://www.mayoclinicproceedings.org). Similarly, inclisiran led to reductions from baseline in total cholesterol, apolipoprotein B (apoB), triglycerides, and non–high-density lipoprotein cholesterol at Day 510 that were generally consistent across subgroups (Supplemental Table 7).

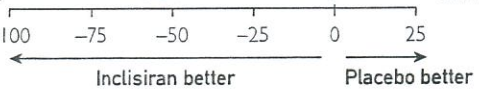
In the total ASCVD population, median Lp(a) levels decreased from baseline to Day 540 with inclisiran (−17.9%; 95% CI, −19.5 to −16.3), and increased with placebo (3.3%; 95% CI, 1.8 to 4.8; inclisiran vs

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A

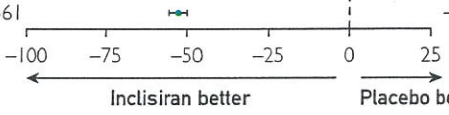
Subgroup	Inclisiran n	Placebo n	LS mean percentage difference (95% CI)	*P*-value
Total ASCVD population	1493	1482	−51.5 (−54.0 to −49.0)	<.001
Sex				
Male	1069	1079	−51.2 (−54.0 to −48.4)	<.001
Female	424	403	−52.5 (−57.3 to −47.6)	<.001
Age (years)				
≥18–<65	614	646	−52.5 (−56.4 to −48.6)	<.001
≥65–<75	655	602	−50.6 (−54.4 to −46.9)	<.001
≥75	224	234	−51.2 (−56.8 to −45.6)	<.001
Race				
White	1350	1380	−52.1 (−54.6 to −49.6)	<.001
Black	121	92	−45.2 (−55.7 to −34.7)	<.001
Other	22	10	−52.0 (−89.5 to −14.5)	.007
Kidney function				
No CKD	387	384	−49.2 (−54.0 to −44.4)	<.001
Mild CKD	832	834	−52.4 (−55.6 to −49.1)	<.001
Moderate-to-severe CKD	274	264	−52.0 (−58.2 to −45.9)	<.001
BMI (kg/m^2)				
<25	195	173	−51.1 (−58.2 to −43.9)	<.001
≥25–<30	577	554	−49.0 (−52.7 to −45.3)	<.001
≥30	721	753	−53.7 (−57.4 to −50.1)	<.001
Glycemic status				
Normoglycemia	271	264	−49.6 (−55.2 to −44.1)	<.001
Pre-diabetes	600	657	−52.0 (−55.5 to −48.4)	<.001
Diabetes	621	561	−52.2 (−56.4 to −48.1)	<.001



B

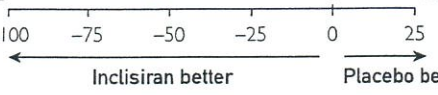
FIGURE 2. Post hoc, pooled analysis of percentage change in LDL-C over time, from baseline to Day 540, with inclisiran and placebo using MMRM (A) and placebo-corrected percentage change in LDL-C from baseline to Day 510, with inclisiran using ANCOVA (B), in participants with ASCVD from ORION-10 and ORION-11. ANCOVA, analysis of covariance; ASCVD, atherosclerotic cardiovascular disease; BL, baseline; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; LDL-C, low-density lipoprotein cholesterol; LS, least squares; MMRM, mixed model for repeated measures.

Subgroup	Inclisiran n	Placebo n	LS mean percentage difference (95% CI)	*P*-value
Total ASCVD population	1493	1482	−52.1 (−53.9 to −50.4)	<.001
Sex				
Male	1069	1079	−51.6 (−53.6 to −49.6)	<.001
Female	424	403	−53.7 (−57.3 to −50.1)	<.001
Age (years)				
≥18–<65	614	646	−52.1 (−55.0 to −49.1)	<.001
≥65–<75	655	602	−52.5 (−55.1 to −49.9)	<.001
≥75	224	234	−51.2 (−55.0 to −47.3)	<.001
Race				
White	1350	1380	−52.5 (−54.3 to −50.7)	<.001
Black	121	92	−48.3 (−55.4 to −41.1)	<.001
Other	22	10	−51.4 (−71.1 to −31.7)	<.001
Kidney function				
No CKD	387	384	−48.8 (−52.1 to −45.6)	<.001
Mild CKD	832	834	−52.9 (−55.2 to −50.5)	<.001
Moderate-to-severe CKD	274	264	−54.4 (−58.9 to −50.0)	<.001
BMI (kg/m^2)				
<25	195	173	−52.1 (−57.4 to −46.8)	<.001
≥25–<30	577	554	−49.7 (−52.4 to −47.0)	<.001
≥30	721	753	−54.2 (−56.8 to −51.6)	<.001
Glycemic status				
Normoglycemia	271	264	−49.9 (−54.1 to −45.8)	<.001
Pre-diabetes	600	657	−52.6 (−55.2 to −50.0)	<.001
Diabetes	621	561	−52.9 (−55.8 to −50.1)	<.001



A

Subgroup	Inclisiran n[a]	Placebo n[a]	LS mean absolute difference, mg/dL (95% CI)	*P*-value
Total ASCVD population	1463	1436	−52.3 (−54.0 to −50.6)	<.001
Sex				
Male	1052	1048	−50.4 (−52.3 to −48.5)	<.001
Female	411	388	−57.3 (−60.9 to −53.7)	<.001
Age (years)				
≥18–<65	602	628	−52.6 (−55.4 to −49.8)	<.001
≥65–<75	641	582	−53.0 (−55.6 to −50.5)	<.001
≥75	220	226	−49.4 (−53.2 to −45.6)	<.001
Race				
White	1324	1338	−52.3 (−54.1 to −50.5)	<.001
Black	117	88	−52.1 (−59.7 to −44.5)	<.001
Other	22	10	−59.7 (−75.9 to −43.5)	<.001
Kidney function				
No CKD	381	371	−48.7 (−51.9 to −45.4)	<.001
Mild CKD	817	808	−53.1 (−55.4 to −50.8)	<.001
Moderate-to-severe CKD	265	257	−55.1 (−59.1 to −51.1)	<.001
BMI (kg/m^2)				
<25	194	167	−52.4 (−57.6 to −47.3)	<.001
≥25–<30	567	539	−50.6 (−53.3 to −47.8)	<.001
≥30	702	729	−53.8 (−56.2 to −51.5)	<.001
Glycemic status				
Normoglycemia	269	251	−50.4 (−54.6 to −46.2)	<.001
Pre-diabetes	591	643	−52.4 (−54.9 to −49.9)	<.001
Diabetes	603	542	−53.4 (−56.1 to −50.6)	<.001



B

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FIGURE 3. Post hoc, pooled analysis of time-adjusted, placebo-corrected percentage change (A) and absolute change (B) in LDL-C from baseline after Day 90 and up to Day 540, with inclisiran, in participants with ASCVD from ORION-10 and ORION-11. [a]Participants with missing data were excluded from this analysis. To convert LDL-C from mg/dL to mmol/L, multiply by 0.0259. ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; LS, least squares.

placebo, $P<.001$). Reductions in Lp(a) from baseline with inclisiran were comparable in female vs male participants (−15.5% and −18.3%) and Black vs White participants (−19.3% and −17.7%) (Supplemental Table 7).

Significantly more participants treated with inclisiran in the total ASCVD population reached the LDL-C goals of less than 100 mg/dL, less than 70 mg/dL, and less than 25 mg/dL vs placebo at one or more visits (97.9%, 93.5%, and 35.3% vs 81.1%, 38.0%, and 0.6%, respectively; $P<.001$ for inclisiran vs placebo for all goals) (Figure 4A). The exploratory LDL-C less than 55 mg/dL and less than 40 mg/dL goals were met, at one or more visits, by significantly more participants treated with inclisiran vs placebo (87.6% and 68.2% vs 12.4% and 1.6%, respectively; $P<.001$ for both goals). Overall, LDL-C was reduced from a statin-treated baseline by 50% or more in 87.9% of participants treated with inclisiran vs 6.0% with placebo ($P<.001$) at one or more visits (Figure 4B).

Safety

A summary of safety analyses by treatment arm for the total ASCVD population and subgroups is presented in Supplemental Table 8. The incidence of TEAEs was broadly similar between treatment arms in the total ASCVD population (inclisiran: 77.2%, placebo: 77.8%; RR, 0.99; 95% CI, 0.96 to 1.03) and across subgroups (inclisiran, 68.2% to 81.7%; placebo, 61.5% to 85.5%; RR, 0.95 to 1.12). Rates of treatment-emergent serious adverse events were also similar between treatment arms in the total ASCVD population (inclisiran, 22.5%; placebo, 25.3%; RR, 0.89; 95% CI, 0.78 to 1.01) and across subgroups ranged from 4.5% to 30.8% with inclisiran and 20.0% to 35.0% with placebo (RR, 0.23 to 1.04). The incidence of study drug-related treatment-emergent serious adverse events was low and similar between treatment arms, irrespective of subgroup (inclisiran, 0% to 0.9%; placebo, 0% to 1.1.%; RR, 0.40 to 2.10) (Supplemental Table 8).

Overall, TEAEs leading to study discontinuation were reported in 0.8% of participants receiving inclisiran and 0.3% of participants receiving placebo (RR, 2.37; 95% CI, 0.84 to 6.72); the incidence of participant deaths was 1.7% in both treatment arms (RR, 0.99; 95% CI, 0.57 to 1.71) (Supplemental Table 8). Clinically relevant TEAEs at the injection site were more common with inclisiran vs placebo (54 [3.6%] vs 11 [0.7%]; RR, 4.85; 95% CI, 2.55 to 9.24), and all were mild or moderate (Table 1). Clinically relevant TEAEs at the injection site were generally more common with inclisiran vs placebo across subgroups (Supplemental Table 8).

DISCUSSION

This post hoc, pooled analysis of ORION-10 and ORION-11 evaluated the efficacy, safety, and tolerability of inclisiran vs placebo in participants with ASCVD, and according to sex, age, race, kidney function, BMI, and glycemic status.

Twice-yearly inclisiran (after initial doses at Days 1 and 90) resulted in a mean placebo-corrected LDL-C reduction from baseline to Day 510 of 51.5%, and a placebo-corrected, time-adjusted reduction in LDL-C from baseline of 52.1%. In addition, inclisiran had a similar safety profile to placebo and was well tolerated except for TEAEs at the injection site, which were all mild or moderate. These results are consistent with the overall ORION-10 and ORION-11 populations and other phase III

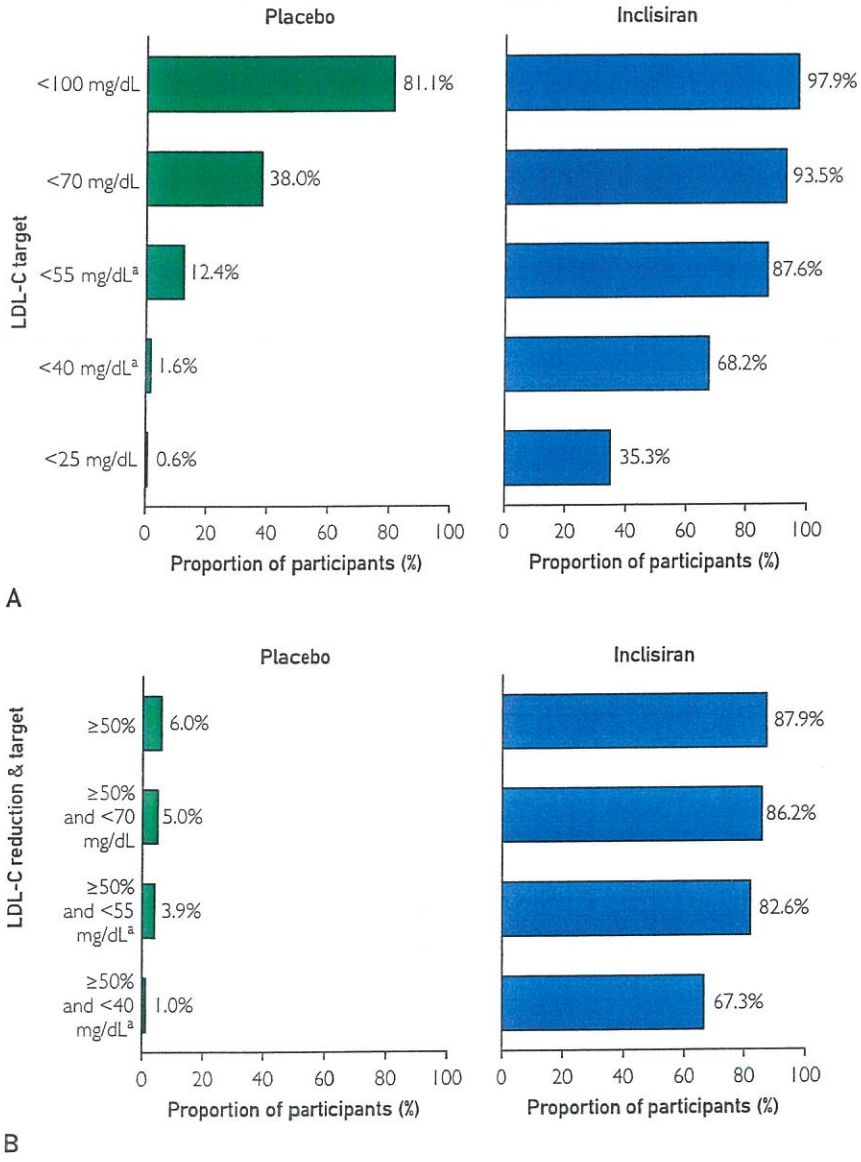


FIGURE 4. Post hoc, pooled analysis of the proportion of participants with ASCVD in ORION-10 and ORION-11 reaching guideline-recommended LDL-C goals (A), and with a 50% or greater reduction from baseline in LDL-C and reaching LDL-C goals (B), at one or more visits. [a]The less than 55 mg/dL and less than 40 mg/dL LDL-C goals were added as exploratory analyses because of their inclusion in recent lipid management guidelines and consensus statements.[1,7] $P<.001$ for inclisiran vs placebo for all goals. ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

inclisiran studies.[20,21,23,24] Compared with the 203 ORION-11 participants with ASCVD risk equivalent, participants with ASCVD in the current analysis showed numerically larger placebo-corrected reductions in LDL-C from baseline (to Day 510, 51.5% vs 43.7%; time-adjusted, 52.1% vs 41.0%) and a numerically lower incidence of TEAEs (inclisiran: 77.2%, placebo: 77.8% vs inclisiran: 92.9%, placebo: 83.8%).[25]

The Cholesterol Treatment Trialists' meta-analyses have shown that every

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TABLE 1. Summary of Participants With One or More Clinically Relevant TEAE at the Injection Site, by Treatment Arm, in the ASCVD Safety Population

	Inclisiran (n=1494[a])	Placebo (n=1477[a])	Total (N=2971[b])	RR[c] (95% CI)
Participants with ≥1 clinically relevant TEAE at the injection site[d]	54 (3.6)	11 (0.7)	65 (2.2)	4.85 (2.55 to 9.24)
Mild	35 (2.3)	10 (0.7)	45 (1.5)	3.46 (1.72 to 6.96)
Moderate	19 (1.3)	1 (0.1)	20 (0.7)	18.78 (2.52 to 140.13)
Severe	0	0	0	—

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; RR, risk ratio; TEAE, treatment-emergent adverse event.

Data are n (%) unless otherwise specified.

[a]Two participants assigned to the inclisiran group were not dosed; two participants assigned to the placebo group were not dosed; three participants assigned to the placebo group received inclisiran and were analyzed as part of the inclisiran safety population.

[b]Only participants who received one or more dose of inclisiran or placebo comprised the safety population, with treatment classification based on actual treatment received.

[c]RR of inclisiran/placebo.

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

1-mmol/L reduction in LDL-C reduced cardiovascular event risk by 22%.[1] The clear correlation between degree of LDL-C lowering and reduction in cardiovascular events is further emphasized by medical society recommendations to treat patients to LDL-C goals for secondary ASCVD prevention.[1,3,5,7] Despite this, the majority of patients with ASCVD do not meet guideline-recommended LDL-C goals due to factors including poor adherence, clinical inertia, health inequities, and barriers to care.[13,26-28] In this analysis, most participants treated with inclisiran in combination with maximally tolerated statins and/or additional LLT experienced a reduction in LDL-C from baseline of 50% or more (87.9%) and/or reached the goals of LDL-C less than 70 mg/dL (86.2%) or less than 55 mg/dL (82.6%) at one or more visits. These observations suggest that the use of inclisiran can facilitate LDL-C goal attainment in high-risk patients with ASCVD who are not achieving adequate LDL-C reduction despite the use of statins and other oral LLT.

Of the approximately 24 million US adults with ASCVD, 39.1% have diabetes and 15.8% have CKD.[13] Both comorbidities can alter an individual's lipid profile and increase the risk of ASCVD events.[1,3,5,6,29-32] Race, excess weight, older age (≥65 years), and sex-related factors, including adverse pregnancy outcomes and premature menopause, have also been associated with increased ASCVD risk, and in some cases altered lipid profiles.[1,3,27,33,34] Medical society guidelines recommend that a patient's race is considered when determining ASCVD risk and statin intensity due to heterogeneity in medication responses and risk for ASCVD, elevated lipid levels, and other cardiovascular risk factors that are observed between groups.[3] Certain cardiovascular risk factors (eg, hypertension and diabetes) are more prevalent among Black populations than White populations in the United States, and Black patients with ASCVD are less likely to receive prescriptions for LLT (eg, statins) compared with White patients.[16,27] In addition, some patient groups, including female patients, older patients (≥65 years), and those with severe CKD, are typically more likely to experience drug-related adverse events.[35-37] Thus, the efficacy and safety of twice-yearly inclisiran vs placebo was examined across patient subgroups, and inclisiran was shown to be effective and well tolerated, irrespective of sex, age, race, kidney function, BMI, and glycemic status.

Across all subgroups, the placebo-corrected mean reductions in LDL-C from baseline to Day 510 with inclisiran treatment ranged from 45.2% to 53.7%, and the mean

placebo-corrected, time-adjusted LDL-C reductions from baseline after Day 90 and up to Day 540 ranged from 48.3% to 54.4%. These results were consistent with the overall study population and other clinical trials showing the efficacy of twice-yearly inclisiran regardless of age, race, sex, glycemic status, BMI, and kidney function.[20,21,23,24] In addition, this finding is similar to those reported with statins and PCSK9 monoclonal antibodies which have also shown consistent LDL-C–lowering across demographic and clinical subgroups.[38-45] As a first-in-class LDL-C–lowering small-interfering RNA with the potential to be administered to diverse patient populations, our analysis demonstrates the generally consistent efficacy of inclisiran in these specific demographic groups.

In addition to LDL-C, elevated levels of other atherogenic apoB-containing lipoproteins, including Lp(a), are associated with increased risk of ASCVD events.[4,46–52] In the total ASCVD population, mean total cholesterol (−31.9%), apoB (−43.3%), triglycerides (−6.7%), non–high-density lipoprotein cholesterol (−46.0%), and median Lp(a) (−17.9%) were significantly reduced from baseline vs placebo after 18 months of inclisiran treatment, consistent with results from other inclisiran clinical trials.[20,21,23,24] In this ASCVD population, as has been consistently reported in other studies,[53–56] Black participants and female participants had higher median Lp(a) levels than White participants and male participants, respectively. The 2.0-fold or greater difference in baseline median Lp(a) levels between female and male participants in this subanalysis is greater than reported in other population analyses (1.2-fold to 1.4-fold).[53–56] Despite the differences in median baseline Lp(a) levels, inclisiran treatment significantly reduced Lp(a) levels vs placebo by a similar proportion compared with the total ASCVD population in both female and Black participants.

Study Limitations

This analysis was not adequately powered to make formal statistical comparisons between subgroups. Although the effects of inclisiran were generally uniform across subgroups, the proportions of participants identified as Black (7.2%), "other" race (1.1%), female (27.8%), or with moderate-to-severe CKD (18.1%) were relatively small. This limits the ability to detect any potential differences in efficacy and/or safety of inclisiran in these patient categories. Consequently, the effect of race, kidney function, and sex on the efficacy and safety of inclisiran necessitates further investigation in studies with larger numbers of participants in each category to confirm our initial findings. We were unable to determine the exact proportion of participants who achieved a guideline-recommended 50% or greater LDL-C reduction from an untreated baseline, as baseline LDL-C for most participants was measured on a background of statin and/or other LLT. However, at a minimum, 87.9% of participants had a reduction of LDL-C of at least 50% from that baseline.

CONCLUSION

Lowering LDL-C to guideline-recommended goals is critical to reduce the risk of cardiovascular events in patients with clinical ASCVD. Twice-yearly inclisiran (after initial doses at baseline and 3 months) administration for up to 18 months was well tolerated and provided significant and sustained LDL-C reductions of approximately 50% in participants with ASCVD stratified by age, race, sex, kidney function, BMI, and glycemic status. Inclisiran is an effective therapeutic option for health care professionals to consider when selecting LLT for patients with ASCVD across a range of comorbidities and characteristics.

POTENTIAL COMPETING INTERESTS

Dr Wright has received advisory board fees from Novartis; and has received consulting fees regarding lipid issues with The Medicines Company. Dr Ray has received grants, paid to his institution, from Amgen, Daiichi Sankyo, and Regeneron Pharmaceuticals/Sanofi; has received personal fees for serving on steering committees, executive committees, or advisory boards from Abbott, Amgen,

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AstraZeneca, Bayer, Boehringer Ingelheim, Cargene, CRISPR, CSL Behring, Daiichi Sankyo, Eli Lilly, Esperion, Kowa, NewAmsterdam Pharma, Novartis, Novo Nordisk, Sanofi, Scribe, Silence Therapeutics, and Vaxxinity; and has received personal fees for CME and non-CME lectures from Amgen, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Novartis, Novo Nordisk, Sanofi, and Viatris. Dr Landmesser has received personal fees from Abbott, AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, and Sanofi; has received advisory fees from The Medicines Company; and has received grant support, lecture fees, and advisory fees from Amgen, Bayer, and Novartis. Dr Koenig has received consulting fees and lecture fees from Amgen, AstraZeneca, and Novartis; has received consulting fees from Corvidia Therapeutics, Daiichi Sankyo, DalCor Pharmaceuticals, Esperion, Genentech, Kowa, LIB Therapeutics, NewAmsterdam Pharma, Novo Nordisk, OMEICOS, Pfizer, TenSixteen Bio, and The Medicines Company; has received lecture fees from Berlin-Chemie, Bristol Myers Squibb, and Sanofi; and has received grant support and provision of reagents from Abbott, Dr Beckmann Pharma GmbH, Roche Diagnostics, and Singulex. Dr Raal has received advisory board fees from Amgen and Novartis; and has received consulting and lecture fees from Amgen, LIB Therapeutics, Novartis, Regeneron Pharmaceuticals, and Sanofi-Aventis. Dr Leiter has received grants (paid to his institution) and advisory board fees and fees for CME from Amgen and Novartis; has received advisory board fees and fees for serving on a steering committee from Esperion; has received grants (paid to his institution) and fees for serving on a steering committee from Kowa, Novartis, and The Medicines Company; and has received advisory board fees and fees for CME from Amarin, AstraZeneca, HLS, Merck, Pfizer, and Sanofi. Dr Conde and Ms Jackie Han report being employed by Novartis at the time of publication. Dr Schwartz has received research support (paid to his institution) from AstraZeneca, Resverlogix, Sanofi, Silence Therapeutics, and The Medicines Company; and has a pending patent (62/806313) on a method for reducing cardiovascular risk assigned in full to the University of Colorado.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **apoB**, apolipoprotein B; **ANCOVA**, analysis of covariance; **ASCVD**, atherosclerotic cardiovascular disease; **BMI**, body mass index; **CI**, confidence interval; **CKD**, chronic kidney disease; **eGFR**, estimated glomerular filtration rate; **LDL-C**, low-density lipoprotein cholesterol; **LLT**, lipid-lowering therapy; **Lp(a)**, lipoprotein(a); **MMRM**, mixed model for repeated measures; **PCSK9**, proprotein convertase subtilisin/kexin type 9; **RR**, risk ratio; **TEAE**, treatment-emergent adverse event

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