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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 82, NO. 24, 2023
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ORIGINAL INVESTIGATIONS

Safety and Tolerability of Inclisiran for Treatment of Hypercholesterolemia in 7 Clinical Trials

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ABSTRACT

BACKGROUND Inclisiran is a small interfering RNA agent to lower low-density lipoprotein cholesterol.

OBJECTIVES The purpose of this study was to provide reliable evidence to date on the long-term safety profile of inclisiran.

METHODS This post hoc analysis comprised patients treated with 300 mg inclisiran sodium or placebo in the completed (ORION-1, -3, -5, -9, -10, and -11) and ongoing (ORION-8) trials. Exposure-adjusted incidence rates and Kaplan-Meier estimates of cumulative incidence of reported treatment-emergent adverse events (TEAE), abnormal laboratory measurements, and incidence of antidrug antibodies were analyzed.

RESULTS This analysis included 3,576 patients treated with inclisiran for up to 6 years and 1,968 patients treated with placebo for up to 1.5 years, with 9,982.1 and 2,647.7 patient-years of exposure, respectively. Baseline characteristics were balanced between groups. Kaplan-Meier analyses showed that TEAEs that were serious or led to discontinuation; hepatic, muscle, and kidney events; incident diabetes; and elevations of creatine kinase or creatinine accrued at a comparable rate between groups for up to 1.5 years, with similar trends continuing for inclisiran beyond this period. Numerically fewer major cardiovascular events reported as TEAEs occurred with inclisiran during this period. Treatment-induced antidrug antibodies were uncommon with inclisiran (4.6%), with few of these persistent (1.4%) and not associated with greater incidence of TEAEs leading to study drug discontinuation or serious TEAEs.

CONCLUSIONS Long-term treatment with inclisiran was well tolerated in a diverse population, without new safety signals, supporting the safety of inclisiran in patients with dyslipidemia. (J Am Coll Cardiol 2023;82:2251–2261)
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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received June 1, 2023; revised manuscript received September 15, 2023, accepted October 4, 2023.

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2023.10.007

JACC VOL. 82, NO. 24, 2023
DECEMBER 12, 2023:2251–2261

ABBREVIATIONS AND ACRONYMS

ADA = antidrug antibodies

ASCVD = atherosclerotic cardiovascular disease

EAIR = exposure-adjusted incidence rate

K-M = Kaplan-Meier

LDL-C = low-density lipoprotein cholesterol

LLT = lipid-lowering therapy

MACE = major adverse cardiovascular event

OLE = open-label extension

PCSK9 = proprotein convertase subtilisin/kexin type 9

TEAE = treatment-emergent adverse event

TESAE = treatment-emergent serious adverse event

Extensive evidence has shown that lowering low-density lipoprotein cholesterol (LDL-C) levels reduces the risk of cardiovascular (CV) events, whereby the risk decreases in correspondence to the duration of treatment with lipid-lowering therapy (LLT).[1-3] As such, guidelines recommend specific target levels to lower LDL-C related to CV risk, and recommend maintaining those levels indefinitely.[4,5] However, a considerable proportion of patients do not achieve or maintain the recommended treatment goals with existing therapies, resulting in a diminished effectiveness in mitigating CV risk.[6,7] Therefore, new approaches to LLT are needed to improve attainment and maintain treatment goals.

SEE PAGE 2262

Inclisiran is a first-in-class small interfering RNA (siRNA) administered twice-yearly (after the initial and 3-month doses) by a health care professional via subcutaneous injection that decreases production of proprotein convertase subtilisin/kexin type 9 (PCSK9) in the liver to lower plasma LDL-C levels.[8] Multiple studies, including the 4-year open-label extension (OLE) trial, ORION-3, have demonstrated that twice-yearly dosing with inclisiran reduces LDL-C levels by ~50% in combination with maximally tolerated oral LLT in a range of patients, including those with heterozygous familial hypercholesterolemia, atherosclerotic cardiovascular disease (ASCVD), and ASCVD risk equivalent (a high-risk primary prevention cohort comprising individuals with type 2 diabetes mellitus, familial hypercholesterolemia, or a 10-year risk of a CV event ≥20% [by Framingham Risk Score or equivalent]).[9-12]

As the first and only siRNA currently approved to treat hypercholesterolemia,[8,13-15] it is important for clinicians and patients to have the fullest possible understanding of the safety and tolerability profile of inclisiran. To date, the safety and tolerability have been demonstrated in a pooled analysis of data from the 3 pivotal placebo-controlled Phase 3 trials (ORION-9 [NCT03397121], ORION-10 [NCT03399370], and ORION-11 [NCT03400800]), in which treatment with inclisiran for up to 18 months was well tolerated in 1,833 patients, with treatment-emergent adverse events (TEAEs) of any cause reported at a frequency similar to placebo. More patients experienced TEAEs at the injection site with inclisiran, which were predominantly mild, and none were severe or persistent.[16] These findings were confirmed in the ORION-3 trial (NCT03060577), a 4-year OLE study of the Phase 2 ORION-1 trial (NCT02597127).[11] To obtain more information on the long-term safety of inclisiran, ORION-3, -9, -10, and -11 trials were extended in the ongoing, OLE study, ORION-8 (NCT03814187).

In this analysis, we provide comprehensive information on the long-term safety profile of inclisiran by investigating safety and tolerability in a large, pooled data set from 7 completed and ongoing studies, with inclisiran exposure of up to 6 years. This analysis was conducted to determine whether any new potential safety signals arise with ongoing exposure to inclisiran.

METHODS

PATIENTS AND STUDY DESIGNS. Patient-level data were pooled from 7 clinical trials including ORION-1, -3, -5, -8, -9, -10, and -11. The study designs and inclusion criteria for these trials have been published previously[9-12,17] and are described in Supplemental Table 1. This pooled post hoc analysis included patients from ORION-1, -5 (part I), -9, -10, and -11 who received either the recommended formulation of 300 mg inclisiran sodium (equivalent to 284 mg inclisiran) or placebo, administered via subcutaneous injection on day 1, day 90, and 6-monthly (injections during ORION-1 were only administered on days 1 and 90) thereafter for the respective trial durations up to 1.5 years. Patients who received twice-yearly 300 mg inclisiran sodium in OLE trials, ORION-3, -5 (part II), and -8 were also included. For this analysis, the database lock of ORION-8 was March 9, 2022. All other trials were complete and had a database lock before this date. Each clinical trial included in this analysis was conducted in accordance with the ethical principles established by the Declaration of Helsinki and Good Clinical Practice guidelines. Study protocols were approved by local Institutional Review Boards or independent ethics committees; specific names of review boards and ethics committees are described in Supplemental Table 2. All patients provided written informed consent before they were included in the clinical trials.

SAFETY ASSESSMENTS. During each trial, safety was assessed by continuously monitoring TEAEs through medical history, health records, assessments of vital signs, physical examinations, clinical laboratory assessments, and electrocardiography. Investigator-reported TEAEs were identified using standard nomenclature from the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0, preferred terms, and classified by MedDRA System Organ Class

designations. Antidrug antibodies (ADA) were measured in serum as previously published.[9] Samples for detecting ADA were collected at every study visit during ORION-8, -9, -10, and -11; on day 1 and every 90 days after during ORION-3; and on days 1, 90, 330, and 720 during ORION-5. Patients from ORION-1 were excluded from ADA analysis because the laboratory assay used in ORION-1 differed from the other studies.

The endpoints for this pooled safety analyses include the cumulative incidence over time for up to 6 years and exposure-adjusted incidence rates (EAIRs) of treatment-emergent serious adverse events (TESAEs), TEAEs leading to drug discontinuation, scientifically relevant TEAEs (liver-, muscle-, and kidney-related events, incident diabetes, and major adverse cardiovascular events [MACE]), and changes in related laboratory parameters, as well as the incidence of treatment-induced ADA. TEAEs of scientific relevance were determined based on previous clinical reports for inclisiran, known effects associated with LLTs such as statins, and events related to ASCVD; identification criteria for prespecified TEAEs of scientific relevance are listed in Supplemental Table 3, including hepatic-, muscular-, and kidney-related events; incident diabetes; and MACE including CV death, cardiac arrest, nonfatal myocardial infarction, and nonfatal stroke.

Patients without diabetes at baseline were defined as having no medical history of diabetes, not receiving antidiabetic medication, and either hemoglobin A1c (HbA1c) <6.5% or fasting glucose <126 mg/dL at baseline. Incident diabetes was defined as the earliest date after study drug administration when any of the following occurred: laboratory results indicating diabetes; diabetic TEAEs identified by search criteria (Supplemental Table 3); or initiation of antidiabetic medication at any time postbaseline. The laboratory results indicating diabetes could be any of the following: HbA1c ≥6.5% on 2 consecutive tests; a fasting glucose ≥126 mg/dL on 2 consecutive fasted tests; HbA1c ≥6.5% and fasting glucose ≥126 mg/dL on the same occasion; HbA1c ≥6.5% on 1 occasion and fasting glucose ≥126 mg/dL on the succeeding occasion; or a fasting glucose ≥126 mg/dL on 1 occasion and HbA1c ≥6.5% on the succeeding occasion. For laboratory criteria involving 2 consecutive occasions, the first occasion determines the event time.

Patients with treatment-induced ADA were defined as those with a negative ADA sample at baseline and ≥1 confirmed positive ADA sample postbaseline. Treatment-induced ADA were categorized as persistent and transient. Persistent ADA were defined as a negative ADA at baseline and first and last positive postbaseline ADA samples separated by at least 16 weeks, or last sample as positive, or there is at least 1 positive ADA sample <16 weeks before the negative last sample. Transient ADA were defined as a negative ADA at baseline, and the first and last positive postbaseline ADA samples separated by <16 weeks, and the last positive sample at least 16 weeks before a negative last sample.

DURATION OF EXPOSURE. The duration of exposure to study medication in years was categorized into >5, >4 to ≤5, >3 to ≤4, >2 to ≤3, >1 to ≤2, and ≤1 year. It was calculated as a minimum of:

- (Date of last dose of study medication − Date of first dose of study medication + 180)/365.25 and
- (Date of last known visit/contact − Date of first dose of study medication)/365.25

For patients enrolled in the ongoing ORION-8 trial, the cutoff date, ie, March 9, 2022, was used as the date of last known visit or contact.

EXPOSURE-ADJUSTED INCIDENCE RATES. EAIRs (per 100 patient-years) were calculated for each TEAE of interest as the number of patients with the event divided by the total patient-years of exposure times 100. Exposure was defined as the duration from the first study drug administration to the onset date of the first occurrence of the event, up to the last visit or contact date.

STATISTICAL ANALYSIS. Safety analyses were conducted using descriptive statistics with the safety populations from each trial, including all patients who received at least 1 dose of the study drug (inclisiran) or placebo. Data for demographic and clinical characteristics were reported for all patients from the parent studies, ORION-1, -5, -9, -10, and -11. The number and percentage of patients with at least 1 event, and EAIR with 95% CI were reported for TEAEs. For selected comparison of event rates, the difference in EAIRs was presented with 95% CI calculated using the Miettinen and Nurminen method[18] and Kaplan-Meier (K-M) estimates of cumulative event rates of TEAEs were plotted to show the probability of events in intervals containing follow-up data for both inclisiran and placebo groups up to 1.5 years, and during the subsequent interval with follow-up data for inclisiran only up to 6 years.

RESULTS

PATIENTS. Overall, 5,544 patients were included in this analysis, of whom 3,576 were in the inclisiran group and 1,968 in the placebo group. Baseline demographic and clinical characteristics were generally comparable between treatment arms (Table 1).

TABLE 1 Baseline Demographic and Clinical Characteristics

	Inclisiran Pool (n = 3,576)	Placebo Pool (n = 1,968)
Age, y	63.5 ± 10.32	63.6 ± 10.22
≥75 y	451 (12.6)	270 (13.7)
Female	1,184 (33.1)	645 (32.8)
Male	2,392 (66.9)	1,323 (67.2)
BMI, kg/m^2	30.3 ± 5.71 (3,570)	30.6 ± 5.78 (1,966)
White	3,298 (92.2)	1,838 (93.4)
eGFR, mL/min/1.73 m^2	79.2 ± 20.84 (3,575)	78.9 ± 20.93 (1,967)
CV risk factors		
ASCVD	2,990 (83.6)	1,655 (84.1)
ASCVD risk equivalent	586 (16.4)	313 (15.9)
Coronary heart disease	2,690 (75.2)	1,504 (76.4)
Cerebrovascular disease	478 (13.4)	255 (13.0)
Peripheral artery disease	319 (8.9)	168 (8.5)
Diabetes mellitus	1,226 (34.3)	660 (33.5)
Hypertension	2,793 (78.1)	1,552 (78.9)
Current smoker	555 (15.5)	288 (14.6)
LLT		
Statin only	2,416 (67.6)	1,316 (66.9)
Nonstatin LLT only	141 (3.9)	69 (3.5)
Statin and nonstatin LLT	842 (23.5)	468 (23.8)
No LLT	177 (4.9)	115 (5.8)

Values are mean ± SD, n (%), or mean ± SD (n).
ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CV = cardiovascular; eGFR = estimated glomerular filtration rate; LLT = lipid-lowering therapy.

TABLE 2 Duration of Exposure to Inclisiran and Placebo

	Inclisiran (n = 3,576)	Placebo (n = 1,968)
Patient-y of exposure	9,982.1	2,647.7
Duration of exposure, y	2.791 ± 1.0832	1.345 ± 0.3186
Proportion of patients by duration of exposure		
>5 y	75 (2.1)	0 (0.0)
>4-≤5 y	309 (8.6)	0 (0.0)
>3-≤4 y	1,167 (32.6)	0 (0.0)
>2-≤3 y	1,415 (39.6)	0 (0.0)
>1-≤2 y	375 (10.5)	1,703 (86.5)
≤1 y	235 (6.6)	265 (13.5)

Values are mean ± SD or n (%), unless otherwise indicated.

A majority of patients in both groups had ASCVD (83.6% and 84.1%, respectively) and were treated with statins (91.1% and 90.7%, respectively).

Due to OLE, the mean duration of exposure was greater for patients in the inclisiran vs placebo group (2.8 ± 1.1 years and 1.3 ± 0.3 years, respectively) (**Table 2**). Overall, 2,582 (72.2%) patients were treated with inclisiran for >2 to ≤4 years, with 309 (8.6%) and 75 (2.1%) patients treated for >4 to ≤5 and >5 years (up to 6 years), respectively (**Table 2**).

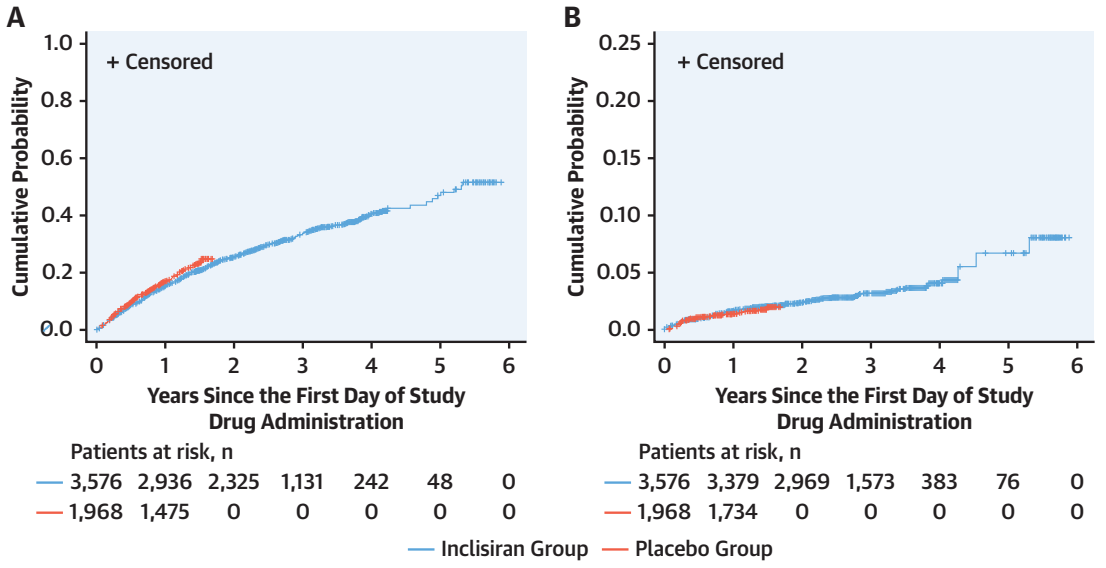
TREATMENT-EMERGENT ADVERSE EVENTS. TESAEs and TEAEs leading to study drug discontinuation accrued at a comparable rate over time in the inclisiran and placebo groups for the first 1.5 years during which there were follow-up data for both groups. Beyond that period, when there was follow-up data for inclisiran only, the accrual of TESAEs and TEAEs leading to study drug discontinuation maintained similar trajectories as during the first 1.5 years (**Figure 1**), in a sense that neither K-M curve nor EAIR showed increased risk of these TEAEs post the 1.5-year landmark (Supplemental Figure 1). Moreover, EAIRs were comparable in both treatment groups (Supplemental Tables 4 and 5). At least 1 TESAE was reported in 32.2% and 22.1% of patients in the inclisiran and placebo groups, respectively, with corresponding EAIRs of 13.80 (95% CI: 13.01-14.62) and 18.14 (95% CI: 16.48-19.93) per 100 patient-years, respectively. The difference in the EAIRs was −4.34 (95% CI: −6.30 to −2.51) (Supplemental Table 6). The most common TESAEs were cardiac, reported in 11.6% and 9.0% of patients, respectively. When adjusted for exposure, cardiac EAIRs were 4.39 (95% CI: 3.98-4.84) per 100 patient-years for inclisiran and 6.90 (95% CI: 5.92-7.99) per 100 patient-years for placebo.

At least 1 TEAE led to study drug discontinuation in 3.2% and 1.7% of patients in the inclisiran and placebo groups, respectively, with corresponding EAIRs of 1.12 (95% CI: 0.93-1.35) and 1.27 (95% CI: 0.88-1.77) per 100 patient-years, respectively. The difference in the EAIRs was −0.14 (95% CI: −0.68 to 0.29) (Supplemental Table 6).

The most common TEAE leading to study drug discontinuation was neoplasm (1.0% for inclisiran and 0.5% for placebo). Corresponding EAIRs in the inclisiran and placebo groups were 0.36 (95% CI: 0.25-0.49) and 0.37 (95% CI: 0.18-0.68) per 100 patient-years, respectively.

TEAEs at the injection site were more frequent with inclisiran (9.3%) compared with placebo (1.8%) groups, with corresponding EAIRs of 3.54 (95% CI: 3.17-3.95) and 1.31 (95% CI: 0.91-1.83) per 100 patient-years, respectively (Supplemental Table 7). In the inclisiran group, TEAEs at the injection site were more common in women (n = 171; 14.4%) compared with men (n = 160; 6.7%), with corresponding EAIRs of 5.90 (95% CI: 5.05-6.86) and 2.48 (95% CI: 2.11-2.90) per 100 patient-years, respectively. Regardless of gender and after adjusting for exposure, TEAEs at the injection site leading to study drug discontinuation were higher on inclisiran (0.1 per 100 patient-years) than on placebo (0.0 per 100 patient-years) (Supplemental Table 7, Supplemental Figure 2), and the difference in the EAIRs was 0.10 (95% CI: −0.05 to 0.19) (Supplemental Table 6).

FIGURE 1 Cumulative Incidence of Treatment-Emergent Serious Adverse Events and Treatment-Emergent Adverse Events Causing Study Drug Discontinuation



Kaplan-Meier curves depicting the cumulative rate of (A) treatment-emergent serious adverse events and (B) treatment-emergent adverse events leading to study drug discontinuation during up to 1.5 years of treatment with placebo (red), and 6 years of treatment with inclisiran (blue). The patient numbers at risk in each treatment group for each year of treatment are indicated.

TEAEs OF SCIENTIFIC RELEVANCE. K-M analyses of the hepatic-, muscle- and kidney-related events showed no differences between inclisiran and placebo treatment arms for up to 1.5 years. In the inclisiran group, compared with the placebo group, K-M analyses showed no evidence of excess incidence of incident diabetes, while numerically fewer MACE-related safety events were reported (**Figure 2**). Beyond that period where there was only follow-up data with inclisiran, the rate of accrual of these TEAEs maintained a similar trajectory (Supplemental Figure 1).

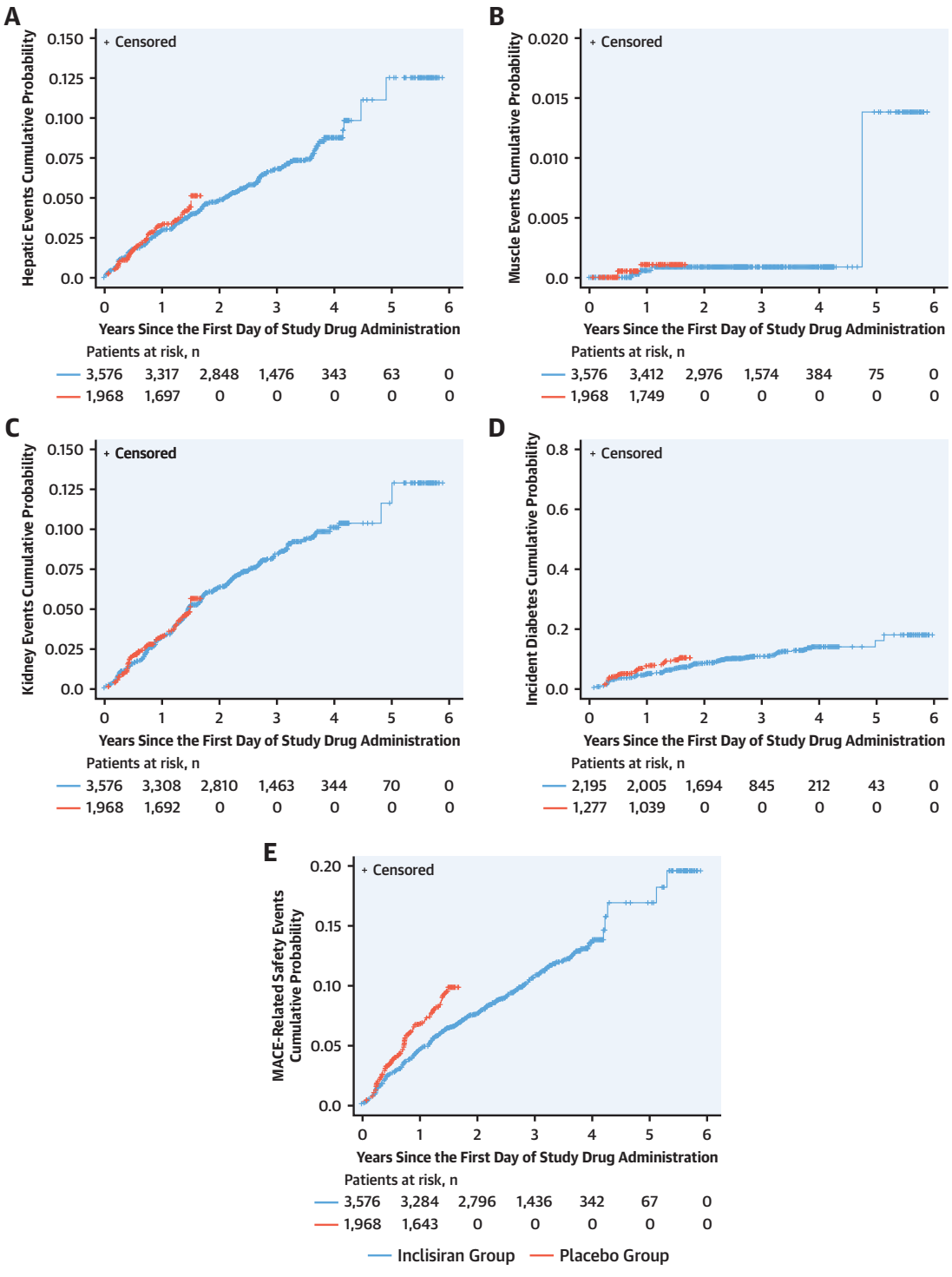
Specific EAIRs are reported in Supplemental Table 8. Proportions of patients with TEAEs of scientific relevance were similar in the inclisiran and placebo groups when corrected for exposure duration. In the inclisiran group, 6.5%, 0.1%, and 7.9% of patients had reported hepatic-, muscle-, and kidney-related events, respectively, with total exposure to treatment ranging from 9,678.6 to 10,105.1 years; in the placebo group, these TEAEs were reported in 4.1%, 0.1%, and 4.6% of patients, respectively, with exposure ranging from 2,642.3 to 2,705.5 years. When corrected for exposure, the EAIRs were 2.39 (95% CI: 2.09-2.71), 0.04 (95% CI: 0.01-0.10), and 2.92 (95% CI: 2.59-3.29) per 100 patient-years with inclisiran vs 3.06 (95% CI: 2.43-3.80), 0.07 (95% CI: 0.01-0.27), and 3.41 (95% CI: 2.74-4.19) per 100 patient-years with placebo. The difference in EAIR with 95% CI are shown in Supplemental Table 6.

Elevations in alanine aminotransferase levels >3× upper limit of normal were infrequent and similar between treatment groups when corrected for exposure. Elevations in creatine kinase (>5× upper limit of normal) and creatinine (≥50% increase from baseline) were also infrequent for both treatment groups but were reported at a lower incidence with inclisiran vs placebo when corrected for exposure (EAIR: 1.24 [95% CI: 1.03-1.48] and 2.12 [95% CI: 1.84-2.43] vs 2.41 [95% CI: 1.86-3.08] and 2.70 [95% CI: 2.11-3.40] per 100 patient-years, respectively). Corresponding K-M analyses are shown in Supplemental Figure 3, and the difference in EAIR with 95% CI are shown in Supplemental Table 6.

Overall, incident diabetes and MACE-related safety events were reported in 10.7% and 10.2% of patients in the inclisiran group (5,819.2 and 9,595.9 years of exposure, respectively), compared with 9.2% and 8.9% of patients in the placebo group (1,652.6 and 2,591.3 years of exposure, respectively) (Supplemental Table 8). However, EAIRs for incident

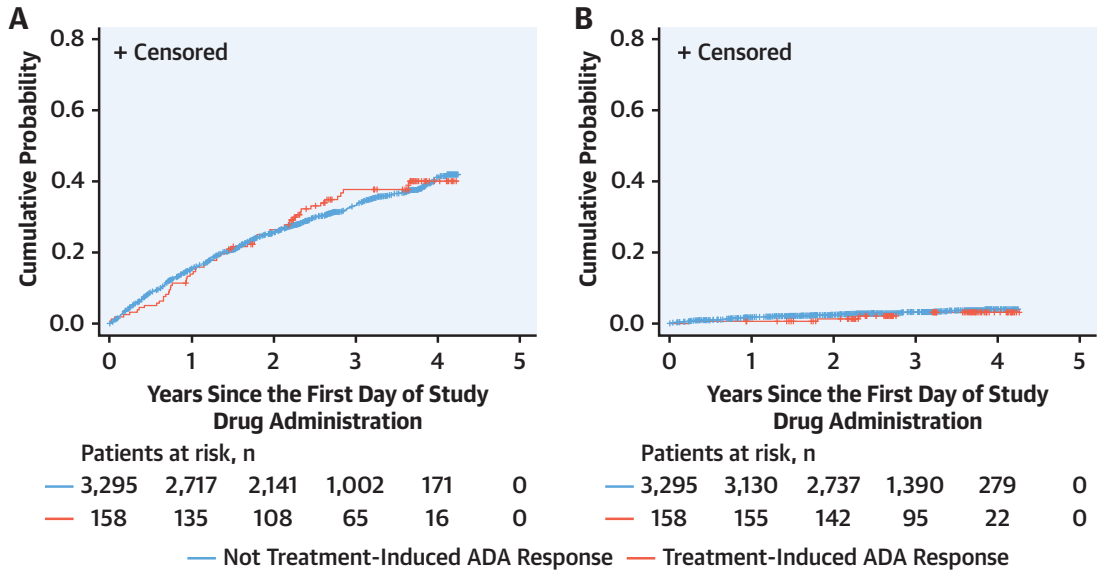
JACC VOL. 82, NO. 24, 2023
DECEMBER 12, 2023:2251-2261

FIGURE 2 Cumulative Incidence of Treatment-Emergent Adverse Events of Scientific Relevance



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FIGURE 3 Cumulative Safety Event Incidence by ADA Response to Inclisiran Treatment



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	Inclisiran (n = 3,576), n (%)
Treatment-Induced ADA Response	158/3,453 (4.6%)
Persistent	49/3,453 (1.4%)
Transient	109/3,453 (3.2%)
Not Treatment-Induced ADA Response	3,295/3,453 (95.4%)

Kaplan-Meier curves depicting the cumulative rate of (A) treatment-emergent serious adverse events and (B) treatment-emergent adverse events leading to study drug discontinuation during treatment with inclisiran in patients with a reported treatment-induced antidrug antibody (ADA) response (red), and no treatment-induced ADA response (blue). The patient numbers at risk in each treatment group for each year of treatment are indicated. (C) Table showing the number of patients with reported treatment-induced and not treatment-induced ADA. Patients from ORION-1 were excluded from this analysis because the laboratory protocol used in ORION-1 for this assessment differed from that of the other trials. The denominator indicates the number of patients with negative baseline ADA and at least 1 postbaseline ADA assessment.

diabetes were numerically lower with inclisiran (4.04 [95% CI: 3.54-4.59]) vs placebo (7.08 [95% CI: 5.86-8.48]) per 100 patient-years, with difference in EAIR of −3.04 (95% CI: −4.53 to −1.74). Similarly, EAIRs for MACE were numerically lower with inclisiran vs placebo (3.79 [95% CI: 3.41-4.20] vs 6.75 [95% CI: 5.79-7.83] per 100 patient-years, respectively), with difference in EAIR of −2.96 (95% CI: −4.10 to −1.94) (Supplemental Table 6).

IMMUNOGENICITY. Treatment-induced ADA were uncommon with inclisiran, reported in 158 of 3,453 (4.6%) patients, were mostly transient (3.2%), and were unrelated to TESAEs or TEAEs leading to study drug discontinuation (**Figure 3**).

FIGURE 2 Continued

Kaplan-Meier curves depicting the cumulative rate of treatment-emergent adverse events of scientific relevance, including (A) hepatic, (B) muscle, (C) kidney events, (D) incident diabetes, and (E) major adverse cardiovascular event (MACE)-related safety events during up to 1.5 years of treatment with placebo (red), and 6 years of treatment with inclisiran (blue). The patient numbers at risk in each treatment group for each year of treatment are indicated. The number of baseline-at risk patients for incident diabetes was lower than other treatment-emergent adverse events (TEAEs) because of exclusion of patients with diabetes at baseline. MACE was defined as cardiovascular death, cardiac arrest, nonfatal myocardial infarction, and nonfatal stroke.

DISCUSSION

This pooled analysis of data from 7 clinical trials investigating the safety and tolerability of inclisiran, a first-in-class siRNA, provides the largest data set to date showing that twice-yearly inclisiran treatment is well tolerated in combination with statins and/or other oral LLT in patients with elevated LDL-C levels, including those with ASCVD, ASCVD risk equivalent, and heterozygous familial hypercholesterolemia, as well as a small number with homozygous familial hypercholesterolemia (Supplemental Table 1). The purpose of this analysis was to evaluate potential safety signals with prolonged exposure to inclisiran. The findings presented include data from 3,576 patients treated with inclisiran, representing approximately 10,000 patient-years of exposure, which, considering twice-yearly dosing (after the initial and 3-month doses), corresponds to up to 20,000 injections (**Central Illustration**). Among these patients, 43.3% were treated with inclisiran for >3 years. Other than TEAEs at the injection site, no other safety event had an evident excess EAIR with inclisiran compared with placebo. There was heterogeneity across trials in the EAIR for some adverse events (Supplemental Table 9), which might be expected because of differences in demographics and baseline characteristics across trials.[9,10,12,19]

Despite conclusive evidence that lowering LDL-C levels with LLT reduces CV risk, a substantial proportion of patients do not achieve guideline-recommended LDL-C goals.[2,6,7] One contributing factor relates to suboptimal adherence to therapy, in part because of side effects reported with traditional therapies like statins, primarily myopathy, or diabetes mellitus.[20,21] Elevated creatine kinase levels, while uncommon, are a marker for myopathy identified with statins.[22] In this analysis, there was no evidence of excess incidence of elevated creatine kinase levels or muscle-related events in inclisiran-treated patients compared with placebo. Similarly, there was no evidence of excess incidence of incident diabetes with inclisiran compared with placebo. These findings will need to be confirmed in longer-term studies. With some K-M curves (**Figures 2A to 2C**), the cumulative incidence of TEAEs became more pronounced after 4 years in the inclisiran group. However, these specific changes depicting increased variability are likely caused by the small number of patients at risk during the 4- to 6-year period. Newer LLT options, such as anti-PCSK9 monoclonal antibodies, have not been associated with side effects like myopathy or diabetes, and large, long-term studies have not identified any concerning safety signals.[23,24] Overall, the data presented here suggest that targeting the PCSK9 pathway to lower LDL-C using a siRNA mechanism is safe and well tolerated in the long term.

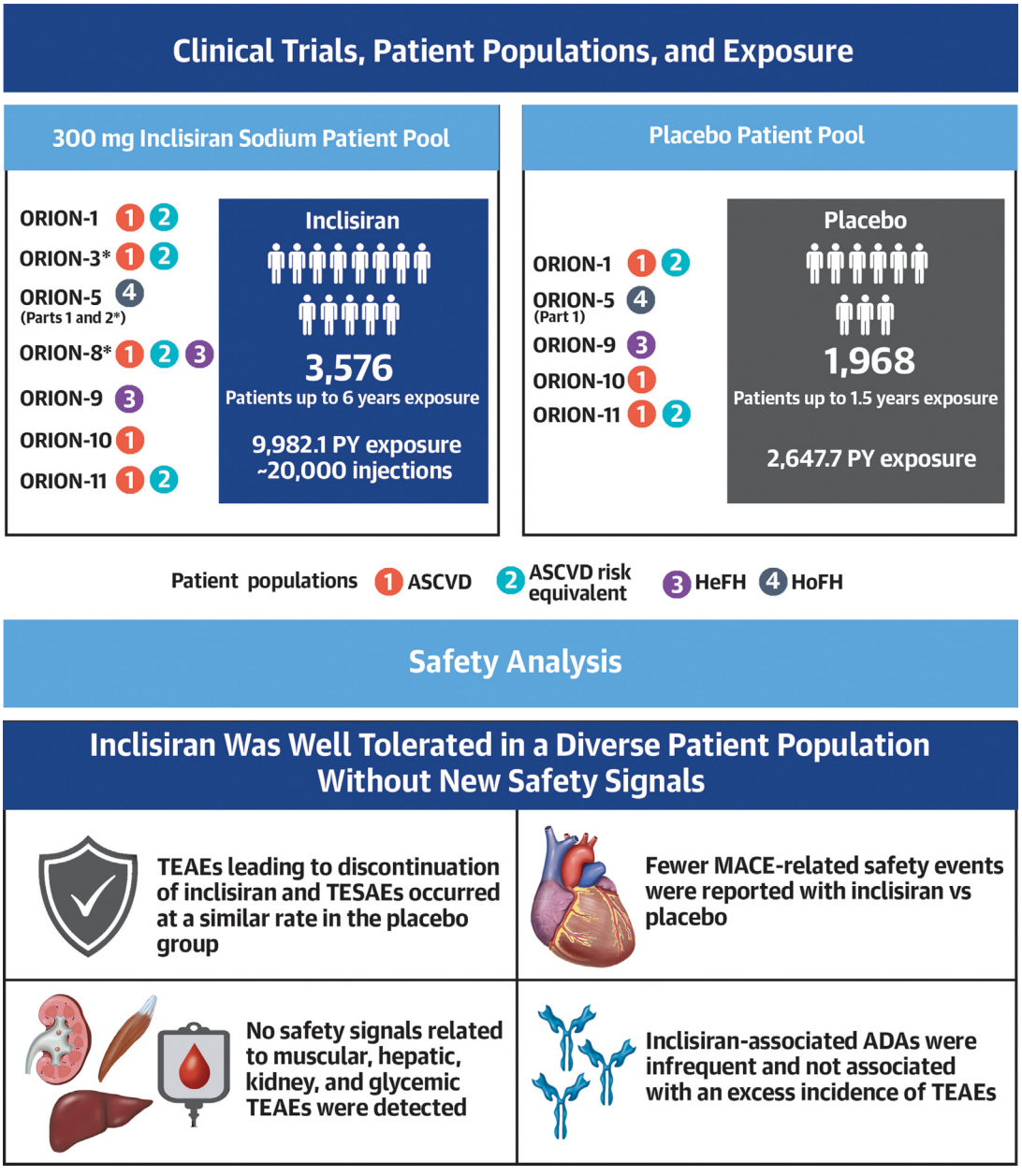
In this analysis, when TEAEs were examined over time, there were no new safety signals identified, particularly those of scientific relevance to this type of therapy. Inclisiran is conjugated to triantennary N-acetylgalactosamine for targeted delivery to hepatocytes and is cleared renally with undetectable plasma levels 24 to 48 hours postdosing[15,17,25]; thus, evaluating the effect of inclisiran on liver and kidney function has importance. In fact, liver- and kidney-related events accrued with inclisiran at a similar rate to placebo for the first 1.5 years. Beyond that time period, when there was follow-up data for inclisiran only, there was a consistent accrual rate. Similarly, elevations in liver enzyme levels and/or creatinine with inclisiran were infrequent and similar to placebo.

Prior studies have shown more TEAEs at the injection site with inclisiran,[9,11,12] a finding that was confirmed in this analysis. Prior analyses demonstrated that TEAEs at the injection site with inclisiran were typically mild and transient in nature.[11,16] A higher incidence of TEAEs at the injection site has been reported for anti-PCSK9 monoclonal antibodies, without evidence they lead to excess study drug discontinuation.[23,24,26] Similarly, this analysis demonstrates that TEAEs at the injection site with inclisiran seldom lead to study drug continuation. Furthermore, the detection of ADA against inclisiran was rare, and was not associated with a difference in reported TESAEs or TEAEs leading to study drug discontinuation. Prior analyses of post-treatment samples of patients from the ORION-9, -10, and -11 trials have demonstrated that the presence of ADA was not associated with changes in pharmacologic and clinical measurements.[9,12,14]

Previously, the safety of inclisiran has been evaluated in individual clinical trials or smaller pooled analyses.[9-12,16] The use of pooled data across numerous studies affords an enhanced potential to identify events that occur less frequently. Moreover, additional data on long-term use can show whether there are negative effects of repeated exposures. As such, it is encouraging that the current data demonstrate no new safety findings.

The purpose of LLT is to reduce the risk of CV events. The effect of inclisiran on CV events is currently under investigation in large, long-term,

CENTRAL ILLUSTRATION **Long-Term Pooled Safety Analysis of Inclisiran**



Wright RS, et al. J Am Coll Cardiol. 2023;82(24):2251–2261.

A pooled post hoc analysis of patient-level safety data from 7 completed and ongoing inclisiran clinical studies in patients with high cardiovascular (CV) risk. The placebo pool was smaller and had a shorter treatment duration than inclisiran; this is caused by patients transitioning from placebo-controlled trials to open-label extensions. Extended exposure to inclisiran does not result in an increased incidence of safety events, providing confidence in the safety and tolerability profile of inclisiran in high CV risk patients. *Open-label extension trials. ADA = antidrug antibody; ASCVD = atherosclerotic cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; MACE = major adverse cardiovascular event; PY = patient-years; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

JACC VOL. 82, NO. 24, 2023
DECEMBER 12, 2023:2251–2261

placebo-controlled CV outcomes trials, ORION-4 (NCT03705234), VICTORION-1 Prevent (A Study of Inclisiran to Prevent Cardiovascular Events in High-risk Primary Prevention Patients; NCT05739383), and VICTORION-2 Prevent (Study of Inclisiran to Prevent Cardiovascular [CV] Events in Participants With Established Cardiovascular Disease; NCT05030428). Confirmation of a CV benefit of inclisiran awaits the completion of these studies. Notwithstanding this evidence gap, nonadjudicated CV events reported as TEAEs accrued at a lower rate with inclisiran compared with placebo in a previous analysis[27] and in the current analysis.

STUDY LIMITATIONS. The findings are derived from pooled data from several clinical trials with specific inclusion criteria, and, thus, may not be fully reflective of a general population. Although EAIRs were calculated, no direct comparison of events with inclisiran vs placebo is possible beyond the first 1.5 years. Few patients were exposed to inclisiran for more than 4 years. The large, ongoing placebo-controlled trials cited in the previous text will provide more safety and definitive efficacy data. Together, these trials are expected to provide >100,000 patient-years of exposure to inclisiran.

CONCLUSIONS

This analysis indicates that long-term inclisiran is safe and generally well tolerated in a diverse population of patients with dyslipidemia treated for as long as 6 years. Taken together with the effective and consistent LDL-C-lowering ability of inclisiran, these data lend support to its long-term use in patients at high CV risk.

ACKNOWLEDGMENTS The authors thank all the investigators, trial site staff, and patient volunteers who participated in the trials. The authors thank Aisling Towell, PhD, and Tony Walsh, PhD (Novartis Ireland Ltd), as well as Vennila Dharman, MBBS (Novartis, Healthcare Pvt. Ltd India), for providing medical writing support in accordance with Good Publication Practice 2022 and Klaus Molle, PhD (Novartis Pharma AG) for critical review of the manuscript.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was sponsored by Novartis Pharma AG. Dr Wright has received advisory board fees from Boehringer Ingelheim; and has received past fees for consulting on lipid issues with The Medicines Company. Dr Koenig has received consulting fees and lecture fees from AstraZeneca, Novartis, and Amgen; has received consulting fees from Pfizer, The Medicines Company, Novartis, DalCor Pharmaceuticals, Kowa, Corvidia Therapeutics, Esperion, Genentech, OMEICOS, Novo Nordisk, LIB Therapeutics, Daiichi-Sankyo, New Amsterdam Pharma, and TenSixteen Bio; has received lecture fees from Berlin-Chemie, Bristol Myers Squibb, and Sanofi; and has received grant support and provision of reagents from Singulex, Abbott, Roche Diagnostics, and Dr Beckmann Pharma. Dr Landmesser has received lecture fees and advisory fees from AstraZeneca, Boehringer Ingelheim, Sanofi, Berlin-Chemie, and Abbott; has received advisory fees from The Medicines Company; and has received grant support, lecture fees, and advisory fees from Amgen, Bayer, and Novartis. Dr Leiter has received grant support paid to his institution and advisory board fees and fees for CME from Amgen and Novartis; has received fees for serving on a steering committee and advisory board fees from Esperion; has received grant support paid to his institution and fees for serving on a steering committee from Kowa, The Medicines Company, and Novartis; and has received advisory board fees and fees for CME from Amarin, AstraZeneca, HLS, Merck, Pfizer, and Sanofi. Dr Raal has received advisory board fees and lecture fees from Amgen, Sanofi, Regeneron Pharmaceuticals, Novartis, and LIB Therapeutics. Dr Schwartz has received research support paid to his institution from AstraZeneca, Resverlogix, Sanofi, Silence Therapeutics, and The Medicines Company; and has a patent (62/806313) on a method for reducing cardiovascular risk assigned in full to the University of Colorado. Drs Lesogor, Maheux, Stratz, Zang, and Ray were employed by Novartis at the time of analysis. Dr Ray has received support from the National Institute for Health and Care Research (NIHR) Imperial Biomedical Research Centre; his institution (Imperial College London) receives support from the National Institute for Health and Care Research Applied Research Collaboration Northwest London; has received lecture fees from Aegerion Pharmaceuticals, Kowa, Cipla, Algorithm, and Zuelling Pharma; has received grant support paid to his institution, lecture fees, and advisory board fees from Amgen, Regeneron Pharmaceuticals/Sanofi, and Pfizer; has received lecture fees and fees for serving on steering committees for trials from AstraZeneca and Eli Lilly; has received fees for serving on steering committees for trials from Cerenis Therapeutics, The Medicines Company, and Esperion; has received advisory board fees from Akcea Therapeutics, Novartis, Silence Therapeutics, Bayer, and Daiichi-Sankyo; has received lecture fees and advisory board fees from Takeda, Boehringer Ingelheim, and Dr Reddy's Laboratories; has received grant support and advisory board fees from Merck Sharp and Dohme; has received fees for serving on a clinical events adjudication committee from AbbVie; and has received fees for serving as principal investigator for a trial from Resverlogix.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In a pooled analysis of patient-level data from 7 clinical trials involving patients with hypercholesterolemia, twice yearly administration of inclisiran after initial and 3-month doses has been well tolerated for up to 6 years.

TRANSLATIONAL OUTLOOK: Ongoing trials will provide additional data on the safety of inclisiran and its and effect on CV outcomes.

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KEY WORDS ASCVD, inclisiran, LDL-C, long-term safety, PCSK9

APPENDIX For supplemental tables and figures, please see the online version of this paper.