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ORIGINAL RESEARCH

# Real-World Adherence and Effectiveness of Inclisiran in Lowering LDL-C: Results from 1 Year of Follow-Up

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## ABSTRACT

***Introduction***: Atherosclerotic cardiovascular disease (ASCVD) is a global health concern. Reducing low-density lipoprotein cholesterol (LDL-C) is critical in ASCVD prevention and treatment. Inclisiran, a novel RNA therapeutic agent, offers a promising solution by lowering LDL-C with twice-yearly dosing after an initial and 3-month dose. The study objective was to evaluate adherence to inclisiran and its lipid-lowering effectiveness over a year of treatment.
***Methods***: This retrospective cohort study involved patients over 18 years old with ASCVD or hyperlipidemia who initiated inclisiran between January 1, 2022, and May 17, 2023, in US outpatient clinics. LDL-C reduction was evaluated in patients with ≥ 1 pre- and post-index LDL-C measurement by comparing baseline levels to the lowest value within 12 months after initiating inclisiran.
***Results***: Overall, 225 patients initiated inclisiran. The mean age was 69.9 years and 50.7% were female. Most patients (81.8%) had ASCVD. Most patients (91.6%) received a second dose, and 84.5% of these received a third dose. Overall, 202 patients had ≥ 2 LDL-C measurements, with a mean baseline LDL-C of 134.8 mg/dl. Mean absolute LDL-C reduction was 66.1 (standard deviation: 45.6) mg/dl, corresponding to a 46.8% (95% confidence interval: 42.7–51.0) relative reduction, and 46.8% achieved ≥ 50% reduction. Patients on concurrent statins and those without prior anti-proprotein convertase subtilisin/kexin type 9 monoclonal antibodies experienced the largest relative LDL-C reductions: 55.4% and 51.1%, respectively.

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***Conclusions***: Inclisiran significantly reduced LDL-C. The dosing schedule promoted high adherence in a real-world setting, particularly among older adults with ASCVD. These findings indicate inclisiran may be a particularly valuable addition to lipid-lowering strategies.

**Keywords:** Atherosclerotic cardiovascular disease; Inclisiran; LDL-C; Lipid-lowering therapy; Real-world adherence; Statins

**Key Summary Points**

*Why carry out this study?*

Patients with hyperlipidemia and atherosclerotic cardiovascular disease (ASCVD) often do not meet recommended low-density lipoprotein cholesterol (LDL-C) targets despite treatment with statins and therefore may be at risk of future cardiovascular events.

This real-world study design assessed inclisiran adherence in the immediate post-marketing era of the drug as well as efficacy.

*What was learned from this study?*

Patients were adherent to inclisiran, and clinically meaningful reductions in LDL-C levels were observed regardless of prior or current lipid-lowering therapy (LLT).

The lipid-lowering effectiveness of inclisiran was most beneficial in patients receiving concomitant statin therapy and also remains an important treatment option for patients intolerant of statins or other LLTs.

Infrequent administration (twice-yearly doses after initial dose and 3-month dose) in a physician office or clinic could be an effective care model in the long-term treatment of patients with ASCVD and hyperlipidemia.

## INTRODUCTION

Over 315,000,000 individuals worldwide are living with atherosclerotic cardiovascular disease (ASCVD) [1]. Elevated low-density lipoprotein cholesterol (LDL-C) is fundamental to ASCVD pathogenesis, making LDL-C reduction a critical component of ASCVD primary and secondary prevention [2, 3]. To date, over 200 prospective cohort studies, Mendelian randomization analyses, and clinical trials have demonstrated a consistent, log-linear relationship between LDL-C and risk of ASCVD [3]. Therapies that lower LDL-C levels have also been demonstrated to slow ASCVD progression and reduce morbidity and mortality [4, 5]. Consequently, LDL-C targets have been established to guide clinical decision-making toward optimal clinical outcomes for statins and other lipid-lowering therapies (LLTs) designed to reduce LDL-C [5]. Statins are the primary treatment for reducing LDL-C, but most patients do not reach target LDL-C levels with statin therapy alone [6–9]. In one retrospective cohort study, only 10.5% of patients treated with atorvastatin reached an LDL-C of < 70 mg/dl. Among those with diabetes, only 7.5% reached target LDL-C [10]. Current European guidelines recommend a target LDL-C of < 55 mg/dl for certain high-risk groups [11]. Real-world studies have consistently demonstrated that < 30% of patients receiving LLT for secondary prevention will attain an LDL-C of < 55 mg/dl [12, 13]. Poor treatment adherence to statins, in particular, and the suboptimal use of other efficacious lipid-lowering regimens are key reasons for the failure to achieve LDL-C goals [14].

Anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (anti-PCSK9 mAbs) are potent medications that lower LDL-C in ASCVD in combination with statin therapy. Simulation studies suggest that more than one in 10 patients with ASCVD would benefit from treatment with an anti-PCSK9 mAb [12]. Anti-PCSK9 mAbs reduce cardiovascular events but require self-administered subcutaneous injections every 2–4 weeks [15, 16]. Uptake of these agents has been lower than expected [17], and some real-world studies have shown

high discontinuation rates [18] with subpar adherence [19, 20].

Inclisiran, approved by the US Food and Drug Administration in December 2021, is a first-in-class small interfering RNA therapeutic agent that suppresses PCSK9 translation in the liver and lowers circulating concentrations of PCSK9 and LDL-C [21, 22]. In phase 3 clinical trials, inclisiran reduced LDL-C levels by approximately 50% compared with placebo [23, 24], and unlike anti-PCSK9 mAb therapies, inclisiran is given subcutaneously twice yearly after initial doses at baseline and 3 months [22]. Additionally, inclisiran is administered under healthcare supervision in outpatient settings and physician offices [22, 25]. These factors may enhance adherence and reduce the treatment burden of patients who require intervention to reduce their LDL-C levels.

Following pivotal clinical trials, observational cohort studies have demonstrated that inclisiran is also effective at reducing LDL-C in the real-world outpatient setting [26, 27]. One single-center cohort study in 80 patients found that inclisiran reduced LDL-C by 48.6%, from 3.5 mmol/l (135.3 mg/dl) to 1.8 mmol/l (69.6 mg/dl), in the first 2 months of therapy [27]. In another cohort of 503 patients from Israel, inclisiran reduced LDL-C by 60% [28]. While these results provide a promising demonstration of the lipid-lowering effects of inclisiran, characterizing treatment over a full year would provide a more comprehensive understanding of the real-world effectiveness of inclisiran. The objective of this study was, therefore, to evaluate adherence to inclisiran and lipid-lowering effectiveness over a full year of treatment in the immediate post-marketing period.

# METHODS

### Study Design and Participants

This was a retrospective, longitudinal cohort study involving a consecutive series of patients who initiated treatment with inclisiran in the real-world setting between January 1, 2022, and May 17, 2023. Data were collected from US outpatient physician clinics that are part of a network of centers with a central electronic outpatient medical record. Patients were required to be over the age of 18 and to be diagnosed with ASCVD or hyperlipidemia prior to initiating inclisiran to be included in the study. ASCVD was defined as a diagnosis of acute coronary syndrome (including coronary artery disease, myocardial infarction, or stable/unstable angina), coronary or other arterial revascularization procedures, ischemic stroke, transient ischemic attack, or peripheral artery disease. Hyperlipidemia was defined as a recorded diagnosis of either heterozygous familial hypercholesterolemia (HeFH) or hyperlipidemia (primary, mixed, or nonspecified). Patients were followed for 365 days after the index date, defined as the date of inclisiran initiation. Change in LDL-C was assessed among patients who had at least one pre-index LDL-C measurement and one post-index LDL-C measurement.

### Outcomes of Interest

Adherence to inclisiran was defined, descriptively, as the proportion of all patients who received a second dose of inclisiran (3 months after initiation dose) and the proportion of those patients who received a third dose (6 months after second dose). Discontinuation rates prior to the second and third doses and the reasons for discontinuation were reported.

LDL-C reduction was defined as the difference between pre-index LDL-C measurement and LDL-C nadir, the lowest value of LDL-C recorded in the 365 days after treatment initiation. If patients had more than one LDL-C measurement in the 180 days prior to treatment initiation, the value recorded closest to the index date was used. The post-index LDL-C was represented by the lowest LDL-C measurement within the 12-month period after treatment initiation. The absolute change in LDL-C along with the relative change in LDL-C levels, the proportion of patients achieving ≥ 50% reduction, the proportion of patients achieving LDL-C ≤ 70 mg/dl and LDL-C ≤ 55 mg/dl, and time to LDL-C nadir were also reported.

### Other Measures

In addition to patient demographics (age, sex, and payor type), history of cardiovascular disease, comorbidity burden, and prior or concurrent LLT were also characterized. Variables used to describe cardiovascular history included primary treatment indication (ASCVD, HeFH, or other hyperlipidemia) and the prevalence of hypertension, cardiac arrhythmia, valvular disease, and heart failure at baseline that were available in the physician medical record. Comorbidity burden was summarized using the Elixhauser comorbidity score [29]. Finally, patients initiating inclisiran in the real-world setting often vary on exposure to other LLTs prior to, or at the time of initiating, inclisiran. Reductions in LDL-C were, therefore, described in subgroups among those who had concurrent statin use at the time of initiation vs. those who had documented statin intolerance as documented by the physician or other provider, and those with prior use of anti-PCSK9 mAbs vs. those who did not use anti-PCSK9 mAbs. Intensity of statin use at baseline (high-intensity vs. low- or moderate-intensity) and ezetimibe use at baseline were also described.

### Statistical Analysis

Cohort characteristics were summarized using descriptive statistics, including means, standard deviation (SD), medians, and interquartile range (IQR) for continuous variables, and counts and proportions for categorical variables. Relative reductions in LDL-C were calculated for each patient by dividing the difference in LDL-C at nadir and baseline LDL-C by the baseline LDL-C. Means and SD were then used to describe the average relative reduction in LDL-C per patient. Standard errors and 95% confidence intervals (CIs) were calculated for the mean reduction in LDL-C. The Kaplan–Meier method was used to estimate time to LDL-C nadir.

### Compliance with Ethics Guidelines

All procedures were approved by Biomedical Research Alliance of New York, an independent institutional review board (#22-12-927-1297). As this was a secondary analysis of data collected in the provision of care, the study was deemed exempt from human subject restrictions. No participant identifiers were used in the analysis and patients were not required to provide consent for inclusion. Data collection was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and is consistent with the Guidelines for Good Clinical Practice. Reporting followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Guideline for Cohort Studies [30].

## RESULTS

### Study Cohort

In total, 225 patients initiated inclisiran and were eligible for inclusion in the adherence objective. About half (50.7%) were female, and the mean age was 69.9 (SD: 8.6) years. Among these, 81.8% were diagnosed with ASCVD, 32.9% were on statins at baseline, 27.1% were on ezetimibe at baseline, and 44.0% were previously treated with an anti-PCSK9 mAb. Full cohort characteristics are reviewed in Table 1. Treatment persistence was assessed among all 225 patients. Of these, 202 (89.8%) had at least one pre-index and one post-index LDL-C measurement. Characteristics of the 202 patients with two LDL-C measurements are described below in the LDL-C Cohort section.

### Treatment Adherence and Persistence

Among 225 patients who initiated inclisiran, a total of 206 (91.6%) received a second dose of inclisiran. Of the 206 patients who received a second dose, 174 (84.5%) received a third dose (Fig. 1). The most common reasons for

**Table 1** Characteristics of patients treated with inclisiran ($N = 225$) and those with pre- and post-index LDL-C measurements ($N = 202$)

| Characteristic | | Patients with pre- and post-index LDL-C measurements, $N = 202$ | | | | |
|---|---|---|---|---|---|---|
| | All patients, $N = 225$ | All patients, $n = 202$ | Concurrent statin use, $n = 68$ | Statin intolerance[a], $n = 134$ | No prior use of anti-PCSK9 mAbs, $n = 113$ | Prior use of anti-PCSK9 mAbs, $n = 89$ |
| Age in years, mean (SD) | 69.9 (8.6) | 70.0 (8.6) | 67.3 (10.1) | 71.3 (7.3) | 70.5 (8.0) | 69.3 (9.2) |
| Age in years, median (IQR) | 70 (66–75) | 70 (66–75) | 68 (65–73) | 71 (67–75) | 70 (67–75) | 70 (66–75) |
| Age < 65 years, *n* (%) | 37 (16.4) | 33 (16.3) | 16 (23.5) | 17 (12.7) | 15 (13.3) | 18 (20.2) |
| Age 65–74 years, *n* (%) | 126 (56.0) | 115 (56.9) | 40 (58.8) | 75 (56.0) | 67 (59.3) | 48 (53.9) |
| Age ≥ 75 years, *n* (%) | 62 (27.6) | 54 (26.7) | 12 (17.6) | 42 (31.3) | 31 (27.4) | 23 (25.8) |
| Sex, *n* (%) | | | | | | |
| Female | 114 (50.7) | 101 (50.0) | 31 (45.6) | 70 (52.2) | 52 (46.0) | 49 (55.1) |
| Male | 111 (49.3) | 101 (50.0) | 37 (54.4) | 64 (47.8) | 61 (54.0) | 40 (44.9) |
| Body mass index ($kg/m^2$) | | | | | | |
| Body mass index, mean (SD) | 29.8 (5.6) | 29.8 (5.6) | 30.5 (5.4) | 29.4 (5.8) | 30.2 (5.6) | 29.2 (5.7) |
| Body mass index, median (IQR) | 29.7 (26–33) | 29.7 (26–33) | 30.1 (26–34) | 29.4 (26–33) | 30.1 (26–34) | 29.0 (25–33) |
| Body mass index ≥ 30, *n* (%) | 104 (46.2) | 94 (46.5) | 35 (51.5) | 59 (44.0) | 58 (51.3) | 36 (40.5) |
| Payor type, *n* (%) | | | | | | |
| Commercial | 32 (14.2) | 29 (14.4) | 11 (16.2) | 18 (13.4) | 8 (7.1) | 21 (23.6) |
| All Medicare | 193 (85.8) | 173 (85.6) | 57 (83.8) | 116 (86.6) | 105 (92.9) | 68 (76.4) |
| Medicare, traditional | 168 (74.7) | 151 (74.8) | 46 (67.7) | 105 (78.4) | 89 (78.8) | 62 (69.7) |
| Medicare Advantage | 25 (11.1) | 22 (10.9) | 11 (16.2) | 11 (8.2) | 16 (14.2) | 6 (6.7) |

**Table 1** continued

| Characteristic | | Patients with pre- and post-index LDL-C measurements, *N* = 202 | | | | |
|---|---|---|---|---|---|---|
| | **All patients, *N* = 225** | **All patients, *n* = 202** | **Concurrent statin use, *n* = 68** | **Statin intolerance[a], *n* = 134** | **No prior use of anti-PCSK9 mAbs, *n* = 113** | **Prior use of anti-PCSK9 mAbs, *n* = 89** |
| Primary treatment indication, *n* (%) | | | | | | |
| ASCVD | 184 (81.8) | 166 (82.2) | 56 (82.4) | 110 (82.1) | 95 (84.1) | 71 (79.8) |
| Hyperlipidemia | 7 (3.1) | 30 (14.9) | 8 (11.8) | 22 (16.4) | 16 (14.2) | 14 (15.7) |
| Heterozygous familial hypercholesterolemia | 34 (15.1) | 6 (3.0) | 4 (5.9) | 2 (1.5) | 2 (1.8) | 4 (4.5) |
| Overall comorbidities | | | | | | |
| Elixhauser comorbidity score, mean (SD) | 9.8 (11.2) | 9.9 (11.5) | 10.8 (11.7) | 9.5 (11.3) | 9.9 (11.5) | 10.0 (11.4) |
| Diabetes *n,* (%) | 79 (35.1) | 68 (33.7) | 24 (35.3) | 44 (32.8) | 41 (36.3) | 27 (30.3) |
| Cardiac comorbidities, *n* (%) | | | | | | |
| Hypertension | 198 (88.0) | 176 (87.1) | 60 (88.2) | 116 (86.6) | 103 (91.2) | 73 (82.0) |
| Coronary artery disease | 188 (83.6) | 168 (83.2) | 61 (89.7) | 107 (79.9) | 100 (88.5) | 68 (76.4) |
| Cardiac arrhythmias | 61 (27.1) | 55 (27.2) | 20 (29.4) | 35 (26.1) | 36 (31.9) | 19 (21.4) |
| Valvular disease | 52 (23.1) | 46 (22.8) | 19 (27.9) | 27 (20.2) | 28 (24.8) | 18 (20.2) |
| History of myocardial infarction | 48 (21.3) | 41 (20.3) | 20 (29.4) | 21 (15.7) | 28 (24.8) | 13 (14.6) |
| Stroke | 25 (11.1) | 22 (10.9) | 3 (4.4) | 19 (14.2) | 11 (9.7) | 11 (12.4) |
| Heart failure | 18 (8.0) | 17 (8.4) | 9 (13.2) | 8 (6.0) | 12 (10.6) | 5 (5.6) |
| Lipid-lowering therapy, *n* (%) | | | | | | |
| Concurrent ezetimibe use | 61 (27.1) | 56 (27.7) | 23 (33.8) | 33 (24.6) | 35 (31.0) | 21 (23.6) |

**Table 1** continued

| Characteristic | | Patients with pre- and post-index LDL-C measurements, *N* = 202 | | | | |
|---|---|---|---|---|---|---|
| | All patients, *N* = 225 | All patients, *n* = 202 | Concurrent statin use, *n* = 68 | Statin intolerance[a], *n* = 134 | No prior use of anti-PCSK9 mAbs, *n* = 113 | Prior use of anti-PCSK9 mAbs, *n* = 89 |
| Concurrent statin use | 74 (32.9) | 68 (33.7) | 68 (100.0) | 0 (0.0) | 44 (38.9) | 24 (27.0) |
| Low- or moderate-intensity statin | 21 (9.3) | 18 (8.9) | 18 (26.5) | 0 (0.0) | 11 (9.7) | 7 (7.9) |
| High-intensity statin | 53 (23.6) | 50 (24.8) | 50 (73.5) | 0 (0.0) | 33 (29.2) | 17 (19.1) |
| Prior anti-PCSK9 mAbs | 99 (44.0) | 89 (44.1) | 24 (35.3) | 65 (48.5) | 0 (0.0) | 89 (100.0) |

*ASCVD* atherosclerotic cardiovascular disease, *IQR* interquartile range, *LDL-C* low-density lipoprotein cholesterol, *mAb* monoclonal antibody, *PCSK9* proprotein convertase subtilisin/kexin type 9, *SD* standard deviation

[a]Reason for no concurrent statin use: statin intolerance (*n* = 131), lack of efficacy (*n* = 3)

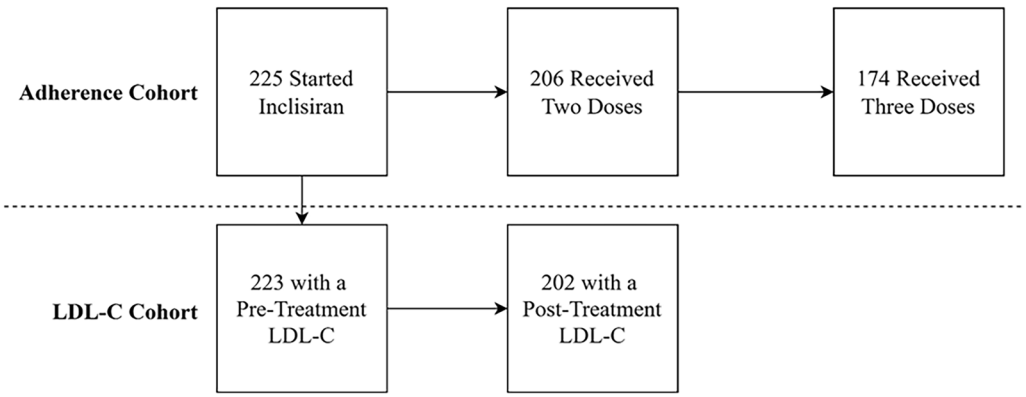


**Fig. 1** Participant flow demonstrating the allocation of patients between the full (*N* = 225) and LDL-C cohorts (*N* = 202). *LDL-C* low-density lipoprotein cholesterol

discontinuation between initiation and second doses were the onset of an adverse event (2.7%) followed by inability to pay (2.2%), as noted in Table 2. Among the 32 patients who received a second dose of inclisiran but did not receive a third dose, the most common reason for discontinuation was loss to follow-up (6.3%) followed by patient or provider decision (5.3%), as noted in Table 2. Detailed information on reasons for discontinuation after the initiation and after second dose are noted in Table 2.

**Table 2** Reasons for discontinuation among patients after the first and second dose of inclisiran

| Reason for discontinuation, *n* (%) | Discontinuation after the first dose, *N* = 225 | Discontinuation after the second dose, *N* = 206 |
|---|---|---|
| Adverse event[a] | 6 (2.7) | 3 (1.5) |
| Inability to pay | 5 (2.2) | 3 (1.5) |
| Lost to follow-up | 4 (1.8) | 13 (6.3) |
| Patient/provider decision | 3 (1.3) | 11 (5.3) |
| Payor denial | 1 (0.44) | – |
| Died | – | 1 (0.49) |
| Transfer of care | – | 1 (0.49) |
| Total discontinuations | 19 (8.4) | 32 (15.5) |

[a]Adverse events resulting in discontinuation included myalgia ($n = 4$), back pain ($n = 1$), diarrhea and dysuria ($n = 1$), injection site reaction ($n = 1$), urticaria ($n = 1$), and unreported ($n = 1$)

### LDL-C Cohort

Of the 225 patients included in the full analysis, 202 patients had at least one pre-index and one post-index LDL-C measurement and constituted the primary cohort for the principal outcome of LDL-C reduction (Fig. 1, Table 1). Among these, the mean age was 70.0 (SD: 8.6) years, 50.0% were female, and 85.6% were Medicare beneficiaries. The most common indication for inclisiran was ASCVD, prevalent in 82.2% of this cohort. Notably, 14.9% were treated for the indication of hyperlipidemia and 3.0% for HeFH. In total, 83.2% of cohort patients initiating treatment had clinically reported coronary artery disease, 20.3% had prior myocardial infarction, and 10.9% had experienced a stroke. The mean Elixhauser comorbidity score was 9.9 (SD: 11.5), 87.1% of patients had hypertension, 27.2% had cardiac arrhythmias, 33.7% had diabetes, and 22.8% had valvular disease. At the time of inclisiran initiation, 68 cohort patients (33.7%) were on a statin, with 50 of these (73.5%) on a high-intensity statin and the remainder on low- or moderate-intensity statins. The remaining 134 (66.3%) patients were statin intolerant at the time of inclisiran initiation. Additionally, 44.1% of cohort patients were previously treated with an anti-PCSK9 mAb, while 27.7% of cohort patients were on ezetimibe at baseline. The characteristics of the 202 patients who received inclisiran with pre- and post-index LDL-C measurements are reported in Table 1.

### LDL-C Reductions

The mean and median LDL-C at baseline were 134.8 (SD: 52.1) mg/dl and 130 (IQR: 94–164) mg/dl, respectively. More than one in four (27.2%) patients had an LDL-C ≥ 160 mg/dl at baseline. The mean time from treatment initiation to lowest LDL-C measurement occurred approximately 6 months (191.2 [SD: 98.4] days) after treatment initiation. Inclisiran reduced LDL-C by an absolute mean of 66.1 (SD: 45.6) mg/dl, corresponding to a mean relative reduction of 46.8% (95% CI: 42.7–51.0). Almost half (46.8%) of all patients treated with inclisiran had a relative LDL-C reduction of 50% or more. At its nadir, the mean LDL-C was 66.9 (SD: 38.1) mg/dl, 56.9% of patients had an LDL-C ≤ 70 mg/dl, and 40.6% had an LDL-C ≤ 55 mg/dl. LDL-C reductions are summarized in Table 3.

Among the 68 patients with concurrent statin use at baseline, the mean pre-index LDL-C was 123.3 (SD: 47.8) mg/dl. Among those

**Table 3** LDL-C at baseline and nadir in patients treated with inclisiran with pre- and post-index LDL-C measurements

| Characteristic | | Subgroups | | | |
|---|---|---|---|---|---|
| | All patients, *N* = 202 | Concurrent statin use, *n* = 68 | Statin intolerance[a], *n* = 134 | No prior use of anti-PCSK9 mAbs, *n* = 113 | Prior use of anti-PCSK9 mAbs, *n* = 89 |
| LDL-C, mg/dl at baseline | | | | | |
| Baseline LDL-C, mean (SD) | 134.8 (52.1) | 123.3 (47.8) | 140.6 (53.4) | 133.6 (46.1) | 136.3 (59.2) |
| Baseline LDL-C, median (IQR) | 130 (94.0–164.0) | 118.0 (90.0–150.0) | 133.5 (103.0–178.0) | 132.0 (100.0–153.0) | 125.0 (93.0–183.0) |
| LDL-C < 100 mg/dl, *n* (%) | 56 (27.7) | 26 (38.2) | 30 (22.4) | 28 (24.8) | 28 (31.5) |
| LDL-C 100–159 mg/dl, *n* (%) | 91 (45.1) | 30 (44.1) | 61 (45.5) | 61 (54) | 30 (33.7) |
| LDL-C ≥ 160 mg/dl, *n* (%) | 55 (27.2) | 12 (17.7) | 43 (32.1) | 24 (21.2) | 31 (34.8) |
| LDL-C, mg/dl at nadir | | | | | |
| LDL-C, mg/dl at nadir, mean (SD) | 66.9 (38.1) | 50.2 (38.0) | 75.4 (35.4) | 61.7 (34.5) | 73.4 (41.4) |
| LDL-C, mg/dl at nadir, median (IQR) | 65.0 (41.0–89.0) | 48.0 (20.0–69.0) | 74 (48.0–96.0) | 58 (38.0–82.0) | 72.0 (47.0–94.0) |
| Time to LDL-C nadir, mean days (SD) | 191.2 (98.4) | 200.9 (99.9) | 186.3 (97.7) | 193.4 (97.7) | 188.4 (99.8) |
| Time to LDL-C nadir, median days (IQR) | 182 (104.0–278.0) | 203.5 (104.0–300.0) | 176.0 (104.0–270.0) | 190.5 (103.0–278.0) | 173 (104.0–297.0) |
| LDL-C reduction at nadir | | | | | |
| LDL-C ≤ 70 mg/dl, *n* (%) | 115 (56.9) | 52 (76.5) | 63 (47.0) | 71 (62.8) | 44 (49.4) |
| LDL-C ≤ 55 mg/dl, *n* (%) | 82 (40.6) | 40 (58.8) | 42 (31.3) | 51 (45.1) | 31 (34.8) |
| Absolute reduction in LDL-C, mean mg/dl (SD) | 66.1 (45.6) | 70.7 (51.4) | 63.8 (42.5) | 69.8 (43.6) | 61.5 (47.9) |
| Relative reduction in LDL-C, mean percent [95% CI] | 46.8 [42.7–51.0] | 55.4 [47.4–63.5] | 42.5 [38.0–47.1] | 51.1 [46.0–56.1] | 41.7 [35.0–48.4] |
| LDL-C reduction ≥ 50%, *n* (%) | 94 (46.8) | 38 (55.9) | 56 (41.8) | 56 (49.6) | 38 (42.7) |

*CI* confidence interval, *IQR* interquartile range, *LDL-C* low-density lipoprotein cholesterol, *mAb* monoclonal antibody, *PCSK9* proprotein convertase subtilisin/kexin type 9, *SD* standard deviation

[a]Reason for no concurrent statin use: statin intolerance (*n* = 131), lack of efficacy (*n* = 3)

with statin intolerance at baseline, the mean pre-index LDL-C was 140.6 (SD: 53.4) mg/dl. Patients with prior use of anti-PCSK9 mAbs had a mean LDL-C of 136.3 (SD: 59.2) mg/dl, and those without had a mean baseline LDL-C of 133.6 (SD: 46.1) mg/dl. A mean relative reduction in LDL-C of 55.4% (95% CI: 47.4–63.5) was observed among patients treated with inclisiran and concurrent statins. A similar relative reduction (51.1%, 95% CI: 46.0–56.1) was observed in patients with no prior use of anti-PCSK9 mAbs. Similar reductions in LDL-C were observed in patients with statin intolerance at baseline (42.5%, 95% CI: 38.0–47.1)

and those with prior use of anti-PCSK9 mAbs (41.7%, 95% CI: 35.0–48.4). The LDL-C reductions stratified by baseline medication use are shown in Table 3.

## DISCUSSION

In this cohort of older, mostly Medicare beneficiaries with ASCVD, inclisiran effectively lowered LDL-C in all patients regardless of their history of pre-index LLTs. While randomized clinical trials demonstrated the efficacy of inclisiran, these results confirm that inclisiran is also effective in the real-world setting. Inclisiran significantly reduced LDL-C levels by a mean of 46.8%, with a mean absolute reduction of 66.1 mg/dl. A substantial proportion of patients (56.9%) achieved LDL-C levels of ≤ 70 mg/dl, and 40.6% reached LDL-C levels of ≤ 55 mg/dl. Concurrent use of other LLTs, such as ezetimibe and statins, was only seen in about a third of patients at baseline, respectively.

Although statins are effective in lowering LDL-C, there are barriers to their optimal use in real-world clinical practice [31–35]. These barriers include intolerance, suboptimal adherence, and high rates of discontinuation [31–35]. Our observation that only 32.9% of patients in our study were receiving statins at baseline is likely reflective of these barriers. Thus, there remains a need to improve lipid management with non-statin LLT in patients with ASCVD or hyperlipidemia. In our study, inclisiran treatment contributed to clinically significant reductions in LDL-C regardless of current or former LLTs. While those with concurrent statin use had the greatest LDL-C reductions (55.4%), the mean reduction in LDL-C among the 134 patients with no statin use at baseline was 42.5%. Similarly, among those previously treated with an anti-PCSK9 mAb, LDL-C was reduced by 41.7%. These data provide evidence to support the effectiveness of inclisiran in the real-world setting, including among patients with statin intolerance.

The lipid-lowering effect observed in this cohort (46.8% reduction) is consistent with that observed in other real-world studies and adds to a growing body of evidence confirming that inclisiran is as effective in the real-world setting as initially observed in clinical trials with more restrictive inclusion criteria [23, 26–28, 36–39]. Other real-world cohorts have experienced similar reductions. In a UK cohort, patients treated with inclisiran experienced a 61.7% reduction in LDL-C within the first 90 days of treatment initiation [36]. In another Italian cohort, LDL-C was reduced by 49% 3 months after treatment initiation [37]. In the ORION-10 and ORION-11 trials, inclisiran reduced LDL-C by 53.8% and 49.2%, respectively, over 510 days of follow-up in patients with concurrent LLT at baseline [23]. Our study, along with other real-world analyses of inclisiran [27, 37, 40] demonstrates that patients are not always on LLT at the time of treatment initiation. In our cohort, only 68 of 202 patients (33.7%) were taking statins at baseline. In other real-world studies, use of statins at baseline has ranged from 31% [40] to 52.5% [27]. Here, patients who used statins at baseline had the most significant reduction in LDL-C (55.4%), consistent with that observed in ORION-10 (57.3%) and ORION-11 (53.3%) [23]. Furthermore, in this cohort, the lipid-lowering effect of inclisiran was robust regardless of historical or concurrent use of LLTs.

The results presented offer one of the most comprehensive analyses of inclisiran adherence and effectiveness performed to date, in that they offer detailed information on time to dose as well as the rate of retention in treatment. In this cohort, 206 of 225 patients who initiated inclisiran (91.6%) returned for a second dose and 174 of 206 received a third (84.5%), indicating high adherence. Studies evaluating statin pharmacotherapy as primary therapy for ASCVD or hyperlipidemia report variable rates of discontinuation. In a national cohort of patients prescribed statins in Germany, 71% discontinued treatment by day 300 [41]. Similarly, in a US study of patients with ASCVD, only 58.2% [42] were adherent to statin pharmacotherapy in the first year of treatment. Given the differences in dosing schedule and method of administration between inclisiran and other LLTs, it is not possible to draw conclusions from our study on comparative rates of discontinuation.

The substantial proportion of patients achieving significant LDL-C reductions underscores the potential of inclisiran as an effective addition to current lipid-lowering strategies. The infrequent dosing regimen likely contributes to the high adherence rates observed, reducing the treatment burden on patients, and potentially improving long-term outcomes. This study's findings are consistent with the growing body of evidence supporting the efficacy and tolerability of inclisiran, positioning it as a valuable option for managing hyperlipidemia in patients with high cardiovascular risk [23, 26–28, 36, 38, 40].

Within this cohort of predominantly older adults, a majority (74.7%) of patients had traditional Medicare coverage, which has coverage for the use of inclisiran, without prior authorization. However, commercial payors and Medicare Advantage plans require a rigorous prior authorization process, many with step therapy requirements, limiting use in these populations [25]. The same issue has been reported for PCSK9 inhibitors, with inability to obtain approvals resulting in a significant increase in the risk of cardiovascular events compared to patients with paid claims [43]. As evidence emerges supporting the effectiveness of inclisiran for the management of dyslipidemia, it will be critical to address this barrier to care that prevents patients at risk of adverse cardiac events from accessing beneficial medications.

Our analysis was limited by the short duration of follow-up. Although 77.3% of patients received three doses of inclisiran, we are unable to assess long-term adherence to inclisiran, and future research to study this is warranted. Additionally, the short follow-up of our study did not allow for the long-term assessment of the safety and tolerability of inclisiran, which is noteworthy due to the long-acting nature of inclisiran [44]. To date, no new safety signals have been identified with long-term inclisiran use, including in the ORION-8 trial where patients received inclisiran for up to 6.8 years [45]. Still, observed reductions in LDL-C among those who remained in treatment at the end of 1 year were promising. It is also important to note that the proportion of patients not receiving background LLTs (statins or ezetimibe among statin-intolerant patients) at baseline in our cohort, consistent with other real-world studies, was low. We were not able to evaluate reasons for discontinuing prior LLT in our study. Prospective studies are underway to evaluate the lipid-lowering effects of inclisiran and impact on improved cardiovascular outcomes. The results observed in this study suggest that inclisiran is likely to confer cardiovascular benefits regardless of prior LLT. However, long-term studies are still needed.

## CONCLUSIONS

In conclusion, this study highlights the significant LDL-C–lowering effect and high medication adherence associated with inclisiran in a real-world cohort consisting predominantly of older adults with ASCVD and Medicare coverage. The observed LDL-C reductions were substantial, with a considerable proportion of patients achieving target levels, indicating that inclisiran provides a robust performance in managing hyperlipidemia. For future research, prospective studies are essential to confirm the cardiovascular benefits of inclisiran observed in this real-world cohort and to explore its long-term impacts on diverse patient populations. The promising results from this study on the effectiveness of inclisiran on LDL-C lowering over a year demonstrate its potential to enhance patient LDL-C management and adherence in clinical practice.

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***Data Availability.*** All data generated or analyzed during this study are included in this published article.

### *Declarations*

***Conflict of Interest.*** Christie M. Ballantyne has received grant/research support (through his institution) from Abbott Diagnostics, Akcea, Amgen, Arrowhead, Ionis, Merck, New Amsterdam, Novartis, Novo Nordisk, and Roche Diagnostics; and consulting fees from 89bio, Abbott Diagnostics, Amarin, Amgen, Arrowhead, AstraZeneca, Denka Seiken, Esperion, Genentech, Illumina, Ionis, Eli Lilly, Merck, New Amsterdam, Novartis, Novo Nordisk, and Roche Diagnostics. Lucinda J. Van Anglen has received grant/research support from Novartis. Xiaoli Niu is an employee and stockholder of Novartis. Sean McElligott is an employee of Novartis and a stockholder of Novartis, Johnson and Johnson, and Merck. Tyler J. Varisco is a consultant with Healix Infusion Therapy, LLC. Tyler J. Varisco is now affiliated with the University of Texas at Austin College of Pharmacy, TX, USA. Timothy E. Graham, Bruce J. Iteld, Harvey Serota, and Kelly E. Hanna have no disclosures to report.

***Ethical Approval.*** All procedures were approved by Biomedical Research Alliance of New York, an independent institutional review board (#22-12-927-1297). As this was a secondary analysis of data collected in the provision of care, the study was deemed exempt from human subject restrictions. No participant identifiers were used in the analysis and patients were not required to provide consent for inclusion. Data collection was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and is consistent with the Guidelines for Good Clinical Practice. Reporting followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Guideline for Cohort Studies [30].



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