# Real-World Use of Inclisiran in Outpatient Physician Clinics

#505-P

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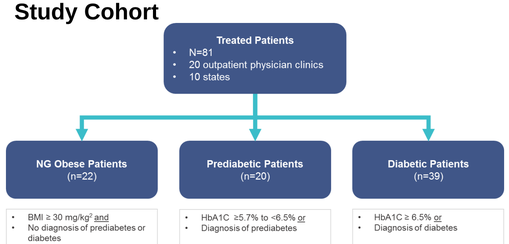
## Introduction

- Inclisiran is a novel, small interfering ribonucleic acid (siRNA) based inhibitor of PCSK9 production in the liver.
- Inclisiran is indicated in the US as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of LDL-C[1]. In two phase 3 ORION-10 and ORION-11 trials, inclisiran was shown to reduce LDL-C by 49.9 - 52.2% [2].
- Inclisiran is administered as a subcutaneous injection by a healthcare provider at three months and then twice yearly after the initial injection [1]. This convenient treatment schedule potentially reduces patient burden.
- Diabetic patients are at an increased risk of cardiovascular disease and thus likely to benefit from LDL-C lowering therapy. Statin treatment has been associated with increases in HbA1C patients with and without diabetes [3,4]. In an ad-hoc analysis of ORION-1, inclisiran was found to effectively lower LDL-C regardless of diabetes status without increasing HbA1C [4]. The post-hoc analysis of ORION-11 confirmed that inclisiran decreased LDL-C in diabetic patients by 56.3%, indicating significant benefit in diabetic patients [1].
- The early evidence suggesting inclisiran reductions in LDL-C with no change in HbA1C is expected to benefit obese, prediabetic, and diabetic patients. The objective of this study was to characterize the process of inclisiran initiation for normoglycemic obese (NG obese), prediabetic, and diabetic patients in outpatient physician clinics and to compare the time to initiation between obese, prediabetic, and diabetic patients.

## Methods

- This was a retrospective, longitudinal, multicenter cohort study of NG obese, pre-diabetic, and diabetic patients who initiated treatment with inclisiran between February and July of 2022 at outpatient physician clinics nationally. Patients were identified from a central electronic medical record and a chart review performed. Baseline characteristics were measured at the time of referral and the length of time in days from referral to inclisiran initiation was calculated.
- Demographic characteristics were collected including age, gender, geographic regions and payor. Clinical characteristics included body mass index (BMI), comorbidities including Elixhauser comorbidity score, cardiovascular comorbidities, baseline LDL-C and history of lipid-lowering therapies.
- Descriptive statistics (mean and standard deviation, median and interquartile range for continuous variables; frequencies and percentages for categorical variables) were used to summarize cohort characteristics. ANOVA and Pearson's $\chi^2$ were used to compare the distribution of baseline covariates between obese, prediabetic, and diabetic patients. The Kaplan Meier method was used to measure time from referral to inclisiran initiation. The Log rank test was used to compare median time to initiation in each group.

## Study Cohort




## Results

- Overall, 81 NG obese, prediabetic, and diabetic patients initiated treatment with inclisiran between January and July of 2022 at 20 outpatient physician clinics in 10 states.

### Table 1. Baseline Characteristics by Group

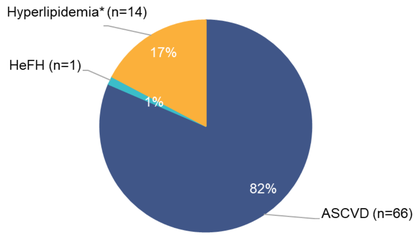
| Characteristic | NG Obese Patients (N=22) | Prediabetic Patients (N=20) | Diabetic Patients (N=39) | All Patients (N=81) | P-value |
|---|---|---|---|---|---|
| Age in years, mean (SD) | 72.1 (4.5) | 68.2 (10.3) | 71.2 (8.4) | 70.7 (8.1) | 0.26 |
| Age in years, median (IQR) | 72.5 (69-75) | 67.5 (63-75) | 71 (68-75) | 71 (68-75) | . |
| **Age in years, categories, n (%)** | | | | | |
| 64 or younger | 1 (4.6) | 7 (35.0) | 4 (10.3) | 12 (14.8) | 0.05 |
| 65-74 | 15 (68.2) | 8 (40.0) | 23 (59.0) | 46 (56.8) | |
| **75+** | 6 (27.3) | 5 (25.0) | 12 (30.8) | 23 (28.4) | |
| **Sex, n (%)** | | | | | |
| Female | 8 (36.4) | 5 (25.0) | 19 (48.7) | 32 (39.5) | 0.20 |
| Male | 14 (63.6) | 15 (75.0) | 20 (51.3) | 49 (60.5) | |
| **Patient Region, n (%)** | | | | | |
| Midwest | 2 (9.1) | 1 (5.0) | 1 (2.6) | 4 (4.9) | 0.03 |
| Northeast | 3 (13.6) | 0 (0) | 0 (0) | 3 (3.7) | |
| South | 16 (72.7) | 19 (95) | 32 (82.1) | 67 (82.7) | |
| West | 1 (4.6) | 0 (0) | 6 (15.4) | 7 (8.6) | |
| **Payor Type, n (%)** | | | | | |
| Commercial | 4 (18.2) | 6 (30.0) | 6 (15.4) | 16 (19.8) | 0.72 |
| All Medicare | 18 (81.8) | 14 (70.0) | 33 (84.7) | 65 (80.2) | |
| Medicare | 16 (72.7) | 13 (65.0) | 29 (74.4) | 58 (71.6) | |
| Medicare Advantage | 2 (9.1) | 1 (5.0) | 4 (10.3) | 7 (8.6) | |
| **Primary Treatment Indication, n (%)** | | | | | |
| ASCVD | 19 (86.4) | 18 (90.0) | 29 (74.4) | 66 (81.5) | 0.13 |
| HeFH | 0 (0) | 1 (5.0) | 0 (0) | 1 (1.2) | |
| Hyperlipidemia | 3 (13.6) | 1 (5.0) | 10 (25.6) | 14 (17.3) | |
| **Elixhauser Comorbidity Score, mean(SD)** | 7.1 (8.5) | 7.1 (7.8) | 13.4 (12.1) | 10.1 (10.6) | 0.03 |
| **Common Comorbidities, n (%)** | | | | | |
| Hypertension | 21 (95.5) | 18 (90.0) | 36 (92.3) | 75 (92.6) | 0.79 |
| Cardiac arrythmia | 8 (36.4) | 9 (45.0) | 7 (18.0) | 24 (29.6) | 0.07 |
| Valvular disease | 8 (36.4) | 6 (30.0) | 9 (23.1) | 23 (28.4) | 0.53 |
| Heart failure | 2 (9.1) | 4 (20.0) | 1 (2.6) | 7 (8.6) | 0.08 |
| **ASCVD Risk Factors, n (%)** | | | | | |
| Acute coronary syndrome | 2 (9.1) | 2 (10) | 3 (7.7) | 7 (8.6) | 0.95 |
| Coronary artery disease | 20 (90.9) | 19 (95) | 31 (79.5) | 70 (86.4) | 0.20 |
| History of myocardial infarction | 7 (31.8) | 9 (45) | 5 (12.8) | 21 (25.9) | 0.02 |
| Stable or unstable angina | 10 (45.5) | 6 (30) | 10 (25.6) | 26 (32.1) | 0.27 |
| Coronary or other arterial revascularization | 16 (72.7) | 16 (80) | 21 (53.9) | 53 (65.4) | 0.10 |
| Stroke | 1 (4.6) | 1 (5) | 6 (15.4) | 8 (9.9) | 0.28 |
| Transient ischemic attack | 3 (13.6) | 2 (10) | 4 (10.3) | 9 (11.1) | 0.91 |
| Peripheral aterial disease | 3 (13.6) | 1 (5) | 2 (5.1) | 6 (7.4) | 0.43 |
| **Cardiac-related procedures, n (%)** | | | | | |
| PCI with stent | 12 (54.6) | 8 (40) | 18 (46.2) | 38 (46.9) | 0.64 |
| PCI without stent | 2 (9.1) | 1 (5) | 3 (7.7) | 6 (7.4) | 0.88 |
| Coronary artery bypass grafting | 6 (27.3) | 7 (35) | 9 (23.1) | 22 (27.2) | 0.62 |
| Endarterectomy | 0 (0) | 1 (5) | 2 (5.1) | 3 (3.7) | 0.56 |
| Non-coronary angioplasty with stent | 2 (9.1) | 1 (5) | 1 (2.6) | 4 (4.9) | 0.53 |
| Non-coronary angioplasty without stent | 0 (0) | 0 (0) | 1 (2.6) | 1 (1.2) | 0.58 |
| **Body Mass Index** | | | | | |
| Mean (SD) | 33.4 (3.8) | 29.9 (6.6) | 31.9 (5.4) | 31.8 (5.4) | 0.12 |
| Median (IQR) | 32.2 (31-34) | 29.3 (25-35) | 30.4 (29-36) | 31.5 (29-35) | . |
| Body mass index ≥30 mg/kg$^2$ | 22 (100.0) | 9 (45.0) | 22 (56.4) | 53 (65.4) | |
| **HbA1C, %** | | | | | |
| Mean (SD) | 5.4 (0.2) | 5.9 (0.2) | 7.2 (1.5) | 6.5 (1.3) | <0.01 |
| Median (IQR) | 5.5 (5-6) | 5.9 (6-6) | 7 (6-8) | 6 (6-7) | . |
| **LDL-C, mg/dL** | | | | | |
| Mean (SD) | 146.2 (76.9) | 145.8 (54.9) | 127.5 (51.0) | 137.1 (59.9) | 0.39 |
| Median (IQR) | 137.5 (103-165) | 155.5 (117-181) | 123 (95-149) | 134 (102-165) | |
| LDL-C <100 mg/dl, n (%) | 5 (22.7) | 4 (20.0) | 11 (28.2) | 20 (24.7) | 0.76 |
| LDL-C 100-159 mg/dl, n (%) | 10 (45.5) | 9 (45.0) | 20 (51.3) | 39 (48.2) | |
| LDL-C ≥160 mg/dl, n (%) | 7 (31.8) | 7 (35.0) | 8 (20.5) | 22 (27.2) | |

Abbreviations: SD: standard deviation; IQR: interquartile range; HbA1c: Hemoglobin A1c; LDL-C: Low-Density Lipoprotein Cholesterol

- Elixhauser score was the highest among diabetic patient group (P=0.01).
- ASCVD conditions and cardiac-related procedures were similar among groups except for prediabetic patients with greater history of myocardial infarction (45% vs 25.9%, P=0.022).
- Average BMI in the cohort was 31.8 mg/kg$^2$ (SD: 5.43). There was no observed difference in BMI between groups.
- Mean HbA1C between groups was 6.5% (SD: 1.3). As expected, diabetic patients had a significantly higher HbA1C than the other groups (Mean: 7.2%, SD 1.46, P<0.01).

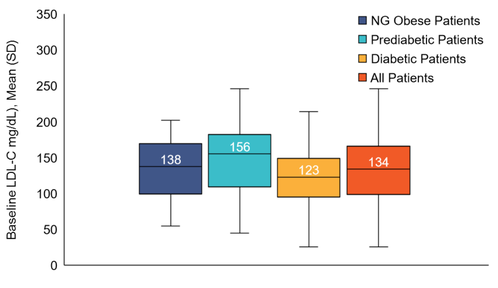
- The majority of patients had ASCVD (81.5%) as primary treatment indication at baseline; 17.3% had mixed hyperlipidemia, and 1 patient had genetically confirmed HeFH. There were no differences in the distribution of treatment indications between NG obese, diabetic, and prediabetic patients. (Figure 1)

### Figure 1: Treatment Indications



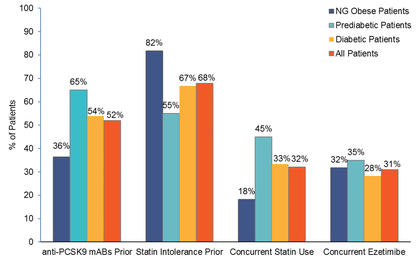

| Primary Treatment Indication, n (%) | NG Obese Patients (N=22) | Prediabetic Patients (N=20) | Diabetic Patients (N=39) |
|---|---|---|---|
| ASCVD | 19 (86.4) | 18 (90.0) | 29 (74.4) |
| HeFH | 0 (0) | 1 (5.0) | 0 (0) |
| Hyperlipidemia | 3 (13.6) | 1 (5.0) | 10 (25.6) |

### Figure 2: Baseline LDL-C by Group



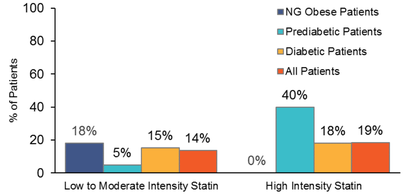

- LDL-C was ≥ 100 mg/dl in approximately three-fourths of patients at baseline, with similarity between the groups (Table 1).

### Figure 3. History of Lipid-Lowering Therapy by Group



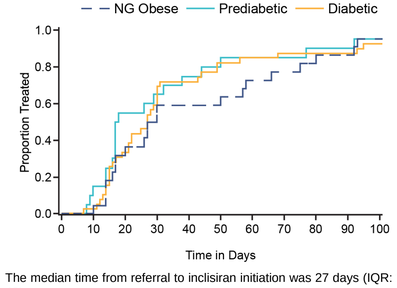

*Defined by provider-documented statin intolerance with discontinuation of statin therapy prior to initiation of inclisiran

### Figure 4. Statin Intensity by Group




- Prediabetic patients were significantly more likely to be on concurrent statins at baseline than NG obese and diabetic patients (P= 0.02).
- Over half of patients (52%) had a history of anti-PCSK9 mAB use prior to inclisiran initiation, with no difference in prior use between groups.

### Figure 5. Time to Inclisiran Initiation between Groups




- The median time from referral to inclisiran initiation was 27 days (IQR: 16-49).
- There was no observed difference in time from referral to inclisiran initiation between NG obese, (median: 28.5, IQR: 17-66), prediabetic (17.5, 15-41), and diabetic (27, 15-44) patients.

## Conclusions:

Inclisiran is an accessible treatment option for patients with ASCVD and elevated LDL-C with normoglycemic obesity, prediabetes or diabetes.

- Normoglycemic obese, prediabetic and diabetic patients who received inclisiran had similar diagnoses, baseline cardiovascular histories, and statin use. The diabetic cohort had a significantly higher comorbidity burden.
- Prior exposure to statins and anti-PCSK9 mAbs was prevalent in this population. Still, mean baseline LDL-C levels were more than double the guideline recommended threshold of <70 mg/dL, leading to the need for further optimization of lipid-lowering therapy.
- Limitations of this study include the site of care, restricted to only physician clinics and the study timeframe starting immediately post-launch.
- Inclisiran can be promptly initiated in the clinic setting for the management of LDL-C in NG obese, prediabetic, and diabetic patients. Diabetes status was not associated with time to inclisiran initiation.
- Prior clinical trial studies, including ORION-1, demonstrate clear efficacy of inclisiran in diabetic patients. We found similarities in the cardiovascular history of NG obese, prediabetic and diabetic patients. Additional research is warranted to establish equivalent, real world effectiveness of inclisiran in these at-risk populations.

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