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Original Research

First Report of Inclisiran Utilization for Hypercholesterolemia Treatment in Real-World Clinical Settings in a Middle East Population

Sajid Iqbal, MPhil, MSc[1,*], Hani Mohamed Sabbour, MD, FACC[1,2], Tanveer Ashraf, MD, MMed[1], Raul D. Santos, PhD, MSc, MD[3,4], Adam Buckley, PhD[1]

[1] *Imperial College London Diabetes Centre, Abu Dhabi, United Arab Emirates*
[2] *Cleveland Clinic, Abu Dhabi, United Arab Emirates*
[3] *Heart Institute (InCor) University of Sao Paulo Medical School Hospital, Sao Paulo, Brazil*
[4] *Hospital Israelita Albert Einstein, São Paulo, Brazil*

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ABSTRACT

Purpose: Inclisiran is the first small interfering RNA–based treatment approved for reducing pro-atherogenic lipoproteins in patients with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of low-density lipoprotein cholesterol (LDL-C). We report the first evaluation of the effects of inclisiran in a Middle East population.

Methods: We conducted a retrospective review of patients initiating inclisiran treatment at an outpatient diabetology, endocrinology, and cardiology center between May 2021 and December 2022. All patients followed up for 90 days or more, or with at least 1 lipid determination post initiation were included. Participants were categorized into primary prevention (n = 57) and secondary prevention (n = 89) groups according to previous atherosclerotic cardiovascular disease.

Findings: Inclisiran was initiated in 146 patients; mean (SD) age was 54.8 (12.12) years, 82 patients (56.2%) were male, 28 patients (19.2%) had received a diagnosis of familial hypercholesterolemia, 89 patients (61%) had received a diagnosis of diabetes mellitus, and 35 patients (23.9%) had a statin intolerance. Median (interquartile range) follow-up was 137 (90 to 193) days. At 90 days, median (interquartile range) reductions in serum LDL-C and triglycerides were –37.9% (–9.5% to –51.2%) and –12.0% (–9.8% to –40.5%), respectively, in primary prevention and –54.1% (–17.1% to –71.4%) and –15.3% (–14% to –38.8%), respectively, in secondary prevention (all, $P < 0.001$). LDL-C goals were attained in 110 patients (75.3%). Nonattainment of LDL-C goal was attributed to system effect in 26 patients (72.2%), biological effect in 5 patients (13.9%), and discontinuation of treatment in 5 patients (13.9%). Therapy was well tolerated.

Implications: This study is the first from the Middle East and North Africa region that reported the real-world efficacy and safety profile of inclisiran in a mixed-risk population of patients with heterozygous familial hypercholesterolemia and other non–familial hypercholesterolemia indications. Clinically meaningful and sustained reductions in pro-atherogenic lipids with good tolerability were observed after inclisiran initiation. Fewer AEs were reported in this predominantly Arabic population, consistent with previous safety reports for inclisiran. It is important to note that no patient stopped inclisiran treatment due to AEs. Strengths of our study included an optimal cohort, patient heterogeneity, and high retention. In addition, we were able to report mean robust effects of inclisiran and good medication tolerability, quite like randomized studies and open-label extension periods. Despite this, our study had some limitations, including selection bias due to the retrospective design and the absence of a comparative group.

Introduction

Low-density lipoprotein cholesterol (LDL-C) is a causal factor for the development and progression of atherosclerotic cardiovascular disease (ASCVD).[1] Robust evidence indicates a direct association between reduction in LDL-C concentrations and improvement in clinical outcomes in patients with dyslipidemia.[1–4] Furthermore, it has also been reported that intensive LDL-C reduction with combination therapies, such as eze-

* Address correspondence to: Sajid Iqbal, MPhil, MSc, Imperial College London Diabetes Centre, Al Khaleej Al Arabi Street, Beside Zayed Military Hospital Abu Dhabi, PO Box 48338, United Arab Emirates.
E-mail address: siqbal@icldc.ae (S. Iqbal).

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timibe and monoclonal antibodies against proprotein convertase subtilisin kexin type 9 (PCSK9), brings additional ASCVD event lowering in comparison with statin therapy alone in people with previous ASCVD.[4–7] Despite this, most high- and very high-risk patients do not achieve the recommended American College of Cardiology/American Heart Association/Multisociety Cholesterol (ACC/AHA/MS)[8] or European Society of Cardiology/European Atherosclerosis Society (ESC/EAS)[9] LDL-C goals, despite maximal conventional lipid-lowering therapy (LLT).[5,10–12] This has been attributed to several factors, including pharmacogenetic effects on statin response; very high baseline LDL-C concentrations, as seen in familial hypercholesterolemia (FH); and lack of adherence to therapy.[13]

Inclisiran is a small interfering RNA (siRNA) molecule directed against the intracellular hepatic synthesis of PCSK9, which upregulates hepatocyte LDL receptors and consequently reduces plasma LDL-C.[14] It is indicated in adults with established ASCVD, hypercholesterolemia (heterozygous FH or nonfamilial forms), mixed dyslipidemia, or in those otherwise unable to achieve target LDL-C.[15] Inclisiran requires less frequent dosing than standard LLTs and, in Phase III studies, has been found to reduce LDL-C by up to 50% at 510 days post initiation when administered subcutaneously at a dose of 284 mg initially, at 3 months, and at 6-month intervals thereafter, whereas statins required daily oral dose administration and PCSK9 monoclonal antibodies every 2 to 4 weeks.[9,16] The ORION development program provided robust evidence of inclisiran's safety profile and efficacy, supporting its use in patients with high risk of ASCVD, including those with established ASCVD and FH.[17,18] However, there is limited evidence in the literature regarding real-world clinical use of inclisiran, particularly in Arab populations in Middle East and North African regions. In this study, we explored the clinical effectiveness and safety profile of inclisiran in a predominantly Arab outpatient population.

Methods

Participants and Study Design

This study followed an observational retrospective cohort design and was conducted at the Imperial College London Diabetes Centre (ICLDC) in Abu Dhabi, United Arab Emirates (UAE). The ICLDC is a leading outpatient facility operating a specialist clinic of endocrinology, diabetology, nephrology, cardiology, ophthalmology, internal medicine, and general practice. Patients enrolling for treatment at ICLDC are given the option of consenting to the use of their anonymized data from their medical records in clinical research. Inclisiran was first approved and made available in UAE in May 2021. As a consequence, anonymized patient data from the ICLDC electronic medical record (EMR) covering the period from May 2021 to December 2022 was retrieved. Furthermore, additional clinical information collected outside of the treatment facility was documented via Malaffi, the region's first health information–sharing platform. The Institutional Research Ethics Committee (IREC078) approved the study protocol and a waiver for informed consent was obtained. The study included all patients aged 18 years and older who initiated inclisiran treatment at ICLDC and who attended follow-up visits with repetition of the lipid panel on at least 1 subsequent occasion. Follow-up visits post initiation of inclisiran were planned at 3-month intervals.

At ICLDC, skilled nurses administered inclisiran as a 284-mg subcutaneous injection at the start, with doses following at 90 and 180 days. Subsequently, inclisiran was injected every 6 months for the remainder of the follow-up period. The patients' demographic characteristics, anthropometric measures, FH status, diabetes status and type of diabetes, adverse events (AEs), and cardiovascular disease diagnoses (*International Classification of Diseases, Tenth Revision* [ICD-10][19] codes: I21–I21.19; I25–125.83; I73–I73.9; Z86.73; Z95.1–Z95.5, I67.9) were recorded. LLTs administered to treat each patient before inclisiran initiation were retrieved from the EMR.

The lipid profile immediately before initiation of inclisiran was considered as baseline. Preexisting or first-visit ASCVD and/or cardiovascular events were reported as ASCVD prevalence and subsequent ASCVD and/or cardiovascular events were reported as incidence. The cohort was classified into primary and secondary prevention groups on the basis of absence or presence of clinical ASCVD events at the initiation of inclisiran, as per the 2018–2019 ACC/AHA/MS guidelines.[8] ASCVD events were defined as acute coronary syndrome; myocardial infarction or unstable angina; stable angina or coronary or other arterial revascularization; atherothrombotic stroke; transient ischemic attack; or peripheral artery disease, including aortic aneurysm. The additional data on the presence of ASCVD events were ascertained through the EMR for all inpatient and outpatient encounters. For the patients in primary prevention, 10-year ASCVD risk before initiation of inclisiran was estimated using the pooled cohort equations.[20] Patients with absolute 10-year ASCVD risk scores of 5%, 5% to 7.5%, 7.5% to 20%, and >20% in those without a prior ASCVD or FH diagnosis were classified as low, borderline, intermediate, and high risk, respectively.[8] Patients with a history of ASCVD or FH, however, were already classified as high risk. Patients in the secondary prevention group were considered to have a high or very high risk of ASCVD per the most recent ESC/EAS guidelines.[9] Both groups were further stratified according to the SCORE2, SCORE2-OP, SMART score, or ADVANCE risk score tool in ESC ASCVD risk calculator[21]; scores ≥5% to <10% and ≥10% categorized patients as high risk and very high risk, respectively. Untreated LDL-C was estimated using the algorithm proposed by Ruel et al.[22] to control for the effect of concomitant statin therapy. The estimated likelihood of an underlying diagnosis of FH was calculated using the Dutch Lipid Clinic Network criteria.[23] FH status was considered definitive in patients with Dutch Lipid Clinic Network scores of >8 or a genetic diagnosis.

Study Outcome Measures

The primary outcome was fulfilling the ACC/AHA/MS-approved LDL-C goals of >30% reduction or LDL-C <2.6 mmol/L (100 mg/dL) in primary prevention or >50% reduction or LDL-C <1.8 mmol/L (70 mg/dL) in secondary prevention.[8] Furthermore, all patients were assessed using an updated target LDL-C value of <1.4 mmol/L (55 mg/dL), as recommended by the ESC/EAS guidelines for 2022.[9]

The secondary outcome was the incidence of new cardiovascular events after inclisiran initiation, expressed as a composite of acute coronary syndrome; transient ischemic attack; atherothrombotic stroke; myocardial infarction or unstable angina; stable angina or coronary or another arterial revascularization; or peripheral artery disease, including aortic aneurysm. Tolerability was assessed according to AEs (eg, injection-site reactions; myalgia; elevation of liver enzymes; nausea; vomiting; and respiratory events, including bronchitis and cough) recorded in the EMR. The treatment adherence was assessed by means of manual review of clinician entries in the EMR and pharmacy records. The standard of care at ICLDC for follow-up of patients with hypercholesterolemia is to perform clinical review and relevant laboratory investigations every 3 months. Prescription and dispensing of medication in the UAE follow a 3-monthly cadence and hence patients who did not collect their prescribed medication during one 3-monthly cycle were considered to have lapsed treatment.

Statistical Analysis

Data are expressed as mean (SD) when normally distributed or as median (interquartile range [IQR]). Wilcoxon signed-rank test was performed to assess change in lipid parameters after initiation of inclisiran. When applicable, this test was also performed to assess the significance of differences among baseline and/or post-baseline characteristics in primary and secondary prevention groups. The Cox proportional hazards model was performed to calculate the hazard ratio and its significance for the secondary outcome measures of the study. When data were miss-

ing, mean values were imputed, amounting to <1% of the data. Statistical analysis was carried out using R software, version 4.0.3 (R Foundation for Statistical Computing) with the *survminer, coin, psych, dplyr, stats19, fBasics, asht, tidyverse,* and *meta* packages. Significance was assessed at $P < 0.05$ and 95% CI. No correction for multiple comparisons was performed.

Results

Overall, 146 patients initiated inclisiran treatment between May 2021 and December 2022, had a baseline and at least 1 follow-up lipid panel, and were included in the analysis. Median (IQR) follow-up period of the patients included in this analysis was 137 (90–193) days.

Baseline Demographic Characteristic

Characteristics at the Initiation of Inclisiran

Baseline characteristics of the participants are presented in Table 1. Mean (SD) age at baseline was 54.8 (12.12) years and 82 participants (56.2%) were male. Overall, 89 participants (61%) were treated for secondary prevention and 57 participants (39%) received inclisiran in a primary prevention setting. None of these patients were lost to follow-up during the study period.

Clinical ASCVD and heterozygous FH were the most commonly recorded indications for inclisiran use, with 89 participants (61%) and 28 participants (19.2%), respectively. Statin intolerance was observed in 35 participants (23.9%) (Table 1).

According to the 10-year estimated ASCVD risk determined using the 2019 ACC/AHA/MS guidelines,[8] 11 primary prevention patients (19.3%) were at high risk. According to the 2019 ESC/EAS guidelines,[9] 24 patients (42.1%) and 6 patients (6.7%) were identified as high risk in primary and secondary prevention, respectively. Furthermore, 2 patients (3.5%) were at very high risk in primary prevention and 83 patients (93.3%) were at very high risk in secondary prevention.

Statin Background

Almost all of the patients included had received LLT before starting inclisiran, with 97.3% receiving at least 1 statin; 68 patients (46.6%) received high-dose, high-potency statins; 82.2% receiving ezetimibe; and 5.5% receiving other PCSK9 inhibitor medications. Among patients who discontinued LLT before starting inclisiran, the most common reason was statin intolerance. This occurred in 18 patients (12.3%) in primary prevention and 17 patients (11.6%) in secondary prevention, according to a National Lipid Association (NLA) statement.[24] Of the 35 patients with statin intolerance, the statin dose was reduced in 26 (74%) and ezetimibe was introduced in 21 (78%). Among these patients, 7 (27%) had discontinued statin treatment due to intolerance before the initiation of inclisiran. AEs attributed to statins, including myalgia, elevation of liver enzymes, bronchitis, headache, and gastroenteritis, were recorded before inclisiran initiation for 17 patients (11.6%) in secondary prevention and 17 patients (11.6%) in primary prevention.

Table 1
Clinical and laboratory characteristics of patients with hypercholesterolemia at the initiation of inclisiran therapy according to the presence or absence of previous atherosclerotic cardiovascular disease.

Characteristic	Primary prevention (n = 57)	Secondary prevention (n = 89)
Age, y, mean (SD)	51.8 (12.6)	56.7 (11.5)
Sex, male, n (%)	32 (56.1)	50 (56.2)
BMI, n (%) (n = 138)		
<18.5	2 (3.6)	–
18.5 to <25	6 (10.7)	11 (13.4)
25 to <30	17 (30.4)	30 (36.6)
≥30	31 (55.4)	41 (50)
Ever smoked, n (%)	14 (24.6)	36 (40.4)
Received diagnosis of HeFH, n (%)	11 (19.3)	17 (19.1)
DM status, n (%) (n = 89)		
Type 1	1 (1.8)	1 (1.2)
Type 2	32 (56.1)	55 (61.8)
Normoglycemia	24 (42.1)	34 (38.2)
HbA_{1c}, % (DM cases), median (IQR)	6.3 (5.6–7.3)	6.6 (5.8–7.8)
Blood pressure, mm Hg, median (IQR)		
Systolic	126 (114–138)	127 (117–138)
Diastolic	78 (70–82)	75 (66–80)
Renal function and diseases		
eGFR, mL/min/1.73 m^2, median (IQR) (n = 91)	103.7 (82–126.5)	103.7 (81.3–117.7)
Diabetic nephropathy (ICD-10 codes E10.21, E11.21), n (%)	4 (7.0)	16 (18)
Comorbidity		
Essential hypertension (ICD-10 code I10)	16 (28.1)	26 (37.1)
Family history of cardiovascular disease, n (%)	18 (31.6)	31 (34.8)
Drugs at baseline before start of inclisiran, n (%)		
Statins	32 (56.1)	57 (64.0)
PCSK9 inhibitor	4 (7.0)	0 (0)
Ezetimibe	32 (56.1)	58 (65.2)
Omega-3 fatty acids	22 (38.6)	17 (19.1)
Fibrates	4 (7.0)	3 (3.4)
Icosapent ethyl	4 (7.0)	2 (2.2)
Lipid profile, mmol/L,* median (IQR)		
LDL-C	3.2 (2.6–4.0)	2.8 (2.0–3.8)
HDL-C	1.3 (1.0–1.4)	1.2 (1.0–1.4)
TC	5.3 (4.1–6.5)	4.4 (3.6–5.5)
TG	1.8 (1.2–2.4)	1.6 (1.1–2.0)

BMI = body mass index (calculated as kg / m^2); DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; ICD-10 = *International Classification of Diseases,* Tenth Revision[19]; IQR = interquartile range; LDL-C = low-density lipoprotein-cholesterol; PCSK9 = proprotein convertase subtilisin kexin type 9; TC = total cholesterol, TG = triglycerides.

* To convert mmol/L cholesterol to mg/dL, multiply by 38.7. To convert mmol/L TG to mg/dL, multiply by 88.6.

Table 2
Low-density lipoprotein cholesterol at initiation and after undergoing inclisiran therapy in patients with familial hypercholesterolemia.

Variable	Primary prevention (n = 11)	Secondary prevention (n = 17)
LDL-C at initiation of inclisiran, mmol/L, median (IQR)	4.9 (4.0 to 5.7)	4.1 (3.5 to 4.4)
Prior use of statins, n (%)	11 (100)	17 (100)
Prior use of ezetimibe, n (%)	8 (72.7)	15 (88.2)
LDL-C at most recent evaluation after inclisiran initiation, mmol/L, median (IQR)	2.9 (2.4 to 3.3)	1.4 (0.9 to 1.9)
Reduction in LDL-C, %, median (IQR)	–46 (–13.3 to –52.2)	–62.7 (–56.4 to –73.8)
Participants achieving ≥50% reduction, n (%)	5 (45.4)	14 (82.4)
Participants achieving ACC/AHA-recommended LDL target of <1.8 mmol/L,* n (%)	2 (18.2)	11 (64.7)
Participants achieving ESC/EAS-recommended LDL-C target of <1.4 mmol/L, n (%)	3 (27.3)	13 (76.5)

ACC/AHA/MS = American College of Cardiology/American Heart Association/Multisociety Cholesterol; ESC/EAS = European Society of Cardiology/European Atherosclerosis Society; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol.
* To convert mmol/L cholesterol to mg/dL, multiply by 38.7.

Macrovascular Complications at Initiation of Inclisiran

At baseline, 8 patients (5.5%) had a history of myocardial infarction (ICD-10[19] codes: I21, I21.3, I21.4, I21.19, I25.2), 57 patients (39.0%) had coronary artery disease (ICD-10 codes: I25.10, 125.83), 19 patients (13.0%) had chronic ischemic heart disease (ICD-10 code: I25, I25.9), and 19 patients (13.0%) had aortocoronary bypass graft (ICD-10 code: Z95.1). Forty-six patients (31.5%) had preexisting peripheral vascular disease (ICD-10 code: I73, I73.9), and 7 patients (4.8%) had previous transient ischemic attacks (ICD-10 code: Z86.73).

Diagnosis of FH at Initiation of Inclisiran

FH was established previously by means of genetic analysis in 2 cases, both were heterozygous and both were in the secondary prevention group. Twenty-eight patients met DCLN criteria for definite FH (**Supplemental Table** in the online version at doi:XXXXXXXXXX). LDL-C values before and after initiation of inclisiran in patients meeting the criteria for FH are presented in Table 2.

Primary Outcome Measure

Changes in LDL-C after initiation of inclisiran during a median (IQR) follow-up of 137 (90–193) days are presented in Figure 1.

ACC/AHA Guideline–Recommended LDL-C Goals

A total of 118 patients (80.8%) achieved individualized ACC/AHA/MS guideline–recommended LDL-C goals within 180 days of inclisiran initiation, of whom 110 (75.3%) sustained these results at each subsequent visit during the median study follow-up.

ESC/EAS Guideline–Recommended LDL-C Goals

A total of 90 patients (61.6%) achieved their individualized ESC/EAS guideline–recommended LDL-C goal within 180 days of inclisiran initiation, of whom 78 (53.4%) sustained these results at each subsequent visit over the median study follow-up. Thirty-two (21.9%) of the 146 patients were classified as very high risk, of whom 16 (50%) maintained an LDL-C level <1.0 mmol/L (40 mg/dL).

Attainment of LDL-C Goals

Fifty-five participants (37.7%) achieved an LDL-C <1.4 mmol/L at ≤90 days of initiation of inclisiran, 23 (15.8%) at 91 to 180 days, and 12 (8.2%) at >180 days. Figure 2 illustrates the achievement of LDL-C values <1.4 mmol/L in patients with definite FH.

Thirty-six participants (24.7%) did not attain ACC/AHA/MS guideline[8]–recommended LDL-C goals at more than 1 evaluation. Of these, 12 patients (33.3%) had an initial reduction in LDL-C or early response to the therapy (reduction in ≤90 days with at least 1 dose of inclisiran administered post initiation), 11 patients (30.6%) had a late reduction in LDL-C or delayed response to the therapy (reduction in >90 days with at least 1 dose of inclisiran administered post initiation) and 13 patients (36.1%) had no reduction or no response to the therapy on any occasion during the entire follow-up. Elevated baseline LDL-C (41.7%) and a high proportion of statin intolerance (33.3%) were among the conditions most commonly associated with failure to sustain the LDL reductions in this cohort. Nonattainment of LDL-C goal at follow-up was attributed to system effects in 26 (72.2%), with 22 patients reporting nonadherence to therapy; 4 patients had an interruption of treatment due to issues with funding or supply of medication. Treatment failure was attributed to biological effects in 5 cases (13.9%), all were diagnosed with FH and had prior statin intolerance. Discontinuation of treatment was considered the cause of failure to achieve targets in 5 participants (13.9%); 2 were due to pregnancy and 3 were due to fear of potential AEs of treatment.

Table 3
Lipid panel at baseline and most recent post initiation of inclisiran therapy.

Variable	At baseline, median (IQR) (n = 146)	Post initiation of inclisiran therapy, median (IQR) (n = 146)
Lipid panel		
LDL-C, mmol/L*	3.0 (2.1–3.9)	1.8 (0.9–2.5)
TG, mmol/L†	1.7 (1.1–2.2)	1.3 (1.0–2.0)
HDL-C, mmol/L	1.2 (1.0–1.4)	1.2 (1.0–1.5)

HDL-C = high-density lipoprotein cholesterol; IQR = interquartile range; LDL-C = low-density lipoprotein-cholesterol; TG = triglyceride.
* To convert mmol/L cholesterol to mg/dL, multiply by 38.7.
† To convert mmol/L TG to mg/dL, multiply by 88.6.

Effect of Inclisiran on Lipid Profile at Follow-Up

The LDL-C levels were examined on a median (IQR) of 2 (1–4) occasions during follow-up. Overall robust median (IQR) relative reductions in serum LDL-C of –47.7% (–13.9% to –66.1%; P <0.0001) and triglycerides of –14.4% (–11.1% to –39.3%; P < 0.01) occurred in the first 90 days post initiation of inclisiran. However, there were no significant changes in HDL-C (ie, median [IQR] 1.4% [–6.5% to 8.6%]; P > 0.05) (Table 3).

The most recent LDL-C response to inclisiran therapy indicated a high degree of heterogeneity among participants; 46.6%, 36.3%, and 17.1% presented reductions in LDL-C ≥50%, from 1% to 50%, and no reduction at all or incremental, respectively (Figure 3).

In the primary prevention group, LDL-C was reduced a median (IQR) of –37.9% (–9.5% to –51.2%; P < 0.0001) and triglycerides were reduced a median (IQR) of –12.0% (–9.8% to –40.5%; P < 0.0001). In the secondary prevention group, the median (IQR) reductions in LDL-C were –54.1% (–17.1% to –71.4%; P < 0.0001) and in triglycerides were –15.3% (–14% to –38.8%; P < 0.03). Median (IQR) increase in HDL-C was 2.3% (–7.2% to 9.9%; P >0.05) in the primary prevention group and 1.2% (–5.9% to 6.7%; P > 0.05) in the secondary prevention group (Figure 4).

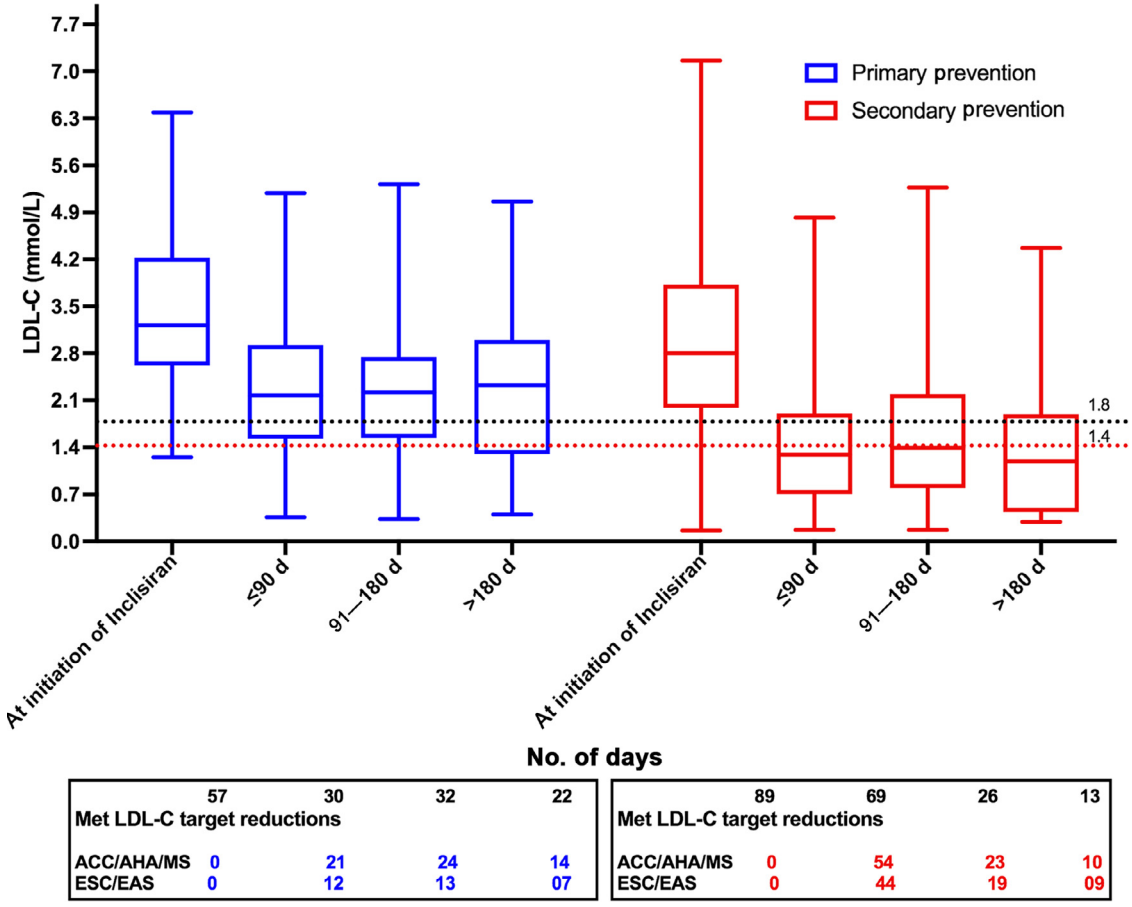

Figure 1. Low-density lipoprotein cholesterol (LDL-C) and achievement of LDL-C goals at initiation and during inclisiran therapy according to previous atherosclerotic cardiovascular disease status. Values are presented as median (interquartile range [IQR]) and numbers. n = number of patients at each time point. Rectangle: IQR; whisker bar: total range. American College of Cardiology/American Heart Association/Multisociety Cholesterol (ACC/AHA/MS)–recommended LDL-C targets: primary prevention group ≥30% reduction or LDL-C <2.6 mmol/L; secondary prevention group: ≥50% reduction or LDL-C <1.8 mmol/L. European Society of Cardiology/European Atherosclerosis Society (ESC/EAS)–recommended LDL-C targets: very high risk <1.4 mmol/L or high risk <1.8 mmol/L. To convert mmol/L cholesterol to mg/dL, multiply by 38.7.

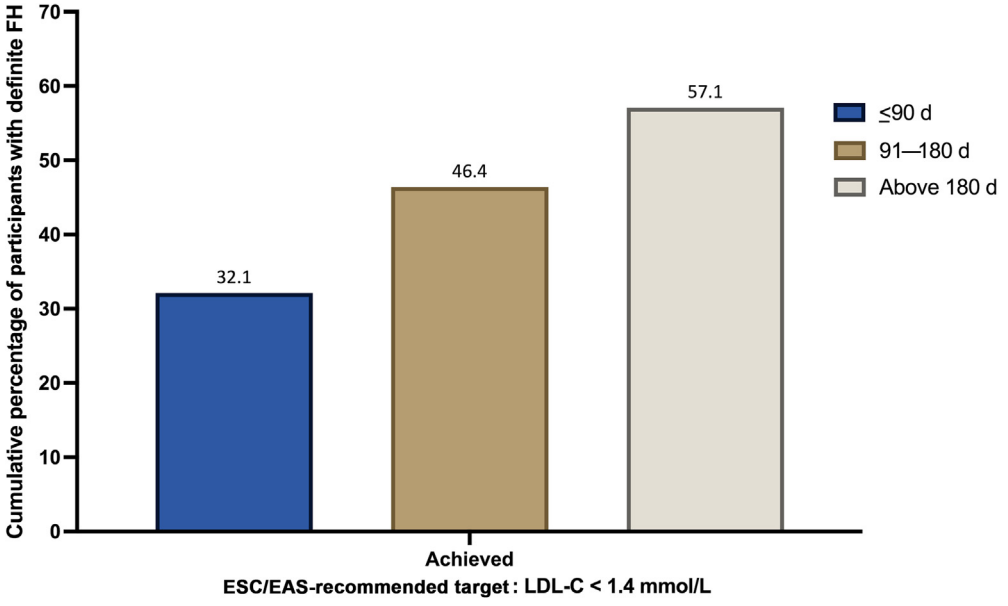

Figure 2. Participants with definite familial hyperlipidemia (FH) diagnosis achieving European Society of Cardiology/European Atherosclerosis Society (ESC/EAS)–recommended goal of low-density lipoprotein cholesterol (LDL-C) <1.4 mmol/L. To convert mmol/L cholesterol to mg/dL, multiply by 38.7.

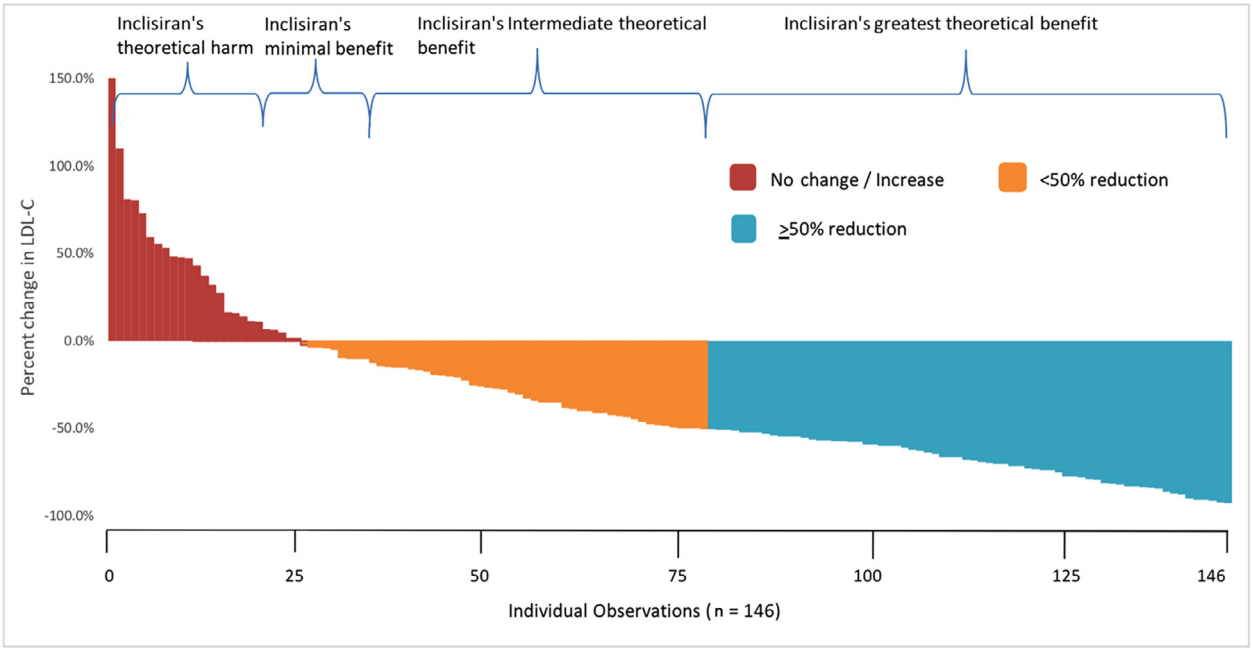

Figure 3. Participants' change in the most recent low-density lipoprotein cholesterol (LDL-C) post initiation of inclisiran. n = 146. No change/increase in LDL-C: n = 25 (17.1%); <50% reduction in LDL-C: n = 53 (36.3%); ≥50% reduction in LDL-C: n = 68 (46.6%).

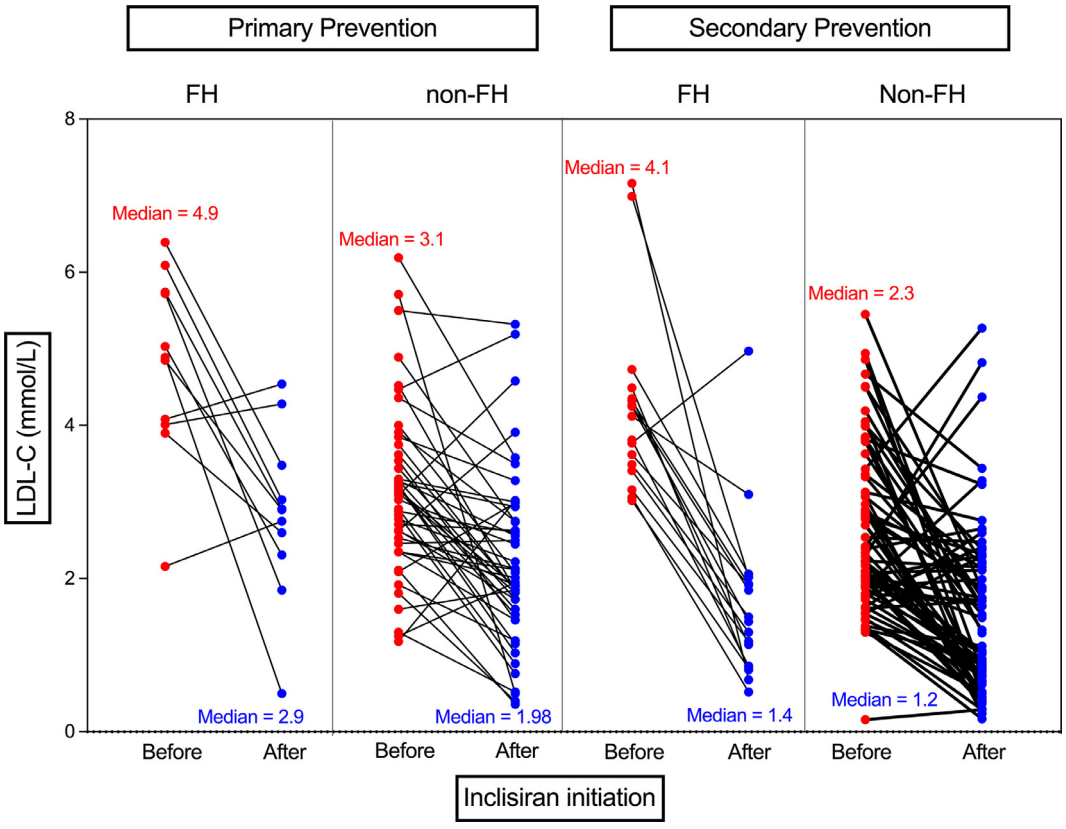

Figure 4. Low-density lipoprotein cholesterol (LDL-C) before and after initiation of inclisiran according to familial hyperlipidemia (FH) and previous atherosclerotic cardiovascular disease status. Primary prevention = no history of macrovascular event; secondary prevention = history of macrovascular event; before = before initiation of inclisiran, after = most recent LDL-C post initiation of inclisiran. To convert mmol/L cholesterol to mg/dL, multiply by 38.7.

Cardiovascular Events During Follow-Up

As a secondary outcome measure, 14 patients (9.6%) experienced a new cardiovascular event during the entire follow-up period. Five of 57 patients (8.8%) of in the primary prevention group and 9 of 89 patients (10.1%) in the secondary prevention group were diagnosed with a new cardiovascular event after initiation of inclisiran. The hazard of a new clinical ASCVD event adjusted for age, sex, smoking status, diabetes status, and FH status was higher in the secondary prevention group than in the primary prevention group (hazard ratio = 1.2; 95% CI, 0.37–3.69; $P < 0.0001$).

Event Reporting and Safety

Participants were assessed for AEs reported previously in association with inclisiran in randomized clinical studies[18,25] as part of ICLDC's inclisiran prescribing protocol, with specific reference to injection-site reactions, myalgia, derangement of liver enzymes, bronchitis, and cough. One patient (0.7%) had an injection-site reaction that was attributed to inclisiran. Twelve participants (21.1%) in the primary prevention group had the same AEs both before and after inclisiran initiation, with myalgia in 7 participants (12.3%), elevation of liver enzymes in 3 participants (5.3%), bronchitis and cough in 1 participant (1.8%), and constipation in 1 participant (1.8%). In the secondary prevention group, 17 participants (19.1%) had the same AEs both before and after inclisiran initiation (myalgia: 11 participants [12.4%], elevated liver enzymes: 5 participants [5.6%], and gastroenteritis: 1 participant [1.1%]).

Discussion

To our knowledge, our study is one of the first reporting real-world experience with inclisiran in the region. In this cohort, inclisiran was well tolerated and provided robust and sustained reductions in pro-atherogenic lipids during a median follow-up of 137 days. Participants with an Arabic, Middle East, and North African background are less commonly included in pharmaceutical studies, and countries in the Middle East and North African region rely on North American and European regulatory opinions in their own drug approvals process. Consequently, studies of real-world experience provide an important part of post-marketing pharmacovigilance in the UAE population.

We performed a literature search for publications reporting real-world experience with inclisiran, which identified works by Klebs et al.,[26] Mercep et al.,[27] Galactionova et al.,[28] Desai et al.,[29] and Chiou et al.[30] These studies described inclisiran use specifically in patients with elevated LDL-C and/or with FH, and in patients with clinical ASCVD and statin intolerance. In these studies, the mean duration was 1 year, with LDL-C reductions of up to 50% after 2 doses of inclisiran. Our outcomes are similar and broaden the experience with this therapy.

We observed sustained reductions in LDL-C, which were achieved and maintained over the study duration with only 2 or 3 injections during a median (IQR) course of 2 (1–4) doses of inclisiran. This sustained effect was particularly notable in patients with high residual baseline LDL-C, including those with FH. In those patients who had a nonsustained LDL-C response, this was primarily attributed by the treating clinician to nonadherence to concomitant statin therapy.

In the ORION-1 trial to Evaluate the Effect of ALN-PCSSC Treatment on Low Density Lipoprotein Cholesterol (LDL-C), up to 50% mean reductions in LDL-C were achieved and maintained for at least 180 days with 2 doses of inclisiran at post initiation; participants achieved an absolute reduction in LDL-C value of 1 mmol/L (38.7 mg/dL) from the baseline for a median duration of 6 to 9 months after the initial dose, and similar reductions were maintained with the second dose for 5 to 10 months post initiation.[31] We observed mean LDL-C reductions of 38% in primary prevention and 54% in secondary prevention, which are comparable with the most recent randomized controlled trial results, including ORION-11 and Phase III trials. The ORION-11 and Phase III inclisiran trials also reported 44% and 51% reductions in LDL-C at 18 months of therapy in primary and secondary prevention, respectively.[32,33]

Of interest, there was individual variability in LDL-C response with inclisiran in our study participants. This was similar to what had been described previously for statins and monoclonal PCSK9 inhibitors, when individual variabilities of 80% and up to 10% in LDL-C reduction were reported, respectively.[34,35] However, despite this, almost 90% of patients attained additional LDL-C reductions on top of standard LLTs. In addition, rates of unusual responders found in our study were similar to those in another real-world investigation reported by Warden et al.[36] Unusual response could be attributed to a significant percentage of patients who did not adhere to their recommended baseline medicines and fewer who had legitimate biological reasons and switched treatment inappropriately. One important lesson from real-life studies like ours is that adequate patient monitoring is necessary, especially in those considered at highest risk of ASCVD.

During follow-up, almost 1 in 10 patients in this study experienced an incident ASCVD event, despite LLT with inclisiran. Our study, however, was severely limited to test any impact of this drug on ASCVD events, considering the short-term follow-up and small number of study participants. Previously, an observational study by Ray et al.[33] suggested a nonadjudicated reduction in major cardiovascular events (odds ratio = 0.74; 95% CI, 0.58–0.94) with inclisiran in 3665 patients receiving either the drug or placebo after 18 months of follow-up. The impact of inclisiran on ASCVD is being tested in properly designed outcome studies like ORION-4 (ClinicalTrials.gov identifier: NCT03705234) and VICTORION 2P "Study of Inclisiran to Prevent Cardiovascular (CV) Events in Participants With Established Cardiovascular Disease" (ClinicalTrials.gov identifier: NCT05030428).

In our study, inclisiran was very well tolerated, despite specific assessment for the common AEs reported previously in clinical trials, only 1 patient experienced injection-site reactions attributed to inclisiran, and other AEs, including myalgia or elevation of liver enzymes, and respiratory symptoms preceded inclisiran initiation and were attributed to concomitant statin use. Of importance, no patient stopped inclisiran treatment due to AEs. In a patient-level analysis of Phase III trials, 2.5% of study participants suspended therapy due to AEs compared with 1.9% of those receiving a placebo[25]; injection-site reactions and cases of bronchitis, respectively, were more frequent in those who received inclisiran (5% vs 0.7% and 4.3 vs 2.7%). Serious AEs attributed to treatment were reported in 20.4% and 23.0% of those receiving inclisiran and placebo, respectively.

This study has several limitations, including its retrospective design; absence of a comparative group; experience from a single center, which may reduce results reproducibility; and the relatively short-term follow-up. However, we were able to report the mean robust effects of inclisiran and good medication tolerability, like randomized studies and open-label extension periods. Longer-term follow-up, however, is necessary to confirm the impacts of inclisiran on adherence, effectiveness, and tolerability of therapy in the real world.

Conclusions

Clinically meaningful and sustained reductions in pro-atherogenic lipids were observed after inclisiran introduction and the drug was well tolerated. This supports the role of inclisiran in the management of hypercholesterolemia in a predominantly Arabic population.

Declaration of competing interest

None.

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Author Contributions

Study conception and design: Sajid Iqbal, Tanveer Ashraf, and Adam J. Buckley. Data collection: Tanveer Ashraf and Sajid Iqbal. Analysis and interpretation of results: Sajid Iqbal, Adam J. Buckley, Hani Mohamed Sabbour, Raul D. Santos. Draft manuscript preparation: Sajid Iqbal, Tanveer Ashraf, Adam J. Buckley, Hani Mohamed Sabbour, and Raul D. Santos. Manuscript critical review: Raul D. Santos, Adam J. Buckley, and Hani Mohamed Sabbour.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2023.12.003.

References

1. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low–density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38:2459–2472.
2. Koren MJ, Hunninghake DBALLIANCE Investigators. Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the ALLIANCE study. *J Am Coll Cardiol*. 2004;44:1772–1779.
3. Giugliano RP, Pedersen TR, Park JG, De Ferrari GM, Gaciong ZA, Ceska R, et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. *Lancet*. 2017;390(10106):1962–1971.
4. Wang N, Fulcher J, Abeysuriya N, Park L, Kumar S, Di Tanna GL, et al. Intensive LDL cholesterol-lowering treatment beyond current recommendations for the prevention of major vascular events: a systematic review and meta-analysis of randomised trials including 327 037 participants. *Lancet Diabetes Endocrinol*. 2020;8:36–49.
5. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med*. 2017;376:1713–1722.
6. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med*. 2018;379:2097–2107.
7. Ridker PM, Revkin J, Amarenco P, Brunell R, Curto M, Civeira F, et al. Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients. *N Engl J Med*. 2017;376:1527–1539.
8. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74:e177–e232.
9. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111–188.
10. Chapman MJ, Stock JK, Ginsberg HN, Forum P. PCSK9 inhibitors and cardiovascular disease: heralding a new therapeutic era. *Curr Opin Lipidol*. 2015;26:511–520.
11. Ray KK, Molemans B, Schoonen WM, Giovas P, Bray S, Kiru G, et al. EU-Wide Cross–Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study. *Eur J Prev Cardiol*. 2021;28:1279–1289.
12. Santos RD. Inadequate control of atherosclerotic cardiovascular disease risk factors in Europe: EUROASPIRE repeats itself. *Eur J Prev Cardiol*. 2019;26:820–823.
13. Landmesser U, Chapman MJ, Farnier M, Gencer B, Gielen S, Hovingh GK, et al. European Society of Cardiology/European Atherosclerosis Society Task Force consensus statement on proprotein convertase subtilisin/kexin type 9 inhibitors: practical guidance for use in patients at very high cardiovascular risk. *Eur Heart J*. 2017;38:2245–2255.
14. German CA, Shapiro MD. Small Interfering RNA Therapeutic Inclisiran: A New Approach to Targeting PCSK9. *BioDrugs*. 2020;34:1–9.
15. Inclisiran (Leqvio) for LDL-cholesterol lowering. *Med Lett Drugs Ther*. 2022;64(1646):43–45.
16. Fernandez-Ruiz I. Twice-yearly inclisiran injections halve LDL-cholesterol levels. *Nat Rev Cardiol*. 2020;17:321.
17. Stoekenbroek RM, Kallend D, Wijngaard PL, Kastelein JJ. Inclisiran for the treatment of cardiovascular disease: the ORION clinical development program. *Future Cardiol*. 2018;14:433–442.
18. Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *N Engl J Med*. 2020;382:1507–1519.
19. *International Classification of Diseases,* Tenth Revision (ICD-10). Centers for Disease Control and Prevention. Accessed December 18, 2023. https://www.cdc.gov/nchs/icd/icd10.htm.
20. ASCVD risk calculator. Pooled cohort risk predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event. ClinCalc. Accessed December 29, 2023. https://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx.
21. Rossello X, Dorresteijn JA, Janssen A, Lambrinou E, Scherrenberg M, Bonnefoy-Cudraz E, et al. Risk prediction tools in cardiovascular disease prevention: A report from the ESC Prevention of CVD Programme led by the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). *Eur J Cardiovasc Nurs*. 2019;18:534–544.
22. Ruel I, Aljenedil S, Sadri I, de Varennes E, Hegele RA, Couture P, et al. Imputation of baseline LDL cholesterol concentration in patients with familial hypercholesterolemia on statins or ezetimibe. *Clin Chem*. 2018;64:355–362.
23. Dutch criteria for familial hypercholesterolemia (FH). Med+Calc. Accessed December 19, 2023. https://www.mdcalc.com/calc/3818/dutch-criteria-familial-hypercholesterolemia-fh.
24. Orringer CE, Blaha MJ, Blankstein R, et al. The National Lipid Association scientific statement on coronary artery calcium scoring to guide preventive strategies for ASCVD risk reduction. *J. Clin. Lipidol.*. 2021;15(1):33–60. doi:10.1016/j.jacl.2020.12.005.
25. Wright RS, Ray KK, Raal FJ, Kallend DG, Jaros M, Koenig W, et al. Pooled patient-level analysis of inclisiran trials in patients with familial hypercholesterolemia or atherosclerosis. *J Am Coll Cardiol*. 2021;77:1182–1193.
26. Klebs S, Lecocq J, Mann C, et al. Characterization of inclisiran use in real world: prescription data from Germany. *J Clin Lipidol*. 2022;16(suppl):e73–e74. doi:10.1016/j.jacl.2022.05.060.
27. Mercep I, Friscic N, Strikic D, Reiner Z. Advantages and Disadvantages of Inclisiran: A Small Interfering Ribonucleic Acid Molecule Targeting PCSK9-A Narrative Review. Cardiovasc Ther. 2022;2022:8129513. doi:10.1155/2022/8129513.
28. Galactionova K, Salari P, Mattli R, Rachamin Y, Meier R, Schwenkglenks M. Cost-Effectiveness, Burden of Disease and Budget Impact of Inclisiran: Dynamic Cohort Modelling of a Real-World Population with Cardiovascular Disease. *Pharmacoeconomics*. 2022;40:791–806.
29. Desai NR, Campbell C, Electricwala B, et al. Cost Effectiveness of Inclisiran in Atherosclerotic Cardiovascular Patients with Elevated Low-Density Lipoprotein Cholesterol Despite Statin Use: A Threshold Analysis. *Am. J. Cardiovasc. Drugs.*. 2022;22:545–556.
30. Chiou TT, Tomasi K, Taub PR, Wilkinson MJ. Inclisiran creates unique opportunities and challenges for patient access to therapy: early experience in a United States Lipid Clinic. *J Clin Lipidol*. 2023;17:73–77.
31. Ray KK, Stoekenbroek RM, Kallend D, Nishikido T, Leiter LA, Landmesser U, et al. Effect of 1 or 2 Doses of Inclisiran on Low-Density Lipoprotein Cholesterol Levels: One-Year Follow-up of the ORION-1 Randomized Clinical Trial. *JAMA Cardiol*. 2019;4:1067–1075.
32. Ray KK, Kallend D, Leiter LA, Raal FJ, Koenig W, Jaros MJ, et al. Effect of inclisiran on lipids in primary prevention: the ORION-11 trial. *Eur Heart J*. 2022;43:5047–5057.
33. Ray KK, Raal FJ, Kallend DG, Jaros MJ, Koenig W, Leiter LA, et al. Inclisiran and cardiovascular events: a patient-level analysis of phase III trials. *Eur Heart J*. 2023;44:129–138.
34. Ridker PM, Mora S, Rose L. Jupiter Trial Study Group. Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents. *Eur Heart J*. 2016;37:1373–1379.
35. Qamar A, Giugliano RP, Keech AC, Kuder JF, Murphy SA, Kurtz CE, et al. Interindividual Variation in Low-Density Lipoprotein Cholesterol Level Reduction With Evolocumab: An Analysis of FOURIER Trial Data. *JAMA Cardiol*. 2019;4:59–63.
36. Warden BA, Fazio S, Shapiro MD. The PCSK9 revolution: Current status, controversies, and future directions. *Trends Cardiovasc Med*. 2020;30:179–185.