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Original Research

First clinical experiences with inclisiran in a real-world setting

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KEYWORDS
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Background and objective: Inclisiran is the first-in-class small interfering RNA (siRNA) PCSK9 inhibitor. In clinical trials inclisiran showed effective and sustained LDL-C reduction of ± 50 %. As data in clinical setting are scarce, we aim to investigate the efficacy and safety in clinical practice.

Methods: We describe a registry of consecutive patients who started with inclisiran at a lipid clinic of a university hospital. Patients were eligible if they fulfilled the reimbursement criteria in the Netherlands. Patients were included if they started with inclisiran as first line (group 1) or switched from PCSK9 monoclonal antibody (mAbs) to inclisiran (group 2). LDL-C levels were measured at 3 and 9 months after initiation of inclisiran. Median change of LDL-C levels was calculated on an individual and group level.

Results: We analysed 65 patients (36 women), median [25th percentile; 75th percentile] age of 63 [54; 68] years. Of these, 44 patients had both a 3 month and 9 month visit. At 3 months, patients who newly started inclisiran (group 1, $n = 45$) showed a LDL-C decrease of 38 [-49;-33] %. Patients who used statins as co-medication ($n = 15$) had a higher median LDL-C decrease compared to those without statin use (n=30; 45 % vs 38 %). However, patients who switched from mAbs to inclisiran (group 2, $n = 20$) had an increase in LDL-C of 38 [+4; +97] %. Adverse effects associated with inclisiran were mild and consisted of mild injection site reactions. Efficacy was slightly less whereas safety results were similar at 9 months.

Conclusion: Our initial experience of inclisiran in a clinical setting showed less reduction in LDL-C levels compared to clinical trials but a similar safety profile. Moreover, patients who switched from PCSK9 mAbs to inclisiran generally showed an increase in LDL-C levels implying that inclisiran is less potent in LDL-C reduction compared to PCSK9 mAbs.

Introduction

Lipid lowering therapy (LLT) in combination with lifestyle modification is one of the cornerstones in atherosclerotic cardiovascular disease (ASCVD) prevention.[1–3] However, despite optimal oral lipid-lowering therapy (LLT), such as statins and ezetimibe, LDL-cholesterol (LDL-C) target levels are often not reached.[4] Moreover, some patients experience LLT-associated side effects which limits treat-

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ment options and can lead to non-adherence.[5] Proprotein Convertase Subtilisin / Kexin 9 (PCSK9) inhibiting therapy is a novel treatment option for patients at very high risk who are not able to reach LDL-C target levels with maximum tolerated oral LLT.

Since 2016, PCSK9 monoclonal antibodies (mAbs) can be prescribed in clinical practice. Inclisiran, the first small interfering RNA (siRNA) PCSK9 inhibitor, is available from 2022 onwards. While the PCSK9 mAbs are administered subcutaneous every 2 or 4 weeks, inclisiran is a subcutaneous injection every 6 months.[6] The ORION trials indicated that inclisiran has a good efficacy and safety profile.[7,8] In the pooled data of the phase III trials a placebo-corrected relative LDL-C reduction of 51% was observed which remained stable over time.[8] The most common reported side-effects were local mild injection site reactions.[7]

However, the participants in trials are not always representative for the patients treated in clinical practice.[9,10] Therefore, it is important to ensure that efficacy and safety data from clinical trials are generalizable to real-life settings. The goal of our study was to evaluate the first real-world experience of PCSK9 siRNA in patients outside clinical trials.

Patients and methods

Patient inclusion and registry

In this open-cohort prospective registry we included all consecutive patients ≥ 18 years who started PCSK9 inhibiting therapy as part of regular care at the outpatient lipid clinic of Erasmus MC university hospital in Rotterdam between February 2022 and March 2023. PCSK9 inhibiting therapy consisted of either PCSK9 mAb (alirocumab or evolocumab) or PCSK9 siRNA (inclisiran).

All patients fulfilled the Dutch reimbursement criteria for PCSK9 inhibitor treatment being: (1) LDL-C target levels not reached with maximum tolerated LLT, and (2) the patient is at very high risk for ASCVD. Very high risk is defined as having either Familial Hypercholesterolemia (FH) based on the Dutch Lipid Clinic Network score (DLCN)[11] or confirmed pathogenic mutation in the *LDLR, APOB,* or *PCSK9* gene; and/or a history of ≥ 2 ASCVD events; and/or diabetes mellitus type 2 and an ASCVD event; and/or or statin intolerance and ≥ 1 ASCVD event. Statin intolerance was defined as documented side effects of at least three statins including low dose statins on non-daily basis.

Further details of this registry have been reported previously.[12] Exclusion criteria for the current analysis were: (1) use of PCSK9 inhibiting therapy as part of a clinical trial, (2) having homozygous FH, and/or (3) using PCSK9 mAbs.

The definition of PCSK9 mAbs intolerance was reported as intolerable side effects after at least two doses of alirocumab 75 mg or 150 mg sc or evolocumab 140 mg sc.

A healthcare professional administered the first 284 mg inclisiran subcutaneous injection at the outpatient lipid clinic. After 3 months, patients had a first follow-up visit to evaluate efficacy and safety and to administer the second dose of inclisiran. Six months later, patients came to the clinic for the 9-month visit and concomitantly the third dose of inclisiran. At all visits, lipids (total cholesterol, LDL-C, ApoB, HDL-cholesterol (HDL-C), triglycerides), glucose, and liver tests (alanine transaminase (ALT), aspartate transaminase (AST), and gamma-glutamyltransferase (GGT)) were performed. In addition, at every visit clinical information including ASCVD events, side effects, and LLT co-medication were recorded.

Patients using PCSK9 inhibitors were categorized on previous use of a PCSK9 mAb. Group 1 consisted of patients of whom lipid levels were available prior to inclisiran initiation without PCSK9 mAb effect. This includes the patients whose first PCSK9 inhibiting therapy was inclisiran or patients who discontinued mAbs more than three months ago. Group 2 consisted of patients who switched from a PCSK9 mAb to inclisiran after the last injection of PCSK9 mAb.

Other LLT was defined as co-medication of statins and ezetimibe.

High-intensity statins were defined as rosuvastatin ≥ 20 mg, atorvastatin ≥ 40 mg, or simvastatin 80 mg.[13] Moderate intensity statins were defined as rosuvastatin 5 to < 20 mg, atorvastatin 10 to < 40 mg, simvastatin 20 to ≤ 40 mg, pravastatin ≥ 40 mg, or fluvastatin ≥ 80 mg. Low intensity statins were defined as rosuvastatin ≤ 2.5 mg, simvastatin < 20 mg, fluvastatin < 80 mg, or pravastatin < 40 mg.

Treatment targets for LDL-C according to the Dutch multidisciplinary cardiovascular risk management (CVRM) guidelines are: < 1.8 mmol/L (< 70 mg/dL) for very high risk patients, and < 2.6 mmol/L (< 100 mg/dL) for high risk patients. Patients with a previous ASCVD event are considered very high risk. High risk patients are patients with FH and no cardiovascular event, patients with 10y cardiovascular mortality risk of ≥ 5 % based on SCORE, patients with diabetes and/or chronic kidney disease, and presence of other ASCVD risk factors such as hypertension.[14] In the 2021 cardiovascular prevention guidelines of the ESC/EAS, LDL-C target levels are defined as < 1.4 mmol/L (< 50 mg/dL) for very high risk patients and < 1.8 mmol/L (< 70 mg/dL) for high risk patients.[15,16] At the time of the study, all relevant scientific societies endorsed the target LDL-C levels according to the Dutch CVRM guidelines instead of the ESC/EAS prevention in the Netherlands. Also reimbursement criteria for PCSK9 inhibiting therapy were aligned with the Dutch CVRM guidelines.

All participating patients gave informed consent to use their clinical information for research. This study was conducted according to the 1975 Declaration of Helsinki and this study received a waiver for medical research involving the Human Subjects Act (MEC-2016-698).

Statistical analyses

Continuous data are shown as median [25th percentile; 75th percentile] and categorical data as count (percentage).

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Table 1 General baseline characteristics of patients starting inclisiran as first PCSK9 inhibiting therapy (group 1) or switched from PCSK9 mAb to inclisiran (group 2).

	Total $n = 65$	Group 1 $n = 45$ (75 %)	Group 2 $n = 20$ (25 %)
Age (years), median [25th; 75th percentile]	63 [54; 68]	64 [55; 67]	60 [45; 73]
Women, n (%)	36 (55)	26 (58)	10 (50)
History of ASCVD, n (%)	37 (57)	28 (62)	9 (45)
BMI (kg/m^2), median [25th; 75th percentile]	26.5 [24.5; 29.6]	26.5 [24.5; 29.4]	27.1 [24.5; 30.1]
Cardiovascular risk factors, n (%)			
Smoking (current or past)	15 (23)	12 (27)	3 (15)
Current smoker	2 (3)	2 (4)	0
Overweight[a]	25 (38)	18 (40)	7 (35)
Obesity[a]	14 (22)	9 (20)	5 (25)
Hypertension	28 (43)	20 (44)	8 (40)
DM type 1 or 2	10 (15)	6 (13)	4 (20)
FH	40 (62)	27 (60)	13 (65)
Lipid lowering therapy, n (%)			
Statin use	24 (37)	15 (33)	9 (45)
High intensity	15 (23)	10 (22)	5 (25)
Moderate intensity	6 (9)	3 (7)	3 (15)
Low intensity	3 (5)	2 (4)	1 (5)
Ezetimibe	65 (100)	45 (100)	20 (100)
Statin intolerance	41 (63)	30 (67)	11 (55)
PCSK9 mAb intolerance	35 (58)	19 (42)	16 (80)
Baseline laboratory values, median [25th; 75th percentile]			
Total cholesterol mmol/L	5.4 [4.3; 7.1]	6.2 [5.2; 8.3]	3.6 [2.8; 5.0]
mg/dL	208 [166; 274]	239 [201; 320]	139 [107; 193]
LDL-cholesterol mmol/L	3.7 [2.4; 4.9]	4.2 [3.5; 5.7]	1.8 [1.1; 2.7]
mg/dL	142 [94; 188]	162 [134; 221]	69 [42; 105]
Apo B g/L	1.06 [0.76; 1.35]	1.10 [0.99; 1.41]	0.59 [0.46; 0.80]
mg/dL	106 [76; 135]	110 [99; 141]	59 [46; 80]
HDL-cholesterol mmol/L	1.31 [1.13; 1.59]	1.31 [1.17; 1.60]	1.33 [1.05; 1.52]
mg/dL	51 [44; 61]	51 [45; 62]	51 [41; 59]
Triglyceride mmol/L	1.55 [1.19; 2.10]	1.73 [1.21; 2.43]	1.43 [1.04; 1.88]
mg/dL	137 [105; 186]	153 [107; 215]	126 [92; 166]
Glucose (mmol/L)	5.6 [5.2; 6.2]	5.7 [5.2; 6.2]	5.5 [5.1; 6.2]
AST (U/L)	24 [19; 29]	24 [19; 30]	23 [19; 27]
ALT (U/L)	23 [16; 35]	23 [16; 34]	25 [17; 39]
GGT (U/L)	26 [20; 37]	25 [19; 33]	37 [33; 47]

LDL= low density lipoprotein; Apo B= apolipoprotein B; HDL= high density lipoprotein; ASCVD= atherosclerotic cardiovascular disease; BMI= body mass index; DM= diabetes mellitus; FH=familial hypercholesterolemia; LLT= lipid lowering therapy, AST = aspartate transaminase, ALT = alanine transaminase, GGT = gamma-glutamyltransferase.
[a]The definition of overweight is a BMI of > 25 and ≤ 30 kg/m^2, and obesity a BMI > 30 kg/m^2.

Lipid levels are presented in mmol/L and in mg/dL employing a conversion factor of 0.0259 for total cholesterol, LDL-C, HDL-C, a conversion factor of 0.01 for ApoB and 0.0113 for triglycerides. Data are shown in total and stratified by PCSK9 initiation group. Also subgroups were investigated through stratification, such as sex and other LLT. Main outcomes were efficacy, defined as relative LDL-C reduction, and safety, defined as any side effects, at 3 and 9 months after first administration of inclisiran. Secondary outcomes were absolute LDL-C reduction, LDL-C target achievement according to Dutch and European guidelines, specific side effects, and discontinuation of PCSK9 siRNA at 3 and 9 months after first administration of inclisiran.

Statistical software SPSS version 28.0 and R version 4.2.1. were employed for data cleaning and data analyses.

Results

We included 65 patients (55 % women, median age of 63 (54; 68) years), who started with inclisiran. Of these patients, 62 % had a diagnosis of FH, 57 % had a history of ASCVD, mostly coronary artery disease (73 %). The most prevalent

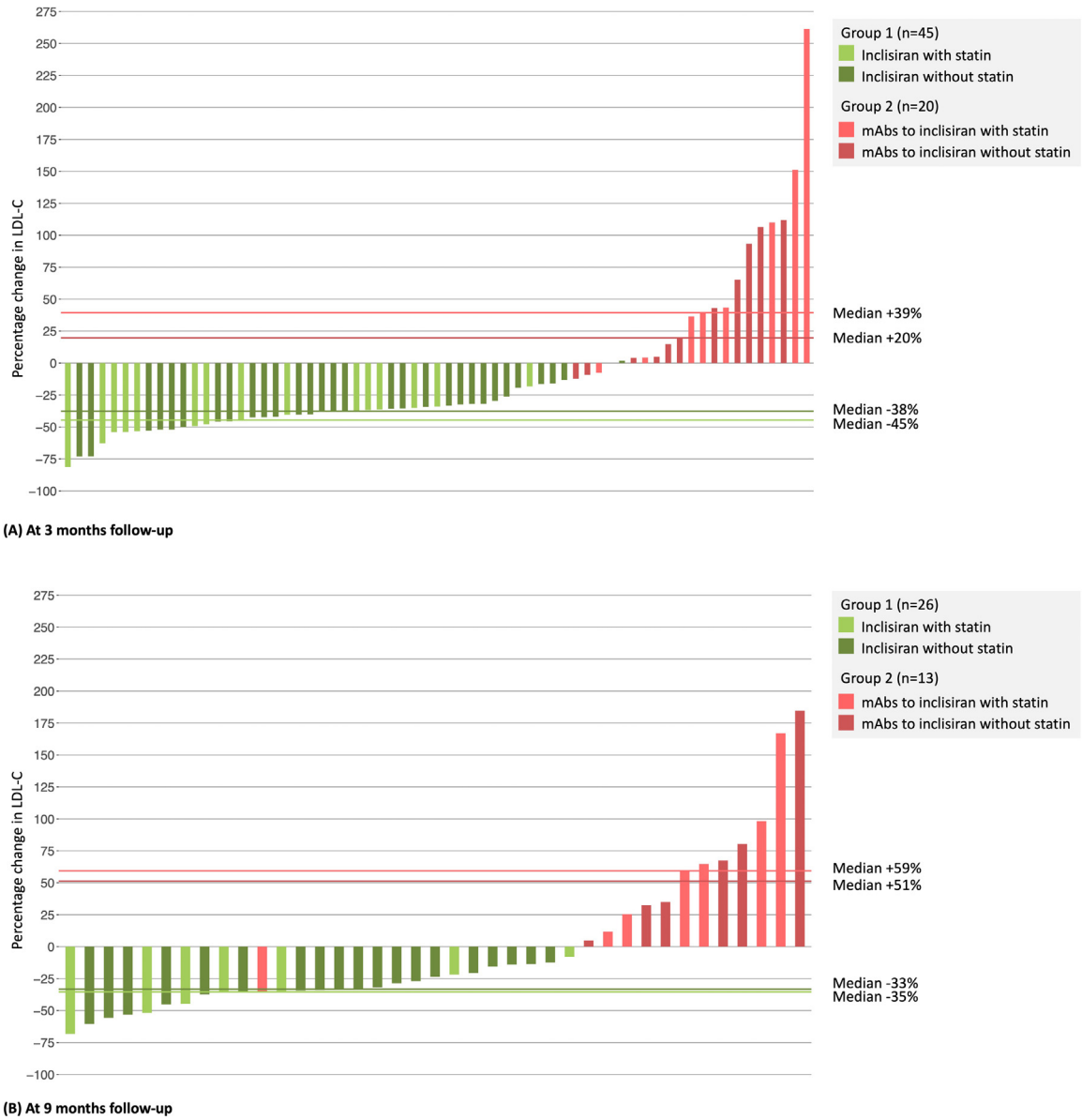

Figure 1 LDL-cholesterol change of individual patients ($n = 65$) at 3 (A) and 9 (B) months after initiation of inclisiran.
LDL-C = LDL-cholesterol; mAbs = monoclonal antibodies. One patient from group 2 restarted rosuvastatin 5mg daily in-between the 3 month and 9 month follow-up visit.

other cardiovascular risk factors were overweight including obesity (60 %), hypertension (43 %), and diabetes mellitus type 2 (15 %). Remarkable was that only two patients smoked. The majority of patients had statin-intolerance, only 37 % of the patients used a statin as co-LLT, 23 % used high intensity statin. Ezetimibe was prescribed in all patients, as this is part of the reimbursement criteria in the Netherlands. The baseline characteristics of these patients in total and per subgroup are shown in Table 1.

Efficacy

We observed a wide variety in LDL-C responses to the PCSK9 siRNA (Fig. 1) at 3 months after a median follow-up of 88 days (84; 91). Patients who newly started inclisiran (group 1, $n = 45$) showed a median LDL-C decrease of -38 % (-49; -33). Patients who used statins as co-medication ($n = 15$) had a higher median LDL-C decrease compared to those without statin use ($n = 30$, -45 % vs. -38% respectively). However, patients who switched from mAbs to inclisiran (group 2) had a median increase in LDL-C of +38% (+4; +97) (Fig. 1). Patients in group 1 had an absolute LDL-C reduction of -1.6 mmol/L (-2.1; -1.2) [-63 mg/dL (-80; -46)] while the patients who switched from PCSK9 mAb to inclisiran (group 2, $n = 20$) showed an absolute increase of 0.5 mmol/L (+0.1; +1.0) [+18 mg/dL (+3; +40)] (Table 2). In five patients LDL-C levels remained stable (Fig. 1).

Of our patients, 44 (group 1 $n = 28$, group 2 $n = 16$) had a 9 month follow-up, at a median 269 days (261; 277) after initiation of inclisiran. Patients who newly started inclisiran

Table 2 Efficacy of PCSK9 siRNA after 3 months and 9 months follow-up of patients newly starting inclisiran (group 1) or switched from PCSK9 mAb to inclisiran (group 2).

Follow-up 3 months	Total $n = 65$	Group 1 $n = 45$ (75 %)	Group 2 $n = 20$ (25 %)
Lipid levels, median (25^{th}; 75^{th} percentile)			
Total cholesterol mmol/L	4.4 [3.6; 5.5]	4.4 [3.6; 5.6]	4.4 [3.8; 5.4]
mg/dL	170 [139; 212]	170 [139; 216]	170 [147; 207]
LDL-cholesterol mmol/L	2.5 [1.9; 3.4]	2.4 [1.8; 3.7]	2.5 [2.1; 3.4]
mg/dL	95 [71; 133]	93 [68; 142]	96 [83; 130]
HDL-cholesterol mmol/L	1.31 [1.10; 1.67]	1.31 [1.10; 1.67]	1.33 [1.11; 1.51]
mg/dL	51 [42; 64]	51 [42; 64]	51 [43; 58]
Apo B g/L	0.75 [0.65; 0.95]	0.74 [0.59; 0.96]	0.78 [0.69; 0.86]
mg/dL	75 [65; 95]	74 [59; 96]	78 [69; 86]
Triglyceride mmol/L	1.44 [1.08; 2.08]	1.43 [1.08; 2.12]	1.47 [1.04; 1.86]
mg/dL	127 [96; 184]	127 [96; 188]	130 [92; 165]
LDL-cholesterol percentage decrease (% median [25^{th}; 75^{th} percentile])	-34.0 [-42.5; +1.8]	-37.9 [-49.4; -33.3]	+38.0 [+4.2; + 96.6]
Statin use	-35.8 [-48.3; +12.3]	-44.6 [-53.6; -36.6]	+39.4 [+4.3; +110.0]
Statin intolerant	-32.4 [-42.1; -9.2]	-37.6 [-44.8; -32.0]	+19.7 [+4.5; +79.2]
LDL-cholesterol absolute decrease mmol/L (median [25^{th}; 75^{th} percentile]) mg/dL	-1.3 [-1.9; +0.1]	-1.6 [-2.1; -1.2]	+0.5 [+0.1; +1.0]
	-48 [-74; +2]	-63 [-80; -46]	+18 [+3; +40]
LDL-cholesterol by treatment goal, n (%)			
Without ASCVD, n (%)			
Dutch guideline (< 2.6 mmol/L | < 100 mg/dL)	12 (43)	7 (41)	5 (45)
ESC/EAS guideline (< 1.8 mmol/L | < 70 mg/dL)	5 (18)	3 (18)	2 (18)
With ASCVD, n (%)			
Dutch guideline (< 1.8 mmol/L | < 70 mg/dL)	11 (30)	9 (32)	2 (22)
ESC/EAS guideline (< 1.4 mmol/L | < 50 mg/dL)	5 (14)	3 (11)	2 (22)
FH with and without ASCVD n (%			
Dutch guideline (< 1.8 or 2.6 mmol/L | < 70 or < 100 mg/dL)	16 (40)	11 (41)	5 (38)
ESC/EAS guideline (< 1.4 or 1.8 mmol/L | < 50 or < 70 mg/dL)	7 (18)	5 (19)	2 (15s)

Follow-up 9 months	Total $n = 44$	Group 1 $n = 28$ (64 %)	Group 2 $n = 16$ (36 %)
Lipid levels, median (25^{th}; 75^{th} percentile)			
Total cholesterol mmol/L	4.6 [4.1; 5.4]	4.7 [4.2; 6.0]	4.3 [3.8; 5.2]
mg/dL	178 [158; 208]	181 [162; 230]	166 [147; 201]
LDL-cholesterol mmol/L	2.8 [2.3; 3.5]	2.9 [2.3; 3.5]	2.7 [2.3; 3.1]
mg/dL	106 [88; 135]	114 [88; 135]	106 [89; 121]
HDL-cholesterol mmol/L	1.34 [1.18; 1.46]	1.35 [1.23; 1.51]	1.32 [0.99; 1.39]
mg/dL	52 [46; 56]	52 [47; 58]	51 [38; 54]
Apo B g/L	0.90 [0.75; 0.97]	0.90 [0.74; 0.97]	0.90 [0.79; 0.93]
mg/dL	90 [75; 97]	90 [74; 97]	90 [79; 93]
Triglyceride mmol/L	1.56 [1.07; 2.27]	1.64 [1.07; 2.26]	1.53 [1.08; 2.23]
mg/dL	138 [95; 201]	145 [95; 200]	135 [96; 197]
LDL-cholesterol percentage change (% median [25^{th}; 75^{th} percentile])	-23.6 [-35.1; +18.6]	-33.8 [-42.8; -22.2]	+59.4 [+25.4; + 80.3]
Statin use	-14.8 [-35.2; +50.9]	-35.3 [-48.2; -28.2]	+59.4 [+18.6; +81.5]
Statin intolerant	-27.0 [-34.3; -12.4]	-33.3 [-36.2; -22.1]	+51.2 [+33.0; +77.0]
LDL-cholesterol absolute change mmol/L (median [25^{th}; 75^{th} percentile]) mg/dL	-1.0 [-1.6; +0.5]	-1.3 [-1.9; -0.9]	+0.9 [+0.6; +1.5]
	-37 [-62; +18]	-51 [-73; -36]	+36 [+25; +57]
LDL-cholesterol by treatment goal, n (%)			
Without ASCVD, n (%)			
Dutch guideline (< 2.6 mmol/L | <100 mg/dL)	7 (37)	3 (27)	4 (50)
ESC/EAS guideline (< 1.8 mmol/L | <70 mg/dL)	1 (5)	0	1 (13)

(*continued on next page*)

Table 2 (*continued*)

Follow-up 3 months	Total $n = 65$	Group 1 $n = 45$ (75 %)	Group 2 $n = 20$ (25 %)
With ASCVD, n (%)			
Dutch guideline (< 1.8 mmol/L | <70 mg/dL)	6 (30)	5 (33)	1 (20)
ESC/EAS guideline (< 1.4 mmol/L | <50 mg/dL)	3 (15)	2 (13)	1 (20)
FH with and without ASCVD n (%			
Dutch guideline (< 1.8 or 2.6 mmol/L | <70 or <100 mg/dL)	9 (38)	5 (31)	4 (50)
ESC/EAS guideline (< 1.4 or 1.8 mmol/L | <50 or <70 mg/dL)	2 (8)	1 (6)	1 (13)

PCSK9= proprotein convertase subtilisin/kexin type 9; siRNA= small interfering RNA; LDL-C= LDL-cholesterol; Apo B= apolipoprotein B; FH= familial hypercholesterolemia; ASCVD= atherosclerotic cardiovascular disease.

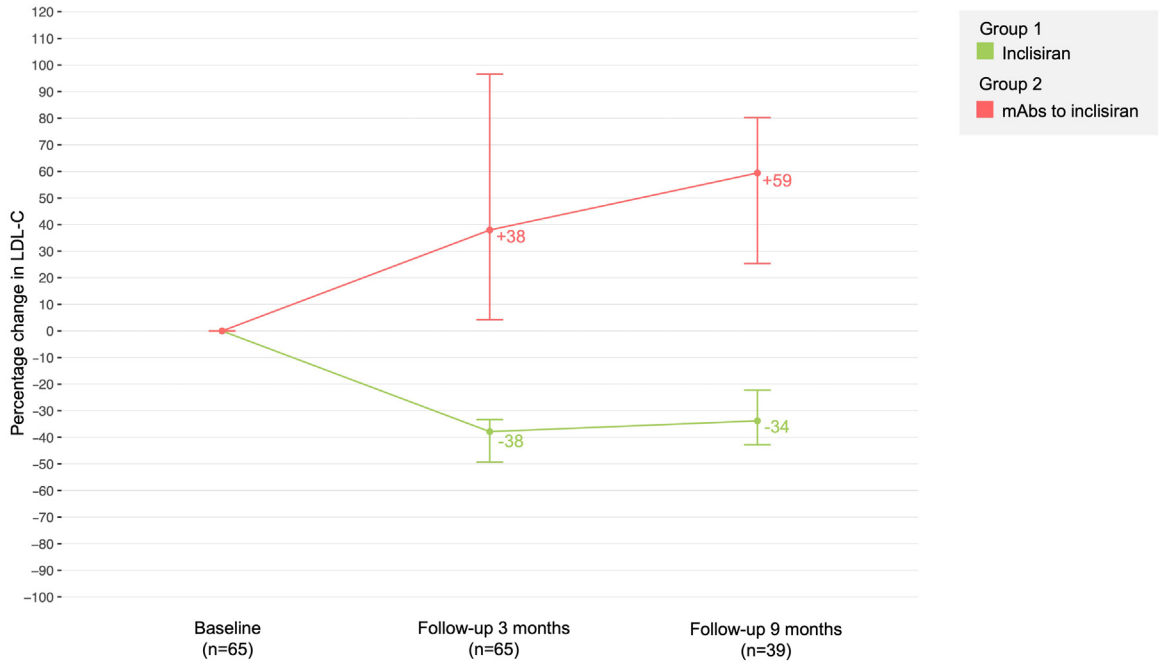

Figure 2 Median (25th percentile, 75th percentile) change in LDL-cholesterol levels at 3 and 9 months follow-up compared to baseline levels.
LDL-C = LDL-cholesterol; mAbs = monoclonal antibodies.

showed a median LDL-C decrease of -34 % (-43; -22) from baseline (Fig. 2). Patients who used statins as co-medication ($n = 9$) had an almost comparable median LDL-C decrease compared to those without statin use ($n = 19$, -35 % vs -33 % respectively). Patients who switched from mAbs to inclisiran (group 2) had a median increase in LDL-C of +59 % (+25; +80).

Patients in group 1 ($n = 28$) had an absolute LDL-C reduction of -1.3 mmol/L (-1.9; -0.9) [-51 mg/dL (-73; -36)] while the patients who switched from PCSK9 mAb to inclisiran (group 2, $n = 16$) showed an absolute increase of 0.9 mmol/L (+0.6; +1.5) [+36 mg/dL (+25; +57)] (Table 2). In only one patient LDL-C levels remained stable.

Despite the addition of inclisiran, less than half of our patients reached treatment targets according to the Dutch CVRM guidelines (43 and 30 % without and with ASCVD respectively after 3 months) and even less according to the ESC/EAS prevention guidelines (18 and 14 % without and with ASCVD respectively; Table 2). After 9 months, only a minority of 5 % without and 15 % with ASCVD reached ESC/EAS treatment targets (Table 2).

Adherence and side effects

Almost half of the patients (42 %) experienced a mild burning sensation during administration (Table 3). At the follow-up visit 3 months after the first injection, 10 patients (15 %) reported side effects such as myalgia, abdominal complaints, fatigue, dizziness, and flu-like symptoms in the first week. Three patients stopped treatment because of perceived side effects like fatigue, myalgia, dizziness, and headache. Patients with statin intolerance reported more side effects than the patients who concomitantly used statins (22 % vs 4 %, respectively). We

Table 3 Reported side-effects and discontinuation of PCSK9 siRNA after 3 months follow-up of patients starting inclisiran as first PCSK9 inhibiting therapy (group 1) or switched from PCSK9 mAb to inclisiran (group 2).

	Total $n = 65$	Group 1 $n = 45$ (75 %)	Group 2 $n = 20$ (25 %)
Side effects of PCSK9 inhibitors, n (%)			
Side effects	10 (15)	6 (13)	4 (20)
Flu-like symptoms	1 (2)	0	1 (5)
Neurological symptoms	3 (5)	1 (2)	2 (10)
Gastrointestinal symptoms	5 (8)	4 (9)	1 (6)
Myalgia	5 (8)	3 (7)	2 (10)
Headache	1 (2)	1 (2)	0
Fatigue	4 (6)	3 (7)	1 (5)
Psychological symptoms	0	0	0
Other	3 (5)	2 (4)	1 (5)
Injection site reaction	27 (42)	15 (33)	12 (60)
Discontinuation of PCSK9 siRNA, n (%)	3 (5)	2 (4)	1 (5)
Discontinuation due to side effects	3 (5)	2 (4)	1 (5)
Liver function tests, median [25th; 75th percentile]			
AST (U/L)	26 [21; 35]	27 [21; 36]	24 [20; 32]
ALT (U/L)	29 [21; 40]	29 [21; 39]	29 [21; 40]
GGT (U/L)	26 [18; 37]	26 [18; 34]	31 [19; 50]

PCSK9: proprotein convertase subtilisin/kexin type 9, siRNA: small interfering RNA, AST = aspartate transaminase, ALT = alanine transaminase, GGT = gamma-glutamyltransferase.

observed a large difference in reported side effects between patients with and without statin intolerance, especially within the group who newly started with inclisiran (20 % vs 0 %, respectively). Patients who previously reported side effects attributed to PCSK9 mAb experienced more side effects than patients without PCSK9 mAb side effects (23 % vs 7 %, respectively). The median change in liver function tests compared to baseline was clinically irrelevant, being 1 [-1; +4] U/L in AST, 2 [-1; +8] U/L in ALT, and 1 [-1; +11] U/L in GGT.

After 9 months, less patients reported a mild burning sensation during administration (16 %). Only 3 patients reported side effects like abdominal complaints and dizziness. All of these patients were intolerant for other lipid lowering therapy. Seven patients stopped inclisiran of which 5 patients because of insufficient LDL-C decrease, one patient deceased due to an acute myocardial infarction, and one patient discontinued due to side effects (supplemental material Table 3). Of all patients, 10 patients discontinued inclisiran at any point during follow-up.

Discussion

Our initial experience of inclisiran in a clinical setting showed less reduction of LDL-C levels but a reassuring safety profile compared to the clinical trials. Moreover, we observed that patients who switched from PCSK9 mAbs to inclisiran showed an increase in LDL-C levels implying that inclisiran is less potent in lowering LDL-C levels compared to PCSK9 mAbs. Concomitant use of statins was associated with increased LDL-C reduction at 3 months follow-up. Inclisiran was well-tolerated, but patients with side effects of other LLT such as statins or PCSK9 mAb reported more side effects of inclisiran compared to the patients without history of side effects with other LLT.

Efficacy

We observed a high variability in relative LDL-C change in both groups. Patients who used inclisiran as initial PCSK9 inhibitor showed a median LDL-C reduction of -38 %, which is lower than the -41 % to -46 % (placebo-adjusted -49 % to -52 %) LDL-C reduction in the pooled analysis of the ORION-9-10-11 trials.[17] An explanation of the lower LDL-C reduction in our cohort is that concomitant statin use was much higher in the ORION-3-9-10-11 trials, being 67–93 % concomitant statin use compared to the 37 % in our study.[17–19] We found that the median relative LDL-C reduction at 3 months follow-up was higher in patients using statin therapy compared to those who did not use statin therapy (-45 % vs -38 %). At 9 months follow-up, 5 (11 %) of our patients discontinued inclisiran because of dissatisfaction with LDL-C reduction.

In a real-world inclisiran study from the UK ($n = 80$) by Padam et al., an average LDL-C reduction of -49% was observed and in the subgroup with statin co-medication even -56 %.[20] The higher efficacy might be explained by several factors. First, the follow-up was 2 months instead of 3 months. The ORION-1 trial showed that the mean LDL-C reduction was approximately -50 % at 2 months and -45 %

at 3 months after inclisiran administration.[21] According to the SmPC the second dose is administered after 3 months.[22] In our opinion the LDL-C level at 3 months is a more clinically relevant reflection of LDL-C reduction as observed in clinical practice. Moreover, the aforementioned British real-world study had a higher percentage of statin users compared to our study population (statin co-medication 53 % vs 37 %, respectively) which might also have played a role as has been shown in PCSK9 mAbs.[20,23,24] However, recently a German study with 153 patients showed a similar reduction at 3 months follow-up of -32 % in non-statin users and -42 % in statin users.[25] At 9 months follow-up, they showed a diminished LDL-C reduction compared to 3 months follow-up. The reduction in group 1 of our study population with stable statin treatment was slightly better at 9 months follow-up compared to the German study (-34 % vs -28 %).

In general, we observed an increase in LDL-C levels of patients who switched from a PCSK9 mAb to the PCSK9 siRNA. This is in line with the ORION-3 trial. The ORION-3 is the open-label, multicentre, long-term extension study of the 1-year blinded, placebo-controlled, phase 2 trial ORION-1. Patients who received placebo in ORION-1 received open-label 140 mg subcutaneous evolocumab every 2 weeks for up to 1 year and then switched to inclisiran. LDL-C reduction was -61.0 % (95 % CI −64.5; −57.4) on evolocumab treatment and decreased to −47.9 % (95 % CI−51.8; −44.0) after 1 year inclisiran, and further to −45.4 % (95% CI −50.8; −40·1), and −43.9 % (95 % CI −49.5; −38.3) after 2 and 3 years inclisiran.[18] Both our study as well as the ORION 3 study suggest a reduced efficacy of inclisiran compared to PCSK9 monoclonal antibodies. However, it was deducted by comparing the efficacy when the drugs were used successively. The most optimal manner to confirm this finding would be to perform a randomized control trial.

In a previous report of our real-world registry we showed that patients using PCSK9 mAbs had a 55 ± 22 % reduction of LDL-C levels comparable to the clinical trials.[26] Also, in this study we showed that patients with statin co-medication had a higher LDL-C reduction compared to patients without concomitant use of statins (-58 % vs -53 % respectively). This highlights the importance of combining therapies that lower free PCSK9 concentrations and increase LDL-receptor concentration together with therapies that increase LDL-receptor transcription to ensure biological synergy. Combination of PCSK9 inhibition with high potent statins can lead to LDL-C reductions up to 75–80 %.[27]

Side effects and discontinuation

The most reported side effect at 3 months follow-up was that 42 % of the patients had a mild burning sensation during the administration of inclisiran, which was for none of the patients a reason to discontinue treatment. At 9 months follow-up, only 16 % experienced mild injection site reactions. In the ORION-3-9-10-11 trials, the prevalence of injection site reaction was 3–17 %.[17-19] The previously mentioned British real-world inclisiran registry mentioned only one patient (1.3 %) and the German study five patients (3 %) with a moderate injection site reaction.[20,25] It is possible that the mild injection site reactions were not reported.

Only a minority (at 3 months follow up 15 % and 9 months follow up 7 %) of our patients had other side effects. Notably most side-effects were variable in nature and without a common pathophysiological pathway. The side-effects were a reason for discontinuation in four patients at 3 and 9 months follow-up (6 %). In the ORION-9-10-11 trials, other types of reported side effects occurred as often in both groups.[17,19] Discontinuation due to side-effects was comparable in the ORION-3 trial to our study (7 % vs 6 %, respectively).[18] In the real-world study of Padam et al. (2022) and Makhmudova et al. (2023) less side effects (4–6 %) were reported, which were of similar nature, being myalgia, dizziness, headache, and fatigue besides the previously mentioned moderate injection site reaction.[20,25] Notably, in our study 77 % of the patients previously experienced side effects of other LLT, including statins and PCSK9 mAbs. Consequently, we included patients who might be more prone to side effects, which could explain the higher percentage of reported side effects in our study population. In fact, with the exception of two patients, the patients reporting side effects with inclisiran also had a history of previous LLT side effects. In a German real-world study with PCSK9 mAbs, most side effects (74 %) were also reported in the patients without concomitant LLT.[28] Although the aetiology is not always known, e.g. in case of myalgia symptoms, it is important to listen to patients in order to come to the most optimal tailored treatment plan to minimize individual ASCVD risk.[29]

Compared to the PCSK9 mAbs users at our lipid clinic, side effects, and in particular flu-like symptoms, were reported less often by patients using inclisiran (any side effect PCSK9 mAbs: 29 % vs inclisiran: 15 %; flu-like symptoms PCSK9 mAbs: 8 % vs inclisiran: 2 %).[26] In addition, liver tests after initiation of inclisiran were comparable to baseline levels.

In conclusion, in line with the clinical trials and the other real-world studies, our findings support that inclisiran has a favourable safety profile.

Inclisiran vs PCSK9 mAbs

In the Netherlands, reimbursement criteria for inclisiran and PCSK9 mAbs are similar and reserved for very high risk patients who do not reach treatment targets despite maximum tolerated LLT. Therefore, healthcare professionals can provide both options to their patients. In our clinic we describe the advantages and disadvantages of both options to the patients to come to a shared decision. Our study population therefore consists of patients who specifically chose for treatment with inclisiran. The main reasons for the choice for inclisiran were side effects of PCSK9 mAbs or preference because of the dosing schedule. As yet the patient preferences for inclisiran of PCSK9 mAbs are not defined, for the future, a decision aid would be helpful as an assistance for shared decision making in the clinic.

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Strengths and Limitations

Our comprehensive registry of all patients who started PCSK9 inhibitor therapy in our clinic provides insights into the efficacy and safety of PCSK9 siRNA in standard clinical practice. In addition, we could compare the effect on LDL-C levels in patients newly starting inclisiran, to patients who switched from PCSK9 mAbs to inclisiran. Moreover, this is the first real-world study which reports short-term safety data on liver outcomes. However, the number of patients included in this study is still small and from a single lipid clinic, therefore it was not possible to stratify our results by sex, FH status, age, comedication with other LLT, history of prior LLT comedication, etc. Longer follow-up data in a larger population and in multiple centres are required to ensure efficacy and safety of inclisiran and to perform these additional analyses.

Conclusions, clinical implications and future directions

Our initial experience of inclisiran in a clinical setting showed a high variability and on average a slightly less reduction in LDL-C levels compared to clinical trials with a reassuring safety profile. Patients who switched from PCSK9 mAbs to inclisiran showed a median increase in LDL-C levels, implying that inclisiran is less potent in LDL-C reduction compared to PCSK9 monoclonal antibodies.

Ethical approval

All participating patients gave informed consent to use their clinical information for research. This study was conducted according to the 1975 Declaration of Helsinki and this study received a waiver for medical research involving the Human Subjects Act (MEC-2016-698).

Use of AI and AI-assisted technologies statement

AI or AI-assisted technologies have not been used.

Data statement

Upon reasonable request, it can be expected that specific anonymous data will be shared to a qualified researcher.

CRediT authorship contribution statement

Janneke W.C.M. Mulder: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Investigation. **Annette M.H. Galema-Boers:** Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Investigation. **Jeanine E. Roeters van Lennep:** Conceptualization, Methodology, Writing – review & editing, Investigation, Supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2023.09.005.

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