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Lipid lowering with inclisiran: a real-world single-centre experience

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ABSTRACT

Objective The reduction in circulating low-density lipoprotein cholesterol (LDL-c) is the primary aim of lipid-lowering therapies as a method of atherosclerotic cardiovascular disease risk reduction. Inclisiran is a new and potent lipid-lowering drug that is shown to be effective in reducing LDL-c in randomised controlled trials, however, real-world data of its use are not yet known. We sought to analyse the early effects of this drug in a tertiary centre lipid and cardiovascular risk clinic.

Methods We performed a retrospective analysis of the first 80 patients who received a single dose of inclisiran at our lipid clinic between 1 December 2021 and 1 September 2022. Data were collected using electronic healthcare records. Baseline blood tests were taken prior to start of treatment and were repeated at 2 months follow-up. Data on adverse events were also recorded.

Results At 2 months after treatment initiation, mean baseline LDL-c fell from 3.5±1.1 mmol/L by 48.6% to 1.8±1.0 mmol/L and total cholesterol from 5.7±1.3 mmol/L by 33.3% to 3.8±1.1 mmol/L (both p<0.0001). Mean high-density lipoprotein-c rose by 7.7% to 1.4±0.4 mmol/L (p=0.02) and median triglycerides fell by 31.3% to 1.1 mmol/L (IQR 0.9–2) (p=0.001). Adverse events (injection site reaction, fatigue and headache) were recorded in three patients and all had self-resolved by time of follow-up.

Conclusion Inclisiran use in line with National Institute for Health and Care Excellence guidelines led to significant lowering of LDL-c at 2 months, with efficacy similar to that reported in trials with good tolerability.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Inclisiran has been shown to reduce low-density lipoprotein (LDL) cholesterol by approximately 50% in phase III randomised controlled trials (RCTs). The effects of this drug in routine clinical practice, however, are not yet known.

WHAT THIS STUDY ADDS

⇒ This study provides real-world evidence demonstrating that similar percentage reduction in LDL-c can be achieved with inclisiran at 2 months to those seen in RCTs.

⇒ Percentage reduction in LDL-c were comparable across white and non-white populations.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings support data from recent clinical trials and suggest that results may be reproducible in the clinical setting.

⇒ This study is the first to provide evidence of early efficacy of inclisiran in routine clinical care and highlights the need for further studies to evaluate longer-term effects and safety.

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death worldwide.[1] Low-density lipoprotein cholesterol (LDL-c) is recognised as an important modifiable risk factor for primary and secondary prevention of ASCVD events. Consequently, LDL-c has been long established as a key therapeutic target in patients with or at risk of ASCVD.[2] Statins remain the first-line treatment for elevated LDL-c and have shown to be effective and generally safe. International guidelines increasingly have recommended lower LDL-c targets largely through the use of combination therapies. The pursuit for further strategies to lower LDL-c concentrations has now led to the development of inclisiran, a first-in-class small interfering RNA that functions to prevent proprotein convertase subtilisin/kexin type 9 (PCSK9) translation in hepatocytes, increasing LDL receptor (LDLR) function and thus lowering LDL-c. ORION-9, ORION-10 and ORION-11 were the first phase III double-blinded, randomised controlled trials (RCTs) that showed significant reductions in LDL-c levels by approximately 50% versus placebo following an initial injection, and then at 3 months, then 6 monthly dosing of inclisiran over 18 months.[3 4] In the UK, the National Institute for Health and Care Excellence (NICE) has approved the use of inclisiran as an option for treating hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia if (1) there is a history of ASCVD (acute coronary syndrome,

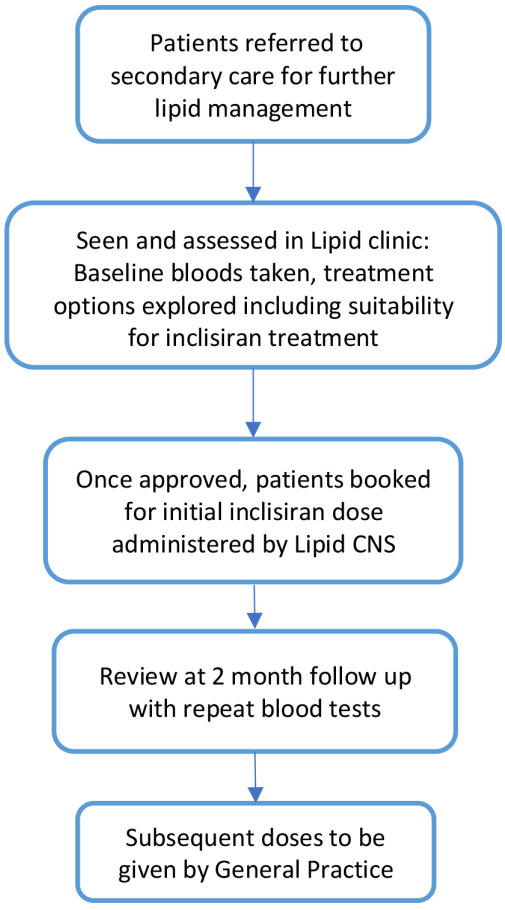

Figure 1 Patient pathway from referral to treatment at our clinic.

coronary disease, ischaemic stroke or peripheral arterial disease) and (2) LDL-c concentrations are persistently ≥2.6 mmol/L, despite maximum tolerated lipid-lowering therapy (LLT).[5] While these LLTs have shown efficacy and safety their applicability in real-world clinical settings remains to be elucidated. In this study we report the results of the use of inclisiran in the first 80 patients at our lipid clinic at Hammersmith Hospital, UK.

METHODS

Lipid clinic background

This is a secondary and tertiary lipid service, conducted at Hammersmith Hospital, Imperial College London National Health Service (NHS) Trust, London. Patients are referred largely from general practitioners (GP) in primary care as well as a smaller proportion coming from other secondary care services including cardiology, vascular, renal and diabetes clinics.

On attending the clinic, patients are comprehensively assessed. Treatment options are then discussed and optimised on repeated visits in order to achieve therapeutic targets. A summary of the patient pathway is shown in figure 1. Patients may also be discussed at weekly multidisciplinary teams where physicians, specialist pharmacists, clinical nurse specialists (CNS) and dieticians are in attendance. Patients were deemed eligible for inclisiran treatment if LDL-c levels were≥2.6 mmol/L with evidence of cardiovascular disease as per NICE criteria.[5]

Patients approved for inclisiran treatment receive a single 284 mg subcutaneous injection administered by a CNS at the clinic. Following treatment patients are encouraged to contact the lipid team to inform them of any adverse effects and discuss concerns. Patients either attend the hospital for a repeat blood test in 2 months time or have a test arranged by their GP with the results forwarded to our clinic. The Lipid CNS team then write to GPs informing them of treatment initiation and the date of second dose.

Data collection

This is a retrospective cohort study of data from the first 80 patients who received their first dose of inclisiran between 1 December 2021 and 1 September 2022. Data were collected using electronic healthcare records and comprised of patient demographics: age, sex, ASCVD history, familial hypercholesterolaemia (FH) status, current lipid-lowering medications, treatment intolerance and other cardiovascular risk factors including hypertension, diabetes and smoking history. FH was defined as either confirmation of a pathogenic variant following genetic testing or those that fulfilled Simon Broome clinical criteria. Those taking statins at baseline were further divided by dose into medium intensity (atorvastatin 10 mg or rosuvastatin 5 mg) and high intensity (atorvastatin ≥20 mg or and rosuvastatin≥10 mg) as categorised by current NHS lipid management guidelines.[6] Those taking three lipid-lowering medications were placed into the triple therapy group and included those on a combination of statins, ezetimibe, colesevelam and/or fibrates. Statin intolerance was defined as those with clinical adverse effects to statin treatment preventing either administration of medication or further increment of statin dose. Baseline blood tests were taken prior to inclisiran treatment including lipid profile, full blood count, urea and electrolytes, liver function tests and thyroid function tests and were repeated at 2 months follow-up for comparison. The Sampson equation was used to calculate LDL-c concentrations for patients with hypertriglyceridaemia between 4.5 and 9 mmol/L.[7] Incidences of adverse reactions and discontinuation were also recorded. The study was registered by the Imperial College Healthcare NHS Trust Audit Committee (CLB_06).

Statistical analysis

Categorical patient demographics were summarised using frequency and percentage with means and SD used for continuous variables. Ethnicities were grouped into white, black, Asian, mixed and other. Paired t-tests were used to test for statistical significance in lipid profile changes at 2 months. Unpaired t-tests were used to test for statistical significance between two different groups. Analysis of variance was conducted to compare mean change in LDL-c from baseline between multiple groups.

Table 1 Baseline characteristics of initial 80 patients receiving inclisiran

	FH n=30	Non-FH n=50	Total n=80
Sex n (%)			
Male	18 (60)	34 (68)	52 (65)
Female	12 (40)	16 (32)	28 (35)
Age, mean (SD, range)	61.7 (±12.6, 34–83)	65.3 (±8.5, 51–83)	64 (±10.3, 34–83)
Ethnicity n (%)			
Asian	8 (26.7)	10 (20)	18 (22.5)
Black	2 (6.7)	–	2 (2.5)
Mixed	1 (3.3)	2 (4)	3 (3.8)
Other	3 (10)	9 (18)	12 (15)
White	16 (53.3)	29 (58)	45 (56.3)
Atherosclerotic disease n (%)			
Coronary artery disease	23 (76.7)	44 (88)	67 (83.8)
CABG	2 (6.7)	7 (34)	9 (11.3)
MI	8 (26.7)	12 (24)	20 (25)
PCI	2 (6.7)	13 (26)	15 (18.8)
Subclinical cor. disease	11 (36.7)	17 (34)	28 (35)
Cerebrovascular disease	4 (13.3)	10 (20)	14 (17.5)
Stroke	1 (3.3)	1 (2)	2 (2.5)
TIA	1 (3.3)	3 (6)	4 (5)
Subclinical carotid disease	2 (6.7)	6 (12)	8 (10)
Peripheral arterial disease	1 (3.3)	3 (6)	4 (5)
Cardiovascular risk factors n (%)			
Hypertension	7 (23.3)	25 (50)	32 (40)
Diabetes mellitus	3 (10)	16 (32)	19 (23.8)
Smoking history	3 (10)	9 (18)	12 (15)
Lipid profile, mmol/L, mean (SD)			
Total cholesterol	5.5 (± 1.3)	5.9 (± 1.4)	5.8 (± 1.4)
LDL-c	3.5 (± 1.2)	3.6 (±1.1)	3.5 (± 1.2)
Triglycerides*	1.4 (1.0–1.4)	1.7 (1.3–2.9)	1.6 (1.2–2.3)
HDL-c	1.4 (±0.3)	1.3 (±0.4)	1.3 (±0.4)
Lipid-lowering treatment † n (%)			
Atorvastatin alone	5 (16.7)	4 (8)	9 (11.3)
Medium intensity	–	–	–
High intensity	5	4	9
Rosuvastatin alone	1 (3.3)	1 (2)	2 (2.5)
Medium intensity	–	1	1
High intensity	1	–	1
Ezetimibe alone	3 (10)	10 (20)	13 (16.3)
Statin and ezetimibe	14 (46.7)	6 (12)	20 (25)
Medium intensity statin	–	1	1
High intensity statin	14	5	19
Colesevelam alone	1 (3.3)	1 (2)	2 (2.5)
Bempedoic acid	–	1 (2)	1 (1.3)
Bempedoic acid and ezetimibe	–	1 (2)	1 (1.3)
Triple combinative therapy‡	6 (20)	7 (14)	13 (16.3)
Medium intensity statin	–	1	1
High intensity statin	6	4	10
No lipid-lowering treatment	–	19 (38)	19 (23.8)

*Triglyceride values reported as median (IQR).
†Denotes medications patients were taking at baseline, statins were further divided into medium and high intensity doses.
‡Defined as those taking three drugs from a combination of statins, ezetimibe, colesevelam and fibrates.
CABG, coronary artery bypass graft; FH, familial hypercholesterolaemia; HDL-c, high-density lipoprotein cholesterol; LDL-c, Low-density lipoprotein cholesterol; MI, myocardial infarction; Non-FH, Non familial hypercholesterolaemia; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

The Wilcoxon signed-rank test was used to compare change in median triglycerides at 2 months. A $p<0.05$ was considered to be statistically significant. Statistical analysis was performed using GraphPad Prism V.9.4.1 (GraphPad Software, San Diego, California, USA).

RESULTS

A total of 80 patients had initiated inclisiran therapy at our clinic during the study period. Baseline characteristics of those receiving treatment are shown in table 1. The mean age was 64±10.3 years, 52 (65%) were men and 28 (35%) were female. Of the 80 patients, 30 (37.5%) had FH. Thirty-five (43.8%) of the patients were non-white.

In total 42 (52.5%) patients from the cohort were taking a statin as part of LLT at baseline. Thirty-seven patients (46.3%) were reported as being intolerant to statins. Statins were contraindicated for 2 (2.5%) patients with diagnoses of myositis and myotonic dystrophy, respectively. Of the total 80 patients, the baseline lipid profile included a mean total cholesterol 5.8±1.4 mmol/L, mean LDL-c 3.5±1.2 mmol/L, mean high-density lipoprotein cholesterol (HDL-c) 1.3±0.4 mmol/L and median triglycerides 1.6 mmol/L (IQR 1.2–2.3).

Response to inclisiran treatment

A total of 80 patients received a single dose of inclisiran at our clinic over 10 months. Seventy-seven patients had been seen at their 2 month follow-up by the time of data collection with 3 patients still awaiting review.

Following treatment with inclisiran, mean LDL-c fell by 48.6%–1.8±1.0% mmol/L ($p<0.0001$) from baseline (figure 2). Total cholesterol fell to 3.8±1.1 mmol/L ($p<0.0001$) accounting for a 33.3% reduction. Mean HDL-c rose by 7.7%–1.4±0.4% mmol/L ($p=0.02$) and median triglycerides fell by 31.3%–1.1% mmol/L (IQR 0.9–2, $p=0.001$). Analysis of FH and non-FH groups showed that mean LDL-c fell by 48.6%–1.8±1.0% mmol/L ($p<0.0001$) and by 52.8%–1.7±1.0% mmol/L ($p<0.0001$) in FH and non-FH groups, respectively (figure 2). Similar reductions were also seen among men vs women, non-white versus white populations and those ≤64 and ≥65 years old (table 2). Thirty-seven patients (46.3%) achieved a 50% or greater reduction in LDL-c from

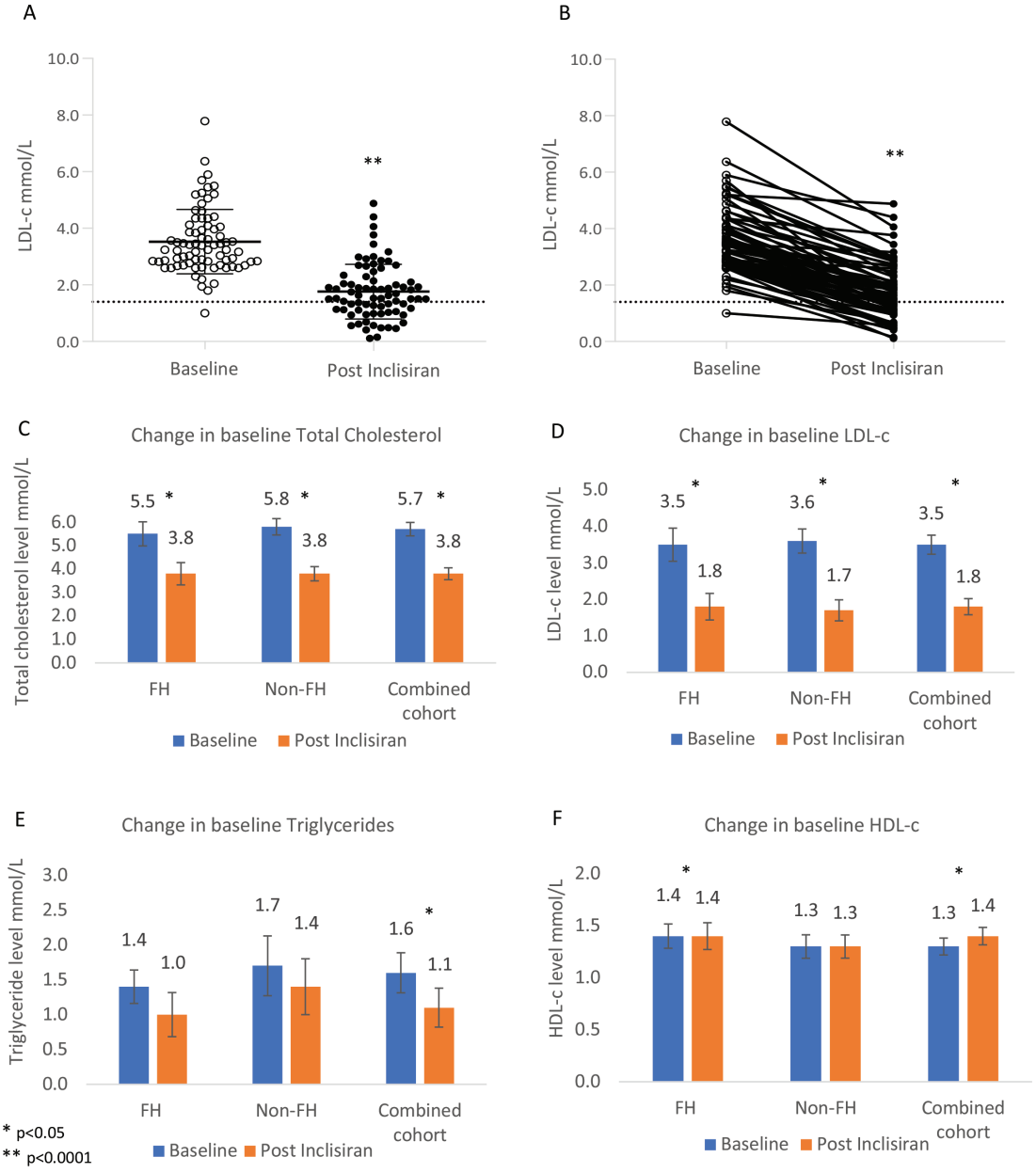

Figure 2 (A) LDL-c at baseline and postinclisiran and (B) individual response to treatment (n=76). Change in mean baseline (C) total cholesterol, (D) LDL-c, (E) triglycerides (median) and (F) HDL-C at 2 months following single dose of inclisiran among FH (n=29), non-FH (n=47) and combined cohort (n=76). One patient had self-discontinued ezetimibe treatment on inclisiran initiation and has been excluded from the graphs. *p<0.05, **p<0.01. FH, familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; non-FH, non-FH.

baseline and 28 patients (36.4%) achieved LDL-c levels of<1.4 mmol/L.

Individual responses to inclisiran treatment are shown in figure 3 and reveal a wide range of measured responses ranging from 6% to 95.8% reduction in LDL-c. One patient had self-discontinued ezetimibe treatment on starting inclisiran and had a 33.6% rise in baseline LDL-c at 2 months. This patient was excluded from further analyses due to inability to assess the direct effect of inclisiran. All other patients reported that they had continued baseline LLT during the 2 months follow-up period.

Effects of inclisiran with background LLT

Analysis of treatment responses according to statin vs no statin use at baseline revealed that statin users experienced a greater reduction in LDL-c (56% vs 44.9% respectively, p=0.01) (figure 4). Further analysis of concurrent treatment categories showed that patients on triple therapy achieved the greatest reduction. Patients taking a statin alone and those on statins combined with ezetimibe achieved similar percentage reductions in LDL-c at 2 months. Comparison of these treatment categories against the no LTT group however did not reach statistical significance.

Table 2 Percentage reduction of LDL-c at 2 months among sex, age and ethnicity

	Percentage LDL-c reduction (%)
Sex	
Male	51.4
Female	47.2
Age	
≤64 years	50
≥65 years	47.2
Ethnicity	
Non-white	51.4
White	48.6

LDL-c, Low-density lipoprotein cholesterol.

Adverse events

Adverse events at 2 months were reported in 3 of the 77 patients (3.9%). This included a moderate injection site reaction (n=1), dizziness and headache (n=1) and fatigue (n=1). All events had self-resolved by the time of 2 month follow-up. One individual reported weakness in legs in addition to abdominal pain and diarrhoea. The patient was reviewed by a physician at the clinic and concluded that these symptoms were a result of the patient's pre-existing medical conditions and not due to treatment. No serious adverse events were reported and no individuals required presentation to hospital.

DISCUSSION

Adherence and perceived side effects of statins pose the greatest shortcomings in real-life practice with approximately 50% discontinuing therapy after 1 year.[8 9] Other medications such as ezetimibe, bempedoic acid and bile acid sequestrants have provided alternative options but many on these treatments alone fail to achieve sufficient LDL-c lowering. The advent of monoclonal antibodies to PCSK9i has added to our repertoire of LLTs. Though effective, the high cost of these medications and the strict eligibility criteria for their use in many countries mean that they still remain out of reach. The recent introduction of inclisiran with relative lower LDL-c threshold needed for approval compared with PCSK9i makes this more attainable for many patients.

This real-world data analysis evaluated the efficacy of inclisiran in patients at a secondary care lipid clinic being treated for hypercholesterolaemia as part of their routine clinical care. Our results show that a single subcutaneous inclisiran injection is effective in reducing LDL-c, achieving a mean reduction of 48.6% at 2 months. LDL-c reductions were consistent among sex, age (≤64 and ≥65 years) and ethnicity (non-white and white patients). In addition, these reductions were achieved on top of an individual's maximum tolerated LLT, which indicates the added potential impact this medication has on reducing LDL-c. The overall changes observed in this study are concordant with those from ORION-10 and ORION-11 trials at 90 days which likewise showed a placebo-corrected reduction in mean LDL-c by approximately 50%.[4]

The baseline demographics of our cohort concerning age and sex are comparable to those in these phase III trials. Our patient population also included a large proportion of FH patients with results consistent with ORION-9.[3] Furthermore, our study population was more ethnically diverse (43.8% non-white vs 2.3% and 16.4%

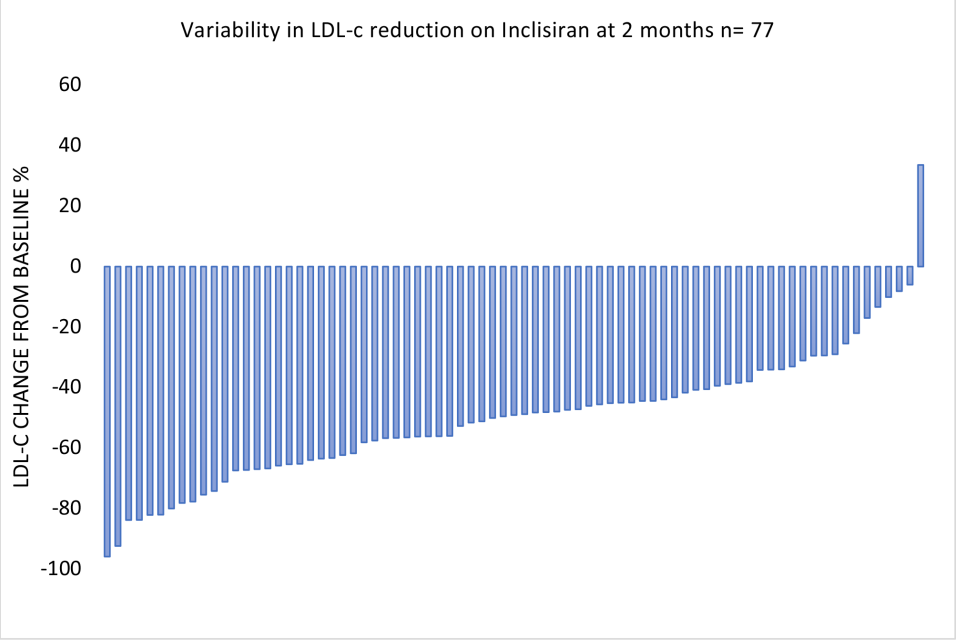

Figure 3 Waterfall plot of variation of LDL-c percentage change of 77 patients after a single dose of inclisiran at 2 months. One patient with a 33.6% increase in LDL-c following self-discontinuation of ezetimibe during study period. LDL-c, low-density lipoprotein cholesterol.

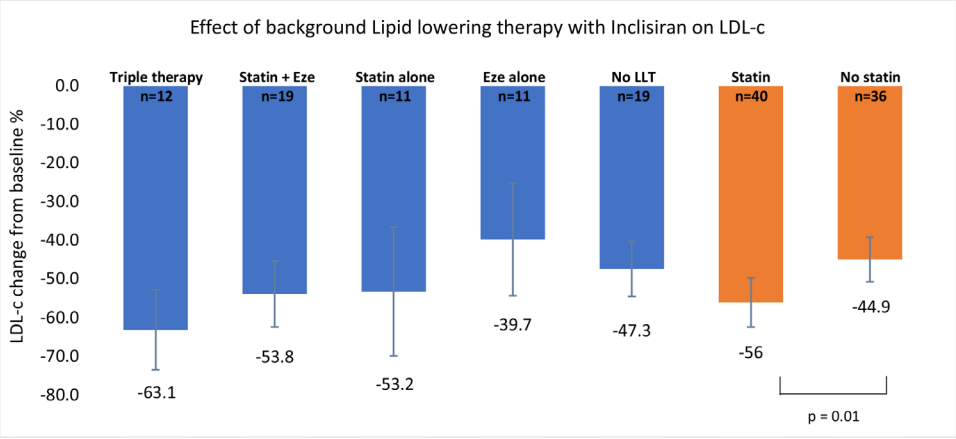

Figure 4 Effects of background lipid-lowering therapy in addition to inclisiran on LDL-c reduction at 2 months. Comparison of background LLT analysed using one-way ANOVA. LDL-c reduction in those taking a statin and no statin (right), analysed using unpaired t-test. ANOVA, analysis of variance; Eze, ezetimibe; LDL-c, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy.

in ORION-11 and ORION-10, respectively). As expected, our real-world cohort had a higher mean baseline LDL-c (3.52 mmol/L) compared with clinical trials (2.7 mmol/L in ORION-10). When considering background LLT, our study comprised of much lower percentage of patients with statin use (52.5%) compared with approximately 90% of patients in the RCTs.

Our results also show a reduction in total cholesterol, triglycerides and a rise in HDL-c levels at 2 months. This trend in lipid profile was likewise reported in the secondary endpoints of ORION-10 and ORION-11 trials over the study duration. Similarity between results, suggests that these trial outcomes can be achieved in the clinical environment.

Concerning guidelines, the joint European Society of Cardiology and European Atherosclerosis Society advise a treatment goal of LDL <1.4 mmol/L in those deemed very high risk.[10] In our study, over one-third of patients achieved LDL-c levels of <1.4 mmol/L following a single dose and nearly half attained a 50% or greater reduction from baseline. This suggests that achieving target LDL-c levels in the future may be more attainable with combination therapy with inclisiran, particularly in this very high-risk population.

All patients with the exception of one achieved reduction in LDL-c levels at 2 months. The 33% LDL-c rise in this single patient was put down to the cessation of baseline LLT during the follow-up period. All other patients had continued baseline LLT throughout the follow-up period. Counselling patients on the continuation of concurrent LLT is paramount. It is also worth noting that not all individuals had sizeable reductions in LDL-c and this interindividual variability suggests that the approach to treatment may still need to be tailored at an individual level.

We considered whether background LLT had an impact on inclisiran efficacy among our study population. Patients on baseline statin had a greater LDL-c reduction than those not on statin. This synergistic effect can be explained by the action of statins in activating sterol regulatory element binding protein-2 and subsequently increasing transcription of both LDLR and PCSK9 mRNA.[11] Blockade of PCK9i mRNA translation by inclisiran therefore leads to unopposed LDLR expression at the cell surface with the overall effect being greater clearance of circulating LDL-c.

Statin intolerance and contraindications were reported in 39 patients (48.75%) and explain why many were not on treatment or could not be further optimised to achieve target levels. For many patients, twice yearly injections are a more convenient and a less burdensome option that could further improve adherence and overall greater LDL-c reductions going forward. The approval of inclisiran for delivery in primary care adds to this and together can lead to an increased number of patients meeting therapeutic targets.

Overall, inclisiran was well tolerated in this patient cohort, despite high prevalence of intolerances to other LLTs. All adverse events were mild to moderate and had self-resolved by the 2-month follow-up. The nature of these events was similar to those reported in ORION trials including injection site reactions and other non-specific symptoms such as headache and fatigue. No patient has discontinued treatment following the first dose, which could lend itself to higher rates of adherence.

Our study has several strengths. This is the first report of real-world data analysing the effect of inclisiran on LDL-c reduction in a routine clinical setting. In this study, we describe that patients treated with a single dose inclisiran can achieve significant reductions in LDL-c on top of maximal tolerated therapy, with these changes notable at 2 months. Furthermore, the ethnic diversity of this study population (43.8% non-white) is not replicated in earlier phase III trials where white patients were the significant majority (97% in ORION-11 trial). Despite this, our results at 2 months are consistent with those seen in RCTs and suggest results may be reproducible in

the clinic setting, though longer-term data are warranted to make a more valid comparison.

This study has limitations. First, our findings represent the experience of a lipid clinic from only a single centre. Second, the sample size was small and therefore incidence of adverse effects may not be truly representative and may be higher. The small sample size will also impact the ability to extrapolate these results to larger populations. Finally, patients were followed up for 2 months, which limited the assessment of the drug's effectiveness only to the short term and not necessarily to peak effect. A greater duration of follow-up is needed to evaluate long-term efficacy of the treatment and whether these effects are sustained.

CONCLUSION

This single-centre experience of the use of inclisiran in a secondary care lipid clinic in a London hospital showed that treatment with Inclisiran was well tolerated with reductions consistent with those observed in randomised placebo-controlled trials.

Contributors JC conceptualised the study. PP and LB collected and analysed the data. First draft was written by PP and JC. All authors contributed to the interpretation of data. All authors provided revisions to each draft of the manuscript and approved the final version. JC is the guarantor.

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REFERENCES

1 Townsend N, Wilson L, Bhatnagar P, *et al*. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J* 2016;37:3232–45.
2 Yusuf S, Hawken S, Ounpuu S, *et al*. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the interheart study): case-control study. *Lancet* 2004;364:937–52.
3 Raal FJ, Kallend D, Ray KK, *et al*. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. *N Engl J Med* 2020;382:1520–30.
4 Ray KK, Wright RS, Kallend D, *et al*. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med* 2020;382:1507–19.
5 NICE. Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia, 2022. Available: https://www.nice.org.uk/guidance/ta733 [Accessed 09 Sept 2022].
6 Rani khatib DD. *Summary of national guidance for lipid management for primary and secondary prevention of CVD*. Natl institutute Heal care Excell, 2020: 1–2. https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/04/Summary-of-national-guidance-for-lipid-management-for-primary-and-secondary-prevention-of-cardiovascular-disea.pdf
7 Sampson M, Ling C, Sun Q, *et al*. A new equation for calculation of low-density lipoprotein cholesterol in patients with normolipidemia and/or hypertriglyceridemia. *JAMA Cardiol* 2020;5:540–8.
8 Banach M, Stulc T, Dent R, *et al*. Statin non-adherence and residual cardiovascular risk: there is need for substantial improvement. *Int J Cardiol* 2016;225:184–96.
9 Maddox TM, Chan PS, Spertus JA, *et al*. Variations in coronary artery disease secondary prevention prescriptions among outpatient cardiology practices: insights from the NCDR (national cardiovascular data registry). *J Am Coll Cardiol* 2014;63:539–46.
10 Mach F, Baigent C, Catapano AL, *et al*. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the task force for the management of dyslipidaemias of the European Society of cardiology (ESC) and European atherosclerosis Society (EAS). *Eur Heart J* 2019;41:111–88.
11 Jeong HJ, Lee H-S, Kim K-S, *et al*. Sterol-dependent regulation of proprotein convertase subtilisin/kexin type 9 expression by sterol-regulatory element binding protein-2. *J Lipid Res* 2008;49:399–409.