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A Real-World Retrospective Analysis of Secondary Prevention Patients Treated with Inclisiran over 27 Months

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Abstract

ASCVD is a global concern as it has become central to significant morbidity and mortality. LDL-C is the most important modifiable risk factor in developing ASCVD. Therefore, lowering LDL-C levels is paramount to tackling ASCVD; the lower the LDL-C, the better. Finding the right combination of medications patients are willing to adhere to is necessary for optimal lipid lowering. Inclisiran is a novel LDL-C lowering LLT that has demonstrated around 50% reduction in LDL-C with a low side effect profile. As long-term data is limited for Inclisiran, this retrospective analysis aims to observe whether Inclisiran's benefits are sustained as monotherapy and in combination with other LLTs. After 27 months, the clinic found sustained drops in LDL-C of 59% with good adherence. Only 4% of patients reported experiencing side effects, with 1 individual needing to discontinue the medication due to these effects. Our data indicates that incorporating Inclisiran into a patient's LDL-C treatment plan can provide long-term LDL-C reduction, thereby helping to decrease cardiovascular events.

Keywords

cardiovascular, outcomes research, patient-reported outcomes

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Introduction

The most significant contributor to morbidity and mortality globally is atherosclerotic cardiovascular disease (ASCVD).[1-3] A well-known causative agent in the development of ASCVD is low-density lipoprotein cholesterol (LDL-C).[4] According to the Global Burden of Disease, having high levels of LDL-C causes 4.5 years of life lost worldwide.[5] LDL-C's effect on cardiovascular risk is not only causative but cumulative. Therefore, the risk of a cardiovascular event increases with the concentration of LDL-C and the length of time exposed to that concentration.[6] One study, using CARDIA (Coronary Artery Risk Development in Young Adults) data, observed 4958 healthy participants over 16 years to assess the effects of LDL-C over time. They found that duration of exposure to LDL-C from 18 to 40 years old was a higher predictor of future ASCVD events than patients who developed hyperlipidaemia later in life (after 40 years old). This highlighted the necessity of treating patients, even healthy ones, when hyperlipidaemia is realised.[7] It also emphasises the importance of maintaining low LDL-C levels once treatment is initiated.

There is a direct relationship between LDL-C concentration and the risk of ASCVD. Meta-analyses have shown that for every 1 mmol/L (39 mg/dl) decrease in LDL-C, there is a 22% reduction in cardiovascular events within 1 year, leading to the expectation that decreases of 2 to 3 mmol/L would reduce cardiovascular events by around 40% to 50%.[2,8] Various guidelines have set LDL-C targets at least below 1.8 mmol/L (70 mg/dl) as this initiates a regression in plaque volume.[9,10] The European guidelines (ESC 2019) specify an LDL-C $<$ 1.4 mmol/L (55 mg/dl) for secondary prevention patients.[5] Despite recent speculation, there are no safety concerns regarding reducing a patient's LDL-C too low; therefore, there is no lower limit.[7,11] These observations were based on meta-analyses involving patients who still found consistent ASCVD benefits with an LDL-C of $<$0.65 mmol/L (25 mg/dl).[11] The FOURIER trial

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and ODYSSEY-OUTCOMES trials demonstrated safety of patients on PCSK9 inhibitors and high intensity statins with LDL-C levels at 0.8 mmol/L (30 mg/dl) and 1.0 mmol/L (40 mg/dl).[5] Further studies found ASCVD benefits with LDL-C levels as low as 0.3 mmol/L (10 mg/dl) with no evidence of adverse effects, even in elderly populations.[11] There is also no evidence of cognitive impairment with low LDL-C levels as the brain can produce its cholesterol through astrocytes and oligodendrocytes and, therefore, does not rely on extra-CNS sources.[11,12]

With such compelling evidence for the benefits of lowering LDL-C, it must be implemented in a real-world setting. UK data suggests that only 3 out of 10 secondary prevention ASCVD patients meet their recommended LDL-C targets despite already being on lipid-lowering therapy (LLT).[2,3,13] This translates to not only unnecessary financial expenditure on ASCVD events but, more importantly, preventable ASCVD patient morbidity and mortality. Barriers to reducing LDL-C have been identified as clinical inertia (not commencing or intensifying treatment), patient adherence, and lack of access/use of add-on therapies.[11] In the USA, only 21% of secondary prevention ASCVD patients on LLT achieved target LDL-C levels ($<$1.8 mmol/L or $<$70 mg/dL).[2,11]

Therefore, to help maintain sustained LDL-C levels, a combination of LLT is a necessity. Alternative and additional therapies to statins include ezetimibe, bempedoic acid, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), and more recently, small interfering RNA (siRNA) therapy (eg, Inclisiran).[2,3] All of these therapies are available to primary care practices in England, except for PCSK9i, which a specialist must initiate.[2] Inclisiran can reduce LDL-C by an average of 50%, making itself comparable in efficacy to atorvastatin 80 mg or a PCSK9i.[1-3,6,11] However, inclisiran offers a lower side effects profile than the 2 medications and is less expensive than PCSK9i's.[1-3,11] While PCSK9 inhibitors are associated with a broader range of adverse effects, including nasopharyngitis, upper respiratory tract infections, and myalgia, inclisiran predominantly causes mild and transient injection-site reactions. This distinct safety profile contributes to inclisiran's suitability for long-term use in managing LDL-C levels[1]

The siRNA treatment works by binding to the mRNA of the PCSK9 protein, thereby preventing its expression. PCSK9 is a protein responsible for the degradation of LDL-C receptors. Therefore, the less PCSK9 available, the more LDL-C receptors there are to remove LDL-C from the circulatory system, resulting in lower plasma LDL-C levels.[1,2,6] Inclisiran operates further upstream in the lipid regulation pathway by silencing PCSK9 mRNA, preventing its translation into protein, compared to PCSK9 inhibitors which target the protein itself.[5] This mechanism not only enhances efficacy but also enables a longer duration of action, requiring only 2 injections per year following an initial dose, compared to the more frequent 2 to 4 weekly dosing of traditional PCSK9 inhibitors. This extended dosing interval provides significant advantages in terms of patient convenience and adherence, particularly in real-world settings.

Objective

Global evidence has emerged over time that LDL-C has a causative and cumulative effect on LDL-C, leading to the notion that 'the lower, the better' and 'time is plaque'.[4,5,7,8,11] It is imperative to reduce LDL-C levels and ensure a sustained reduction to produce the maximum benefit of ASCVD risk reduction.[4,7,8,11] All LLTs available in England to primary care providers have been utilised to help maintain low levels of LDL-C in this rural English practice. However, this analysis will focus on inclisiran and review its longer-term effects. This analysis aims to investigate if inclisiran can produce sustained lowering of LDL-C levels in real-world primary care practice and contribute to ASCVD risk reduction.

Methodology

Within a primary care practice with a 6800-patient registrar, 161 secondary prevention patients were initiated on inclisiran therapy from December 2021 to February 2024. Patient data was extracted by utilising electronic medical records (EMR). The patients' LDL-C levels for those on Inclisiran were retrospectively analysed over 27 months.

Initiation and Intensification of LLT

Patients in practice are initiated on treatment per current National Health Service England (NHSE) guidance.[2] All patients were offered a first-line statin titrated to maximum dosage or patient tolerance. In addition, LLT were then utilised in the form of Ezetimibe, bempedoic acid, and Inclisiran until a patient reaches their LDL-C target. European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines were followed where high-risk patients are recommended an LDL-C of $<$1.8 mmol/L ($<$70 mg/dl). Comparatively, very high-risk patients should be treated to an LDL-C of $<$1.4 mmol/L ($<$55 mg/dl).[14,15] All medication changes were aligned with current guidance and based on a shared decision with the patient. Patients on inclisiran were pooled from the patient data and retrospectively analysed independently.

Incorporating Inclisiran

Patients could be started on Inclisiran if they had established ASCVD and an LDL-C of $\geqslant$2.6 mmol/L (100 mg/dl).[3] Initially, patients were identified using searches within the electronic medical record (EMR). Patients appropriate for inclisiran and agreeable to initiation would visit the clinic for the 284 mg subcutaneous injection. Following this first injection, a further dose would be administered 3 months later; then, maintenance doses would be given every 6 months as per the medication licence. Blood tests were then performed to monitor the lipid profile as clinically indicated. Patients received digital reminders via SMS text (via the Accurx®) when they were due for injections and blood tests. The SMS texts could be pre-dated; therefore, future reminders were set at their appointments.

Table 1. Baseline characteristics.

Characteristic	Values
Number of patients	161
Mean age (years)	71.5 (SD = 10.5)
Sex distribution (male/female)	81/80
ASCVD diagnoses (CVD/CVA/PAD)	83/48/25
Comorbidities (T2DM/hypertension/CKD)	31/125/68
Smoking status (current/ex/never)	20/77/64
Additional lipid-lowering therapies	Statins (97), Ezetimibe (39), Bempedoic Acid (4), Combination (41)
Mean baseline LDL-C (mmol/L)	3.32 (SD = 0.68)

Data Collection

Patient data was collected retrospectively from the EMR to allow a time-series analysis to be performed. There were 161 patients on Inclisiran in the practice from December 2021 to February 2024. Patient demographics were obtained, which included age, gender, BMI, smoking status, ASCVD diagnosis (cardiovascular disease (CVD), cerebral vascular accident (CVA), peripheral arterial disease (PAD)), and comorbidities including diabetes mellitus (T2DM), and chronic kidney disease (CKD). Additional LLTs to inclisiran were also noted.

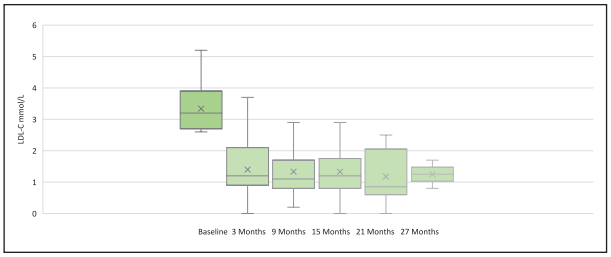

Figure 1. Box-whisker plots for LDL-C (mmol/L) at baseline and each inclisiran treatment.

Data Analysis

Patient demographics were subject to descriptive statistics. LDL-C data was analysed at baseline and where available at 3, 9, 15, 21, and 27 months. LDL-C values were analysed using paired-*T*, unpaired-*T*, and ANOVA tests as appropriate for statistical analysis. Statistical significance was set at $\alpha = .05$.

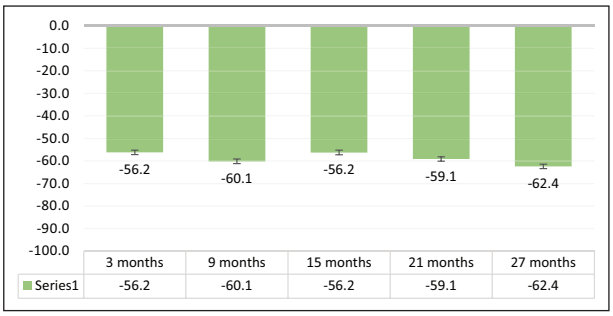

Figure 2. Percentage reduction in LDL-C with inclisiran treatments compared to baseline.

Results

Patient Demographics

All patients on inclisiran were suitable for retrospective analyses (see Table 1). The analysed pool of patients included 80 females and 81 males. The mean age was 71.5 years (SD = 10.5). Patients' ASCVD diagnoses included CVD (83), CVA (48), and PAD (25), with some patients having more than 1 diagnosis. Other comorbidities included T2DM (31), hypertension (125), and CKD (68). Smoking status included current smokers/ vape use (20), ex-smokers (77), and no prior smoking history (64). Additional LLT to Inclisiran included statins (97), ezetimibe (39), bempedoic acid (4), and a combination of Ezetimibe and bempedoic acid tablets (41; Nustendi®). Some patients are on 2 or more LLTs. Of the group, 79 were on icosapent ethyl (Vazkepa®/Vaskepa™) for further ASCVD residual risk reduction as indicated by raised triglyceride levels.

Analysis of Inclisiran

The minimum LDL-C at the time of initiation of Inclisiran was 2.6 mmol/L (100 mg/dl), with a mean of 3.32 mmol/L (SD = 0.68; 128 mg/dl). After initiation of Inclisiran, the mean LDL-C levels were 1.46 mmol/L (SD = 0.83; 56 mg/dl) at 3 months, 1.33 mmol/L (SD = 0.72; 51 mg/dl) at 9 months, 1.42 mmol/L (SD = 0.68; 55 mg/dl) at 15 months, 1.36 mmol/L (SD = 0.71; 53 mg/dl) at 21 months, and 1.25 mmol/L (SD = 0.50; 48 mg/dl) at 27 months (see Figure 1). The mean LDL-C reductions at each time point were statistically significantly lower than at baseline ($P < .05$).

The above represents a percentage change in LDL-C of 56% at 3 months, 60% at 9 months, 56% at 15 months, 59% at 21 months, and 62% at 27 months (see Figure 2). LDL-C reductions were successfully sustained by an average decrease of 59%, statistically significant over the 27 months compared with the baseline ($P < .05$). The mean reduction in LDL-C from 3 to 27 months was similar and sustained with no significant difference between each treatment point ($P > .05$) (see Figure 3).

In terms of reaching targets, 72% of patients reached a target LDL-C of < 1.8 mmol/L (70 mg/dl), and 54% of patients reached a target LDL-C of < 1.4 mmol/L (55 mg/dl). Patients were largely adherent to the medication, with only 1 patient

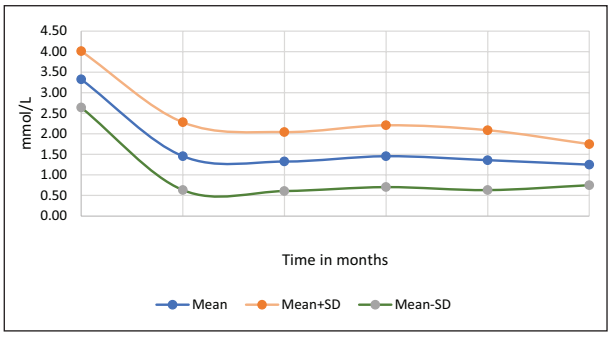

Figure 3. Mean (±SD) LDL-C with inclisiran over time.

stopping the drug due to a patient's perceived unacceptable injection site reaction; this resolved with the discontinuation of the medication. Six patients (4%) experienced mild injection-site reactions, which were transient and did not lead to discontinuation of the drug. No serious adverse effects requiring hospitalisation were recorded in our retrospective review.

Discussion

The ORION trials were integral to providing evidence for the efficacy and safety of Inclisiran.[1,2,6,7,11] ORION-1 trial found that Inclisiran elicited around a 50% reduction in LDL-C over a year with a low side effect profile.[11] This is comparable to our real-world data. ORION-3 established that these reductions were sustained by around 51% by 210 days on Inclisiran, and over 3 years, the safety profile remained consistent with no changes in liver or kidney function.[6,11]

ORION-10 and ORION-11 examined Inclisiran over an 18-month (540 days) period and found that reductions in LDL-C of 52.3% were sustained in ORION-10 and the average for ORION-11 was a sustained 49.9% reduction in LDL-C by the 18-month mark.[1,2,11] Our real-world data is in keeping this with an average sustained reduction in LDL-C of 58% up to 27 months. Both ORION-10 and ORION-11 also found significant decreases in total cholesterol (33.1%, 29.8%), triglycerides (12.6%, 7.0%), and lipoprotein (a) (25.6%, 18.6%) among other components of the lipid profile.[11] Side effects were similar to placebo other than injection-site reactions (2.6%, 4.7%), typically mild and self-resolving.[2,3,6,11] Our data supports this finding that the medication is generally well tolerated, with mild injection site reactions when present in *ca.* 4% of our patients. There were no significant adverse reactions for the patients in our data pool. At the time of publishing, our literature search returned no real-world studies with published LDL-C reductions for 27 months. Our data is helping to expand upon the evidence-base of Inclisiran's long-term benefits on LDL-C in the everyday clinical setting, both when used alone and in conjunction with other LLTs.

Inclisiran's Cardiovascular Benefit

How these LDL-C reductions translate into cardiovascular benefits is being investigated. A meta-analysis conducted by Khan et al involving 3660 patients found consistent decreases of 51% in LDL-C with Inclisiran and a reduction in major adverse cardiovascular events (MACE) by 24%.[16,17] Further long-term data studies are ongoing. For example, ORION-4 CVOT is in process and includes 15 000 patients to evaluate Inclisiran's role in reducing MACE over 5 years. This study is expected to conclude in 2026.[18]

One study estimated the population health impact of Inclisiran alone on patients in England, and its use was in line with NICE guidelines. Their calculations found that over 10 years, with the use of Inclisiran, 138 647 ASCVD events could be avoided.[19]

Addressing Adherence

It is reassuring to see sustained LDL-C levels at 27 months, as adherence and efficacy remain a considerable concern in the cardiovascular realm. When examining statin use, it was found that less than a quarter of patients initiated on statins remained on them after 5 years. Other studies found shorter time frames where only 43% of patients adhered to their LLT status post-six months after a myocardial infarction (MI).[11] Overall, patients will stop taking 50% of their CVD medications within a year, and 30% of CVD medications that were prescribed will not be filled.[20] Therefore, it is encouraging to see these sustained average reductions in LDL-C of 59% in a real-world setting up to 27 months, surpassing the year mark and displaying patient adherence to the medication. As Inclisiran is given in the practice, clinicians are readily aware of any possible adherence issues to this and other LLT medications. Inclisiran's long half-life also means that the medication has sustained effects once given; it will potentially remain within a treated hepatocyte for its life.[1-3,6] Adherence has become a fundamental need for reducing ASCVD as substantial data shows that early and sustained LDL-C lowering provides the most benefit for reducing cardiovascular risk and events. The side effect profile is also similar to placebo other than injection-site reactions, giving the medication a distinct benefit over traditional oral LLT and even PCSK9 inhibitors.[1-3,6,11,16] A low side effect profile is essential for patient suitability to a medication. For example, up to 29% of patients discontinue statins due to musculoskeletal adverse effects.[9,10] If a patient cannot tolerate a specific LLT, then there are fewer options for combination therapy to reach optimal targets.

Another way to combat the lack of adherence is through education. Educating patients on the importance of LDL-C lowering their cardiovascular risk and addressing patients' concerns/questions regarding the medication leads to improved outcomes. Regular lipid monitoring also helps to ensure patient adherence, as any changes in LDL-C from prior readings should be addressed with the patient directly,[11] a principle that we apply in our clinic.

Addressing Clinical Inertia and Patient Beliefs

As previously mentioned, lack of adherence is only one of the barriers to maximising ASCVD reduction. Adherence is

assuming the patient was started on the medication in the first place. The provider assessment of lipid management (PALM) registry identified that 59% of patients with elevated LDL-C were not offered any form of LLT.[11] This registry data highlighted providers' role in clinical inertia impeding upon LDL-C target lowering goals.[5,7,11] Clinical inertia includes providers being unaware of the benefits of lowering LDL-C and/or updated recommended guidelines, which have become meticulous over time. It is also essential for providers to be educated on using the maximum dose available of an LLT and actively utilising multiple LLT options, as lack of access to/use of add-on LLT is another well-known contributor to patients not reaching targets.[2,11,14] Initiation/intensification of treatment is also marred by patients' belief that lifestyle changes will produce significant enough LDL-C reductions, that their current therapy will continue to improve LDL-C levels over time, and that increasing the dose of current LLT or adding another LLT will lead to increased side effects.[11] The PALM registry quantified that of patients who declined the offer of a statin, 37% stated their reason was fear of side effects.[21] Treatment also fails to be intensified when patients do not have routine blood tests to monitor their LDL-C levels and ensure they reach their targets.

Theoretical Failure of Response due to Immunological Issues

During a pre-specified analysis of ORION-1, concerns about the immune response from Inclisiran's siRNA technology were addressed. The study investigated multiple immune response parameters such as anti-drug-antibodies, platelet count, immune cells (leucocytes, monocytes, and neutrophils), and inflammatory biomarkers (interleukin six and tumour necrosis factor-α. After 180 days, there were no significant differences in immune response as indicated in the markers above with Inclisiran compared to placebo.[22] Our data supports these findings as LDL-C lowering remains significantly sustained up to 810 days after initiating inclisiran treatment.

Analysis Limitations

This study has several limitations that must be considered when interpreting the findings. The data were derived from a single practice in a specific geographic region, resulting in a relatively small sample size and limited demographic diversity, which may restrict the generalisability of the results to broader populations. The retrospective nature of the analysis introduces inherent limitations, including the inability to control for confounding variables such as the initiation of additional lipid-lowering therapies during the study period. Furthermore, as all patients were secondary prevention candidates requiring multiple lipid-lowering therapies, the inclusion of a control group was not feasible.

At the 27-month follow-up, the available data were limited primarily due to the small number of patients initially prescribed inclisiran, meaning only a subset had reached this time point, while others were still early in their treatment course. Despite this, adherence to inclisiran was high, with only 1 patient discontinuing treatment due to perceived side effects. Additionally, the short duration of the analysis precluded a direct assessment of cardiovascular outcomes. Nonetheless, the primary objective of evaluating sustained LDL-C reductions achieved with inclisiran was met, supporting its potential long-term benefit. Future studies with larger, more diverse cohorts and longer follow-up periods are warranted to validate these findings and explore the impact on cardiovascular outcomes.

Comparison with Real-World Studies on Inclisiran

In the context of real-world inclisiran use, our findings align closely with other studies assessing its efficacy and safety. For instance, the study by Padam et al[23] demonstrated significant reductions in LDL-C levels, with sustained efficacy observed over similar follow-up periods. Similarly, research by Makhmudova et al[24] highlighted high adherence rates and minimal adverse events, mirroring our study's findings of only 1 patient discontinuation. Furthermore, Mulder et al[25] emphasised the potential for inclisiran to achieve LDL-C reductions in populations with comorbidities, consistent with our analysis of secondary prevention patients. These comparisons underscore the robustness of inclisiran's real-world efficacy, while also highlighting the need for further research to explore its impact on long-term cardiovascular outcomes across diverse populations.

Conclusion

LDL-C is a well-recognised risk factor for ASCVD, and significant reductions are now recommended. Fortunately, multiple LLT options are available to help achieve these goals and can improve population health in risk groups. Consensus is emerging for the cumulative benefit of having sustained lower LDL-C levels for longer periods. Meta-analyses now suggest that there is no lower limit for which LDL-C lowering is found to be no longer beneficial and/or unsafe. This leads to 'the lower, the longer, the better', becoming the new mantra in secondary ASCVD prevention.[4,5,7,11] This retrospective review of real-world patients, where inclisiran has either been utilised as part combination LLT or as monotherapy when a patient is a statin or other medication intolerant, has allowed for sustained LDL-C lowering over 27 months with 72% of patients reaching a target LDL-C of <1.8 mmol/L (70 mg/dl), and 54% of patients reaching a target LDL-C of <1.4 mmol/L (55 mg/dl).

This has been achieved with few side effects in keeping with trial data and only 1 patient stopping treatment. The key considerations for the delivery of this medication are patient education, ensuring an efficient recall system is in place to give the treatments and performing medication reviews, including adherence at every review to ensure compliance with all medications.

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Ethical Considerations

This study was conducted as a retrospective analysis of previously collected data. The review examined data from the electronic record system, originally gathered for routine clinical work. The local ethics committee (LEC) reviewed the protocol and approved it as a retrospective review (Ref: April-24-27m). All data utilised were de-identified and anonymised before analysis to protect participant confidentiality. To ensure patient privacy and confidentiality, all collected data were anonymised and stored securely in compliance with the UK Data Protection legislation. Access to the data was restricted to authorised personnel only. Patient identifiers were removed from all study-related documents. The authors declare that they have no conflicts of interest that could have influenced this study's design, conduct, or reporting. This review was not funded, although the PCN did receive a non-promotional grant from Bayer to commission the remote service from an external provider. The data were used solely for this retrospective review. All authors, who were directly involved in the data analysis, are trained in ethical research practices and comply with the guidelines and principles of ethical reporting. All findings are reported accurately and honestly, without fabrication, falsification, or inappropriate data manipulation.

Consent to Participate

Informed consent has been obtained for participation in this review. All data presented in this article were anonymised and obtained from medical records and healthcare professionals involved in the patients' care. No personal or identifying details of the patients are included in this report. The cases described herein are based solely on clinical information relayed by the treating physicians and other healthcare team members, ensuring patient confidentiality while maintaining the integrity of the medical observations and outcomes reported.

Consent to Publication

As above.

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Declaration of Conflicting Interests

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Data Availability Statement

The data that support the findings of this study are derived from clinical case notes and healthcare professional observations. Due to the nature of this research, supporting data is not available.

References

1. Koenig W, Conde LG, Landmesser U, et al. Efficacy and safety of inclisiran in patients with polyvascular disease: pooled, post hoc analysis of the ORION-9, ORION-10, and ORION-11 phase 3 randomized controlled trials. *Cardiovasc Drugs Ther*. 2022;38:493-511.
2. Deaney CN, Donaldson MP, Reesby DM, et al. Retrospective evaluation of LDL-C levels following first treatment with Inclisiran as part of secondary prevention ASCVD risk reduction in a real-world primary care setting. *J Prim Care Community Health*. 2024;15:21501319241236339.
3. Deaney C, Donaldson M, Meskauskiene A. Implementing an innovative lipid management technique using siRNA LDL-C lowering therapy: lessons learned in an NHS primary care practice with worked case examples. *J Prim Care Community Health*. 2023;14:21501319231172709.
4. Ference BA, Ginsberg HN, Graham I, 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(32):2459-2472.
5. Mhaimeed O, Burney ZA, Schott SL, et al. The importance of LDL-C lowering in atherosclerotic cardiovascular disease prevention: lower for longer is better. *Am J Prev Cardiol*. 2024;18:100649.
6. Stoekenbroek RM, Kallend D, Wijngaard PL, Kastelein JJ. Inclisiran for the treatment of cardiovascular disease: the ORION clinical development program. *Future Cardiol*. 2018;14(6):433-442.
7. Domanski MJ, Tian X, Wu CO, et al. Time course of LDL cholesterol exposure and cardiovascular disease event risk. *J Am Coll Cardiol*. 2020;76(13):1507-1516.
8. Trialists CT. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670-1681.
9. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA*. 2006;295(13):1556-1565.
10. Iatan I, Guan M, Humphries KH, Yeoh E, Mancini GBJ. Atherosclerotic coronary plaque regression and risk of adverse cardiovascular events: a systematic review and updated meta-regression analysis. *JAMA Cardiol*. 2023;8:937.
11. Underberg J, Toth PP, Rodriguez F. LDL-C target attainment in secondary prevention of ASCVD in the United States: barriers, consequences of nonachievement, and strategies to reach goals. *Postgrad Med*. 2022;134(8):752-762.
12. Hua R, Ma Y, Li C, Zhong B, Xie W. Low levels of low-density lipoprotein cholesterol and cognitive decline. *Sci Bull*. 2021;66(16):1684-1690.
13. CVDPREVENT. Data explorer: cholesterol: CVD treated to threshold (CVDP007CHOL). 2023. Accessed November 3, 2023. https://www.cvdprevent.nhs.uk/data-explorer?period=9&area=1&indicator=30
14. 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*. 2020;41(1):111-188.
15. Cegla J. National Institute for Health and Care Excellence guidelines for lipid management. *Heart*. 2023;109(9):661-667.
16. Kosmas CE, Muñoz Estrella A, Skavdis A, et al. Inclisiran for the treatment of cardiovascular disease: a short review on the emerging data and therapeutic potential. *Ther Clin Risk Manag*. 2020;16:1031-1037.
17. Khan SA, Naz A, Qamar Masood M, Shah R. Meta-analysis of inclisiran for the treatment of hypercholesterolemia. *Am J Cardiol*. 2020;134(20):69-73.
18. Arnold N, Koenig W. PCSK9 inhibitor wars: how does inclisiran fit in with current monoclonal antibody inhibitor therapy? Considerations for patient selection. *Curr Cardiol Rep*. 2022;24(11):1657-1667.
19. Desai NR, Farbaniec M, Karalis DG. Nonadherence to lipid-lowering therapy and strategies to improve adherence in patients with atherosclerotic cardiovascular disease. *Clin Cardiol*. 2023;46(1):13-21.
20. Nelson AJ, Pagidipati NJ, Bosworth HB. Improving medication adherence in cardiovascular disease. *Nat Rev Cardiol*. 2024;21:417-513.
21. Ostwald DA, Schmitt M, Peristeris P, Gerritzen T, Durand A. The societal impact of Inclisiran in England: evidence from a population health approach. *Value Health*. 2023;26(9):1353-1362.
22. Landmesser U, Haghikia A, Leiter LA, et al. Effect of inclisiran, the small-interfering RNA against proprotein convertase subtilisin/kexin type 9, on platelets, immune cells, and immunological biomarkers: a pre-specified analysis from ORION-1. *Cardiovasc Res*. 2021;117(1):284-291.
23. Padam P, Barton L, Wilson S, et al. Lipid lowering with inclisiran: a real-world single-centre experience. *Open Heart*. 2022;9:e002184.
24. Makhmudova U, Schatz U, Perakakis N, et al. High interindividual variability in LDL-cholesterol reductions after inclisiran administration in a real-world multicenter setting in Germany. *Clin Res Cardiol*. 2023;112:1639-1649.
25. Mulder JWCM, Galema-Boers AMH, Roeters van Lennep JE. First clinical experiences with inclisiran in a real-world setting. *J Clin Lipidol*. 2023;17(6):818-827.