



Medicine Optimisation Using PCSK9 Monoclonal Antibodies (Alirocumab and Evolocumab) Concerning the European Atherosclerosis Society (EAS) of < 1.8 mmol/l LDL Cholesterol Target in a Secondary Care Lipid Clinic

J Bolodeoku

Lipid Clinic, Department of Cardiology, Basingstoke and North Hampshire Hospital, Aldermaston Road, Basingstoke, Hampshire RG24 9NA

T Gbaa

Lipid Clinic, Department of Cardiology, Basingstoke and North Hampshire Hospital, Aldermaston Road, Basingstoke, Hampshire RG24 9NA

K Morris

Department of Clinical Biochemistry, Basingstoke and North Hampshire Hospital, Aldermaston Road, Basingstoke, Hampshire RG24 9NA

S Whitehead

Department of Clinical Biochemistry, Basingstoke and North Hampshire Hospital, Aldermaston Road, Basingstoke, Hampshire RG24 9NA

ABSTRACT

Background and Aims: Proprotein convertase subtilisin kexin type 9 (PCSK9) is an essential regulator of cholesterol metabolism. It was introduced as a monoclonal antibody to regulate LDL-R by recycling more LDLR onto the cell's surface. The clinically available PCSK9 monoclonal antibodies are alirocumab and evolocumab. This audit-based assessment aims to evaluate the impact of PCSK9 inhibitors on patient outcomes in achieving the European Atherosclerosis Society (EAS) recommended target for low-density lipoprotein cholesterol (LDL-C) levels (<1.8mmol/l) within a secondary care lipid clinic. **Methods:** This clinic-based, retrospective case note review assessed adults prescribed PCSK9i monoclonal antibodies from March 2017 to July 2022 at a secondary referral lipid clinic, following the ASC/EAS guidelines for LDL-C targets. All adults aged 18 years and above receiving PCSK9i (specifically, SCI Alirocumab or Evolocumab) were included, while patients not prescribed PCSK9i and those lacking calculated LDL-C measurements were excluded from the study. One hundred fifty-one patient files were assessed, and the most recent LDL-cholesterol data was compiled for 89 patients. Among these, 41 (47%) were male and 47 (53%) were female, aged 38 to 82. Age groups were categorised as follows: 38-46.6 years (8%), 46.6-55.2 years (22%), 55.2-63.8 years (20%), 63.8-72.4 years (25%), and 72.4-81 years (25%), with a mean age of 62.4 years. **Results:** The overall percentage of patients who achieved the ESC/EAS guideline-recommended LDL-cholesterol levels of <1.4 mmol/L and <1.8 mmol/L after adding PCSK9 monoclonal antibodies were 18% and

35%, respectively. 26 patients (29%) were at target (≤ 1.8 mmol/L), of which 24 (77%) were on Praluent (5 were on Praluent 75mg) whilst 7 (23%) were on Repatha 140mg. 58 patients [23 men and 35 women] (65%) were not at target (>1.8 mmol/L), of which 38 (77%) were on Praluent (8 were on Praluent 75mg) whilst 19 (33%) were on Repatha 140mg. Most of the patients on PCSK9mAb tolerated the injects. However, 11 (12%) of the 89 patients were switched from one PCSK9mAb to another and 9 (10%) were discontinued from being administered a PCSK9mAb for various reasons. **Conclusion:** This real-world study highlights the impact of PCSK9 monoclonal antibodies (mAb) on reducing LDL-C levels in dyslipidaemia patients. While acknowledging the potential differences in real-world patient responses compared to clinical trials due to individual variations in drug metabolism and genetics, these findings encourage healthcare providers to explore using these newer agents alongside or as an alternative to statins. This strategy effectively lowers LDL-C levels to meet guideline recommendations, ultimately reducing the risk of cardiovascular disease.

Keywords: LDL-cholesterol, PCSK9 Inhibitors, Alirocumab, Evolocumab, Secondary care lipid clinic, Monoclonal antibodies

INTRODUCTION

Cholesterol is crucial in maintaining normal cell function and is a precursor for producing steroid hormones and bile acids. Research has demonstrated that lowering LDL-C levels, typically achieved using statins, significantly reduces cardiovascular disease (CVD) events. Nevertheless, statin therapy alone proves insufficient in effectively lowering LDL-C levels for numerous patients, particularly those diagnosed with familial hypercholesterolemia. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an essential regulator of cholesterol metabolism. Based on its activity, its circulating concentrations could affect low-density lipoprotein cholesterol (LDL-C) levels by regulating Low-density lipoprotein receptor (LDL-R), it has been implicated as a genetic cause of familial hypercholesterolemia. Due to its role in the degradation and recycling of LDL-C receptor levels (Figure 1), it has been proposed and used as a newer lipid-lowering drug in the form of a monoclonal antibody inhibiting the activity of PCSK9. The action of these monoclonal antibodies is shown in Figure 1.

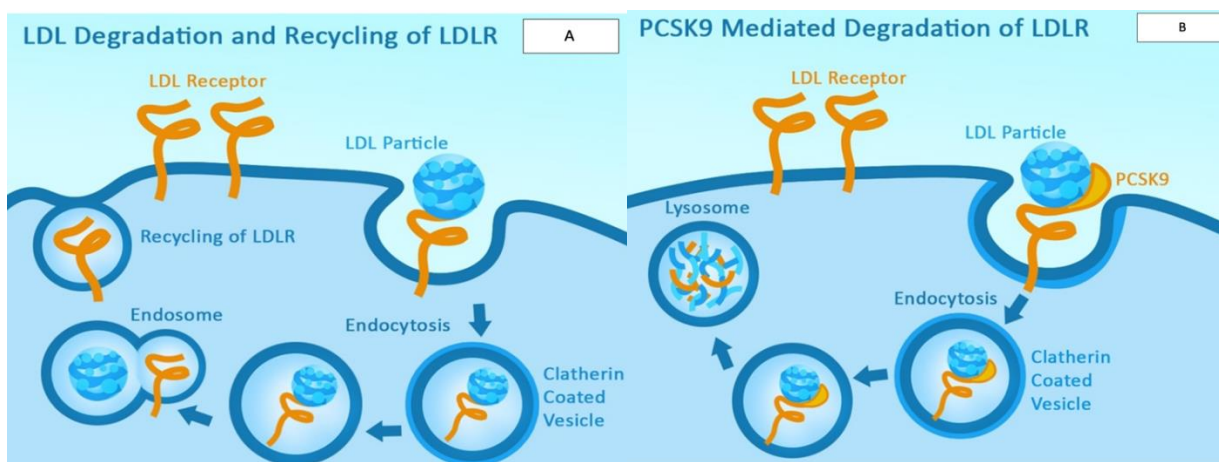


Fig 1: The degradation and recycling of LDLR

- A. The mechanism of the degradation and recycling of LDLR: LDLR binds the LDL particle through an endocytotic process, in which both the LDLR and LDL particle are separated in the endosome, and the LDLR is recycled back to the cell surface.
- B. PCSK9 binds both the LDLR and LDL particles, degrading them both without recycling LDLR back to the cell surface.

Monoclonal antibodies targeting PCSK9 (PCSK9mAb) have demonstrated the ability to reduce plasma LDL-C levels by approximately 60%, even in individuals already on maximum-dose statin therapy (Sabatine, 2018) (1). It has been shown that individuals with lower activity of PCSK9, due to monoclonal antibodies to PCSK9 or genetic polymorphism, have lower circulating LDL-C and a better cardiovascular disease risk (Ji and Lee, 2021) (2). Two injectable monoclonal antibodies are Alirocumab (Praluent®) and Evolocumab (Repatha®), currently prescribed by lipid specialists. PCSK9 mAbs have been introduced into our armamentarium of lipid-lowering treatments in getting our patients towards optimal treatment targets. A recent audit of PCSK9 mAbs and treatment targets showed that 46% of the patients achieved an LDL-cholesterol concentration of < 1.8 mmol/l and 24% of the patients achieved an LDL-cholesterol concentration of < 1.4 mmol/l (Suresh et al., 2022) (3).

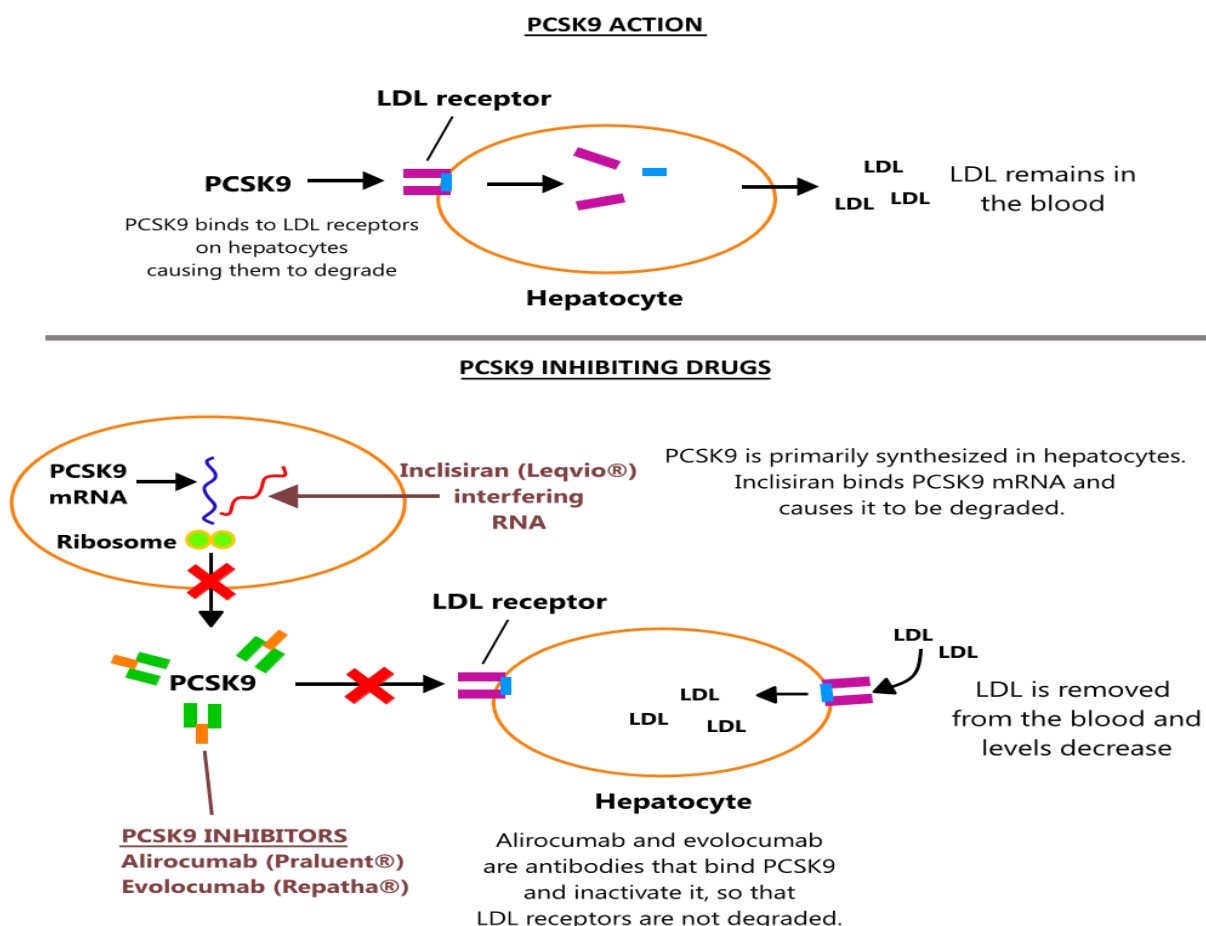


Fig 2: Mechanism of Action of Monoclonal Antibody Inhibitors Targeting PCSK9
PCSK9 Monoclonal antibodies (Alirocumab and Evolocumab) bind the PCSK9, freeing up more LDL-R receptors during the recycling to attach and remove excess LDL from the blood and circulation.

An earlier study showed a much higher number of 67.1% of patients achieving an LDL-cholesterol <1.8 mmol/l (Stoekenbroek et al. 2018) (4).

EAS Guidelines for LDL Cholesterol Targets

The lowering of the Atherosclerotic Cardiovascular disease (ASCVD) risk requires the effective reduction of LDL-C, which different clinical trials have established: ODYSSEY OUTCOMES and FOURIER trials for Alirocumab and Evolocumab, respectively (Schwartz et al., 2018; Sabatine et al., 2017) (5,6). The European Society of Cardiology/European Atherosclerotic Society (ESC/EAS) in 2019 proposed the targets of < 1.4 mmol/L and < 1.8 mmol/L for very high-risk and high-risk individuals in primary and secondary prevention lowering LDL-C by $\geq 50\%$ from the baseline. We started initiating PCSK9 monoclonal antibodies in the clinic in March 2017. We recently audited to determine how many patients have achieved ESC/EAS LDL-C treatment targets of < 1.4 mmol/L and < 1.8 mmol/L in high-risk and high-risk groups, respectively.

AIM

This audit-based case note review aims to evaluate the impact of PCSK9i on patient outcomes in achieving the European Atherosclerosis Society (EAS) recommended target for LDL-C levels within a secondary care lipid clinic.

METHODS

Design

This Clinic-based audit uses a retrospective case note review of adults prescribed PCSK9i monoclonal antibodies from March 2017 to July 2022. This is done at the tertiary referral lipid clinic.

Standards

This audit is based on the standards outlined by the ASC/EAS guidelines for LDL-C targets.

Cohort

All adults (≥ 18 years) who had been prescribed PCSK9is (SCI alirocumab or evolocumab). Patients not prescribed PCSK9i and those without calculated LDL-C measurements were excluded from the cohort.

Data Extraction

One hundred and fifty-one patients' case files were reviewed, and the most recent LDL-cholesterol was compiled from 89 patients, 41 (47%) males and 47 (53%) females with ages ranging from 38 – 82 years: 38 – 46.6 years (8%), 46.6 – 55.2 years (22%), 55.2 – 63.8 years (20%), 63.8 – 72.4 years (25%), 72.4 – 81 years (25%), with a mean age of 62.4 years.

Inclusion Criteria

The inclusion was patients ≥ 18 years old with LDL-C ≥ 3.5 mmol/L, patients who were statin intolerant, and patients not meeting LDL-C targets on other anti-lipids drugs (ezetimibe, bempedoic acid, Fibrates) and patients on PCSK9 inhibitors.

Exclusion Criteria

Patients not prescribed PCSK9i, and those lacking calculated LDL-C results, were excluded from the study.

Primary Outcome

The primary outcome was to lower LDL-C levels to meet the optimal EAS guidelines target of <1.8mmol/l in patients on PCSK9mAb (alirocumab and evolocumab).

Statistical Analyses

Categorical variables were reported as the number (percentage) of patients within each category.

RESULTS

Indications for PCSK9 Inhibitor Treatment

Patients administered with PCSK9i were thoughtfully chosen based on criteria such as their lipid panel, including total cholesterol and LDL-C levels not reaching optimal targets, as well as considerations of aminotransferases, creatine kinase levels, tolerability, and aversion to statins.

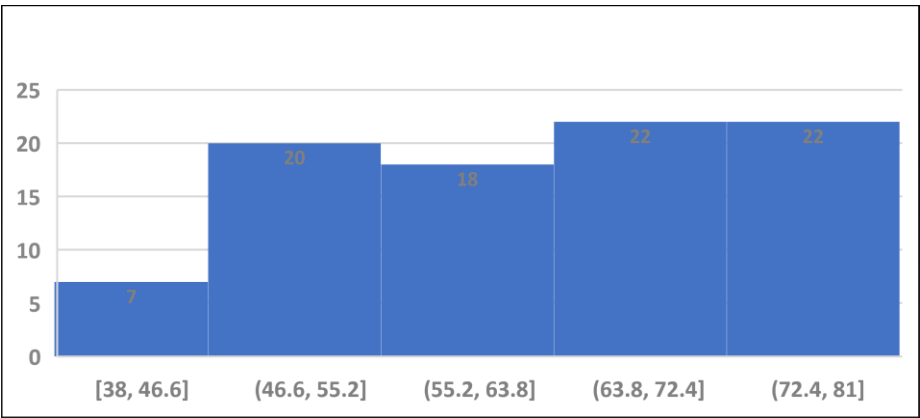


Fig 3: The demographics of patients on PCSK9 inhibitors

The bar chart illustrates the distribution of patients on PCSK9 across different age ranges, revealing a higher patient count in the older age category and a smaller representation in the younger age group.

The age range of 63- 81 comprised the bulk of the population who attended the lipid clinic, while the lowest number of individuals fell between 38 and 47 years (Figure 3). The timeframe for PCSK9 treatment in each group is shown in Table 1 below.

Table 1: Duration of PCSK9 Therapy and the Cohort of Patients

PCSK9 Treatment Duration (Years)	Number of Patients (%)
1	5(6%)
2	24(27%)
3	13 (15%)
4	4 (4%)
5	9 (10%)
6	15 (17%)
7	19 (21%)

The PCSK9 mAb treatment duration ranged from 1 to 7 years; the average PCSK9i treatment was 4.2 years.

The majority of patients (85%) had been referred with statin intolerance, and the remaining 15% had some statin resistance. Of the patients involved, 63 (71%) were on Praluent®, with 26 (29%) of the patients on Repatha: 16% were on Praluent 75mg administered subcutaneously every two weeks, 32% were on Praluent® 150mg administered subcutaneously every two weeks, 17% were on Praluent® 300mg administered subcutaneously every four weeks, while the remaining (35%) were on Repatha® 140mg administered subcutaneously every two weeks (Figure 4).

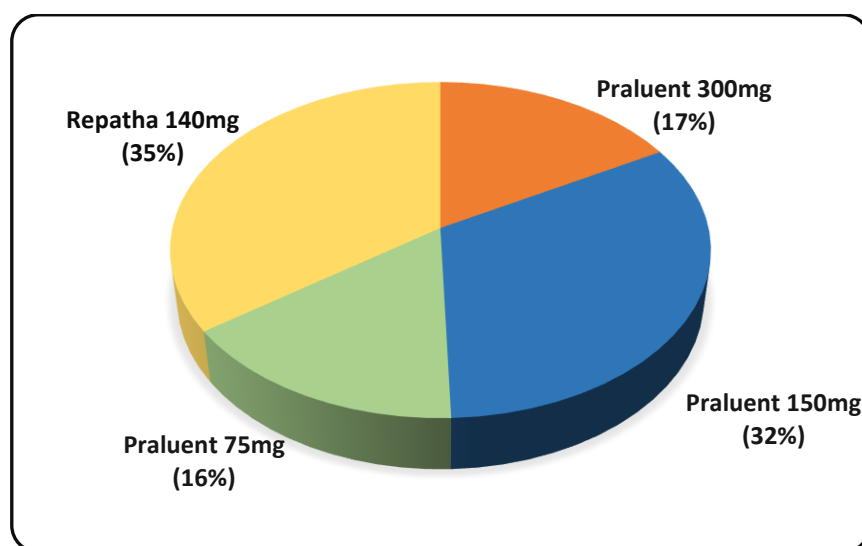


Fig 4: Proportion of Patients Receiving PCSK9 Inhibitors

65% of patients were placed on Alirocumab (praluent) with 16% on 75mg, 32% on 150mg, and 17% on 300mg, while 35% of patients were on Evolocumab (Repatha, 140mg).

We retrieved a referring total and LDL cholesterol value before commencing on the respective PCSK9 mAbs for 73 of the 89 patients. The LDL-C value was used to calculate the absolute reduction achieved. The LDL-C targets, according to the guidelines, are illustrated in Table 2.

Table 2: LDL-C treatment targets according to guideline recommendations

Guidelines	Target group	Treatment target
2019 ESC/EAS guidelines (7)	ASCVD±FH	LDL-C <1.4 mmol/L
2016 NICE guidelines (8)	All patients	LDL-C <1.8mmol/L
2019 ESC/EAS guidelines		
2019 NICE guideline for FH2ASCVD (8)	ASCVD or FH	≥50% LDL-C reduction
ASCVD=atherosclerotic cardiovascular disease; EAS = European Atherosclerosis Society; ESC = European Society of Cardiology; FH = Familial Hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; NICE = National Institute for Health and Care Excellence		

Efficacy

LDL-C values were estimated before the initiation of PCSK9i, showing no value falling <2mmol/L (Figure 5A). However, the LDL-C values retrieved post- PCSK9i treatment ranged

between 0.4 – 8.8 mmol/L, with a mean value of 2.5 mmol/L (Figure 5B). PCSK9i were effective, well-tolerated and safe for use by patients.

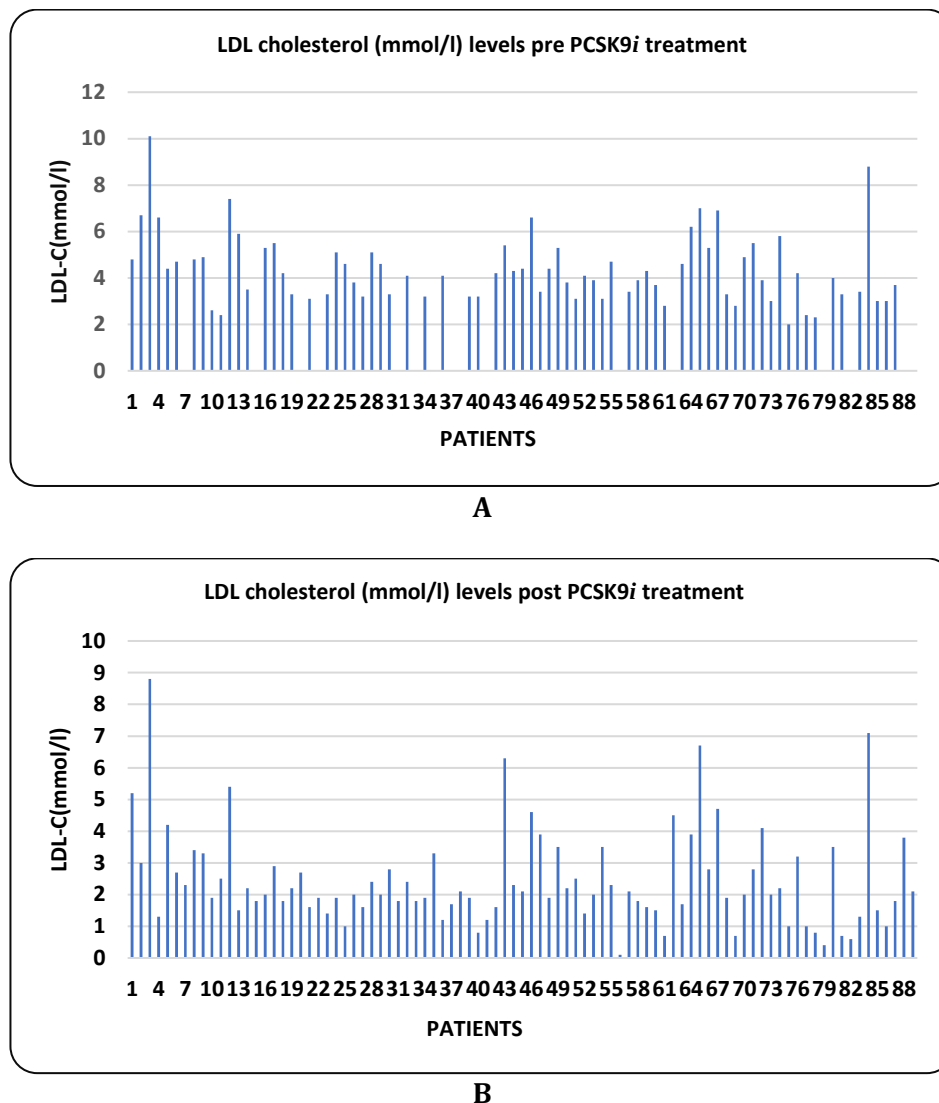


Fig 5 LDL-C concentration before treatment and post-treatment with PCSK9 inhibitor
 The graphs depict LDL-C concentration in patients before (A) and after (B) receiving PCSK9i treatment. There is a noticeable reduction in LDL-C levels following treatment with PCSK9 inhibitors. However, there was no apparent reduction in some patients using PCSK9i. LDL-C = low-density lipoprotein cholesterol; PCSK9 = Proprotein convertase subtilisin/kexin type 9

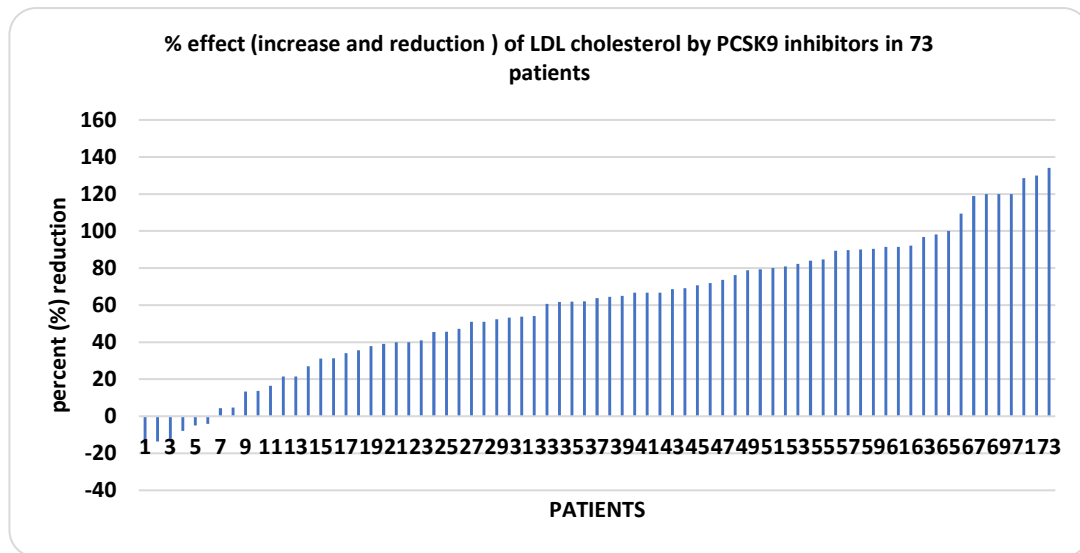
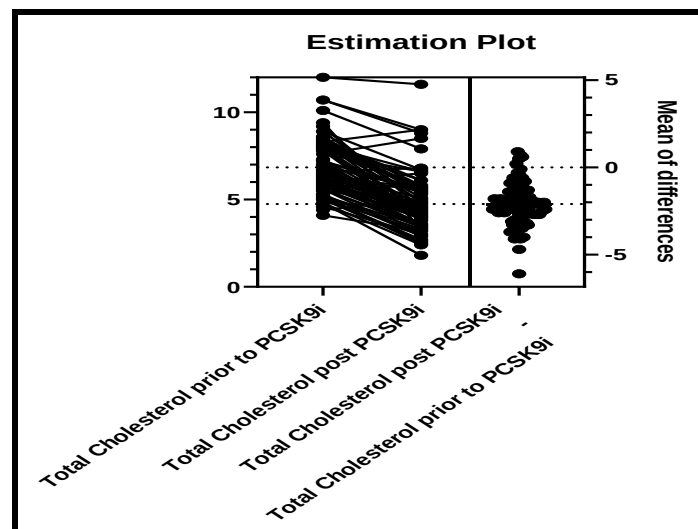


Fig 6: Percentage reduction of LDL-C using PCSK9 inhibitors

The graph shows a trend of reduction or increase of LDL-C using PCSK9i, with the highest reduction at 134%, while the greatest increase was 15%. LDL-C = low-density lipoprotein cholesterol

The overall percentage of patients who achieved the ESC/EAS guideline-recommended LDL-cholesterol levels of <1.4 mmol/L and <1.8 mmol/L after adding PCSK9 monoclonal antibodies were 18% and 35%, respectively. 26 patients (29%) were at target ($\leq$ 1.8 mmol/L), of which 24 (77%) were on Praluent (5 were on Praluent 75mg) whilst 7 (23%) were on Repatha 140mg. 58 patients [23 men and 35 women] (65%) were not at target ($>$ 1.8 mmol/L), of which 38 (77%) were on Praluent (8 were on Praluent 75mg) whilst 19 (33%) were on Repatha 140mg. The effect of PCSK9 mAbs on the patients' LDL cholesterol ranged from an increase of 15% observed to a reduction of 134%, as seen in Figure 6, with an average reduction in LDL-C of 60%.



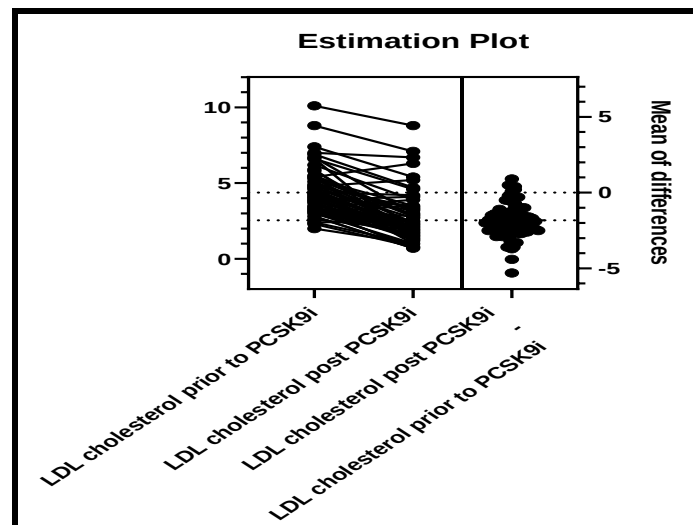


Fig 7: Estimate plot depicting Cholesterol and LDL-C Levels Pre and Post PCSK9 Inhibitor Administration. The plots show that total cholesterol and LDL-C values decreased after the administration of PCSK9I for each sample (A and B).

The total cholesterol estimation plot (Fig 7A) displays the decrease in cholesterol concentration after PCSK9 treatment. The mean differences (post PCSK9i - prior PCSK9i) fell within the range of -4 to 1 (mmol/l); for most individuals, the differences were around 3 mmol/l. Similarly, the LDL-C estimation plot (Fig 7B) showed a decrease in LDL-C concentration after PCSK9 treatment with a mean difference of -5 to 1 (mmol/l). Most individuals exhibited differences (post PCSK9i - prior PCSK9i) around 3 mmol/l, mirroring the patterns observed in total cholesterol. This indicates that PCSK9 has a similar proportional effect on total cholesterol and LDL-C levels.

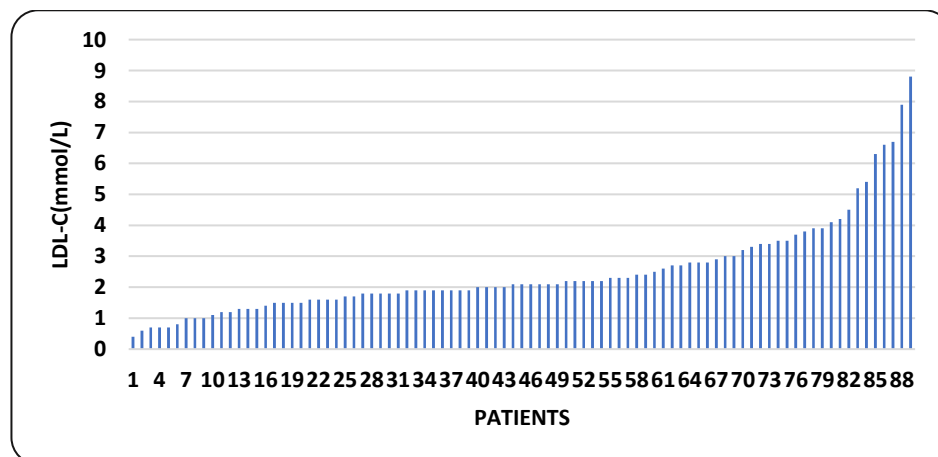


Fig 8: The concentration of LDL-C range in the patient population
The graph illustrates the LDL-C concentration, ranging from the lowest to the highest.

Tolerability

Most of the patients who were prescribed PCSK9mAb tolerated the injectables. However, 11 (12%) of the 89 patients were switched from one PCSK9mAb to another and 9 (10%) were discontinued from being administered a PCSK9mAb for various reasons, as listed in Table 3 below.

Table 3: LDL-C levels of patients and their adjustments toward the utilisation of PCSK9 inhibitors.

Patient Initials reason	LDL-C (mmol/l)	Switched		Discontinued
LB	5.2	√	√	Felt unwell
JS	8.8	√	√	Patient decision
MW	1.3	√	-	N/A
SS	3.4	√	√	Did not respond
AS	5.4	√	√	Limb pain, anxiety and tired
AS	1.8	-	√	Not known
CT	2.9	-	√	Headache and dizziness
LT	1.6	√	-	N/A
DM	3.4	√	√	Did not respond well
DT	6.3	-	√	Felt unwell
DF	2.3	√	-	N/A
CR	3.9	√	-	N/A
KW	4.5	√	-	N/A
DS	7.9	-	√	Refused self-injection
YA	3.8	√	√	N/A

DISCUSSION

The function of PCSK9 encompasses the regulation of not only LDL-R but also the process of lipogenesis (Ferri et al., 2012) (9). PCSK9 mAbs have transformed the management of dyslipidaemias, effectively reducing "bad cholesterol" LDL-C, which has significant cardiovascular implications. Using PCSK9 mAbs in our lipid clinic for eligible patients demonstrated the value of achieving an overall reduction in LDL-C levels over 8-12 weeks. However, some patients did not reach the optimal targets recommended by the ESC/EAS guidelines despite displaying a reduction in LDL-C. Specifically, some patients responded to PCSK9mAbs by lowering their LDL-C but did not attain the recommended target levels (<1.8mmol/l).

In this study cohort, which was an audit-based evaluation in our specialised lipid clinic, it was observed that only around 32% of the patients receiving PCSK9 mAbs met the recent LDL-C targets outlined by the ESC/EAS guidelines. Consequently, achieving the 2019 ESC/ PCSK9i administration was realised by 16 (18%) and 26 (35%) of the 89 patients, respectively. The impact of PCSK9 mAbs on LDL-C levels varied, with reductions ranging from 15% increase to a substantial 134% decrease, averaging a 60% decrease. This aligns with a study by Robinson et al. (2015) (10), which achieved a 59.5% to 62.0% reduction in LDL-C using alirocumab. Remarkably, 67 (92%) patients experienced a reduced LDL-C with PCSK9 mAbs, while only 6 patients (8.2%) exhibited a paradoxical increase. In comparison to a study by Suresh et al. (2022) (3), which also targeted LDL-C levels of <1.4 mmol/L and <1.8 mmol/L, our study fell short, achieving these goals in only 24.1% and 46.3% of patients, respectively. However, our study surpassed the 50% LDL-C reduction target, with 79.8% of patients achieving it.

Despite the effectiveness of PCSK9 mAbs in lowering lipid levels and their convenience, patients encountered various side effects, leading some to switch medications or discontinue treatment. These side effects included discomfort, limb pain, anxiety, headache, and personal choice. Among the 89 patients, 11 (12%) transitioned from one PCSK9 mAb to another, and 10 (11%)

discontinued treatment. PCSK9 did not affect the pharmacokinetics or pharmacodynamics of other orally administered medications, nor did it induce severe adverse effects due to interactions with other drugs. Nevertheless, it did cause discomfort and symptoms, with itching at the injection site and flu-like symptoms being the most frequently reported side effects (Cicero et al., 2014) (11). In our study, about 5% of patients had symptoms in conjunction with PCSK9 use, while 9.1% of patients had symptoms in a multicentre study at a secondary care lipid clinic by Bashir et al. (2022) (12). Patients experiencing these symptoms typically did not reach their optimal LDL-C targets, with the exception of three patients with LDL-C values of 1.3 mmol/L, 1.6 mmol/L, and 1.8 mmol/L. Although they had met their minimum LDL-C target, one patient decided to discontinue PCSK9 treatment, while the other two considered switching despite having already achieved their LDL-C targets. Most patients receiving PCSK9 mAbs tolerated the injections well, although 11 of the 89 patients (12%) changed from one PCSK9 mAb to another, and 9 patients (10%) discontinued the treatment. A study by Kohli et al. (2017) (13) compared two contrasting centres (University Hospital (UH) and District General Hospital (DGH)) and observed that PCSK9mAb was discontinued in 15% of patients (UH 7% vs DGH 25%), however an LDL-C of <2.0mmol/l was achieved by only 20% of patients. Our clinic adheres to the NICE recommendation for initiating PCSK9 therapy, particularly for statin-intolerant patients and those with an LDL-C threshold of ≥ 3.5 mmol/l. Prescriptions are sent from our clinic to the pharmacy, and PCSK9 injections are sent directly to patients at home. Patients are trained by authorised personnel for self-injection. Therefore, achieving the targets outlined in the EAS guidelines should be easily attainable, due to the convenience of this approach and the decreased frequency of use, unlike the oral lipid-lowering drug.

However, this audit had limitations, such as the inability to track patients' compliance with prescribed PCSK9 mAbs. Some patients missed follow-up appointments or failed to complete requested lipid panels before the next clinic visit. Additionally, the reasons for switching or discontinuing PCSK9 therapy could not be ascertained for some of the patients. Although patients had substantial distances to travel, many could have been eligible for drug delivery via a home care delivery service following treatment initiation. However, a new study is needed to investigate the potential advantages of such a service, as the necessary arrangements still need to be more efficiently established.

CONCLUSION

This real-world investigation has revealed the impact of PCSK9 mAbs on reducing LDL-C levels in patients with dyslipidaemia. Nevertheless, it is essential to recognise that real-world patient treatment can significantly differ from controlled clinical trials due to individual pharmacokinetics and pharmacogenomics variations when handling drugs. Moreover, intra- and inter-individual biological variations may influence the response to PCSK9i.

Nonetheless, these findings should encourage healthcare providers to consider using these newer agents in conjunction with statins or as an alternative for patients who cannot tolerate statins. This approach offers the overarching benefit of effectively lowering LDL-C levels to meet optimal levels of specific guideline recommendations, ultimately reducing the risk of cardiovascular disease.

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