PCSK9 inhibitors and treatment targets: an audit-based evaluation of a specialist lipid clinic

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Abstract

Background: Trial evidence for lower LDL cholesterol (LDL-C) treatment targets for cardiovascular benefit were incorporated into recent European Society of Cardiology/European Atherosclerosis Society and NICE guidelines. Treatment targets are LDL-C <1.4mmol/L, LDL-C <1.8mmol/L and ≥50% LDL-C reduction for atherosclerotic cardiovascular disease (ASCVD) and/or Familial Hypercholesterolaemia (FH). There is limited real-world evidence of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is), with enhanced LDL-C lowering, achieving these targets.

Aims: To assess attainment of guideline LDL-C targets using PCSK9is ± oral lipid-lowering therapies (LLT) in ASCVD and/or FH.

Methods: Clinic-based audit using retrospective case-note review of adults prescribed PCSK9is. Anonymised data were collected before and after PCSK9i initiation. Standards were attainment of LDL-C <1.8mmol/L, LDL-C <1.4mmol/L and ≥50% LDL-C reduction.

Results: Fifty-five patients (mean age 60.8 years) receiving PCSK9is (35% monotherapy; median treatment duration 1.5 years) were identified (ASCVD, n=50; FH, n=18). Target attainment was 80% for ≥50% LDL-C reduction, 46% for LDL-C <1.8mmol/L and 24% for LDL-C <1.4mmol/L. Greater attainment of these targets occurred with ≥2 additional LLTs versus one additional LLT or PCSK9i monotherapy.

Conclusion: Most ASCVD and/or FH patients achieved ≥50% LDL-C reductions with PCSK9is. Fewer achieved LDL-C <1.8mmol/L and <1.4mmol/L targets. PCSK9is in combination with other LLT achieved targets more often compared to PCSK9i monotherapy. Achievement of recommended lipid targets may require greater use of PCSK9i combination therapies.

Br J Diabetes 2022;**22**:30-35

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https://doi.org/10.15277/bjd.2022.342

Key words: PCSK9 inhibitors, low-density lipoprotein cholesterol, cardiovascular disease, familial hypercholesterolaemia, guideline targets

Background

Current lipid management guidelines for reducing risk of atherosclerotic cardiovascular disease (ASCVD) have incorporated recent clinical trial data, with recommendations advising lower LDL cholesterol (LDL-C) treatment targets. The 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines for patients with ASCVD recommend an LDL-C target of <1.4mmol/L (this is lowered from <1.8mmol/L detailed in 2016 guidelines) alongside an LDL-C target reduction of ≥50% from baseline.[1] By contrast, current NICE guidelines for secondary ASCVD prevention recommend a non-HDL cholesterol (non-HDL-C) target reduction of >40% from baseline, an absolute non-HDL-C target of <2.5mmol/L (which equates to LDL-C <1.8mmol/L) and, for patients with Familial Hypercholesterolaemia (FH), an LDL-C reduction target of ≥50% from baseline.[2]

Following lifestyle modification, lipid-lowering therapy (LLT) is initiated with a statin, followed by other oral medications (ezetimibe, fibrates and bile acid sequestrants) as required. The different lipid-lowering drug classes do have differing efficacy in lowering LDL-C. However, LDL-C targets are often not achieved due to reduced efficacy or tolerability issues with these oral medications, warranting a switch to subcutaneous injection (SCI) of PCSK9is . In ASCVD, NICE recommends initiating PCSK9i therapy in the case of LDL-C >4.0mmol/L (single cardiovascular event) or LDL-C >3.5mmol/L (recurrent cardiovascular events, polyvascular disease or comorbid FH).[2]

Enhanced LDL-C-lowering efficacy of PCSK9i therapy has been established in the ODYSSEY OUTCOMES and FOURIER trials for alirocumab and evolocumab, respectively.[3,4] Both studies showed significant reductions in LDL-C and cardiovascular event reduction in patients with ASCVD. Furthermore, intensive LDL-C lowering using PCSK9i therapy has been shown to reduce progression, and induce regression, of atherosclerosis and to improve cardiovascular outcomes.[5]

Despite strong evidence of benefit from PCSK9i clinical trials, there is limited evaluation in real-world clinical practice. Importantly, the 2019 ESC/EAS guidelines formally acknowledge the paucity of real-world evidence on attainment of LDL-C targets for very high-risk patients.[1]

Aims

The primary aim of this audit-based evaluation was to assess attainment of guideline-recommended LDL-C targets for patients with ASCVD and/or FH who were started on PCSK9i therapy due to intolerance of other LLTs.

The secondary aims were (i) to quantify the proportion of PCSK9i-treated patients requiring additional LLTs to achieve guideline targets and (ii) to assess the tolerability of PCSK9i therapy in real-world clinical practice.

Methods

Design

The audit used retrospective case-note review of patients prescribed PCSK9i therapy and was conducted in a single-centre tertiary referral lipid clinic.

Standards

Audit standards were attainment of three guideline-recommended LDL-C treatment targets (Table 1): LDL-C <1.8mmol/L, LDL-C <1.4mmol/L and ≥50% LDL-C reduction from baseline.

The cohort

All adults (≥18 years) who had been prescribed PCSK9is (SCI alirocumab or evolocumab), with or without other LLTs, between February 2020 and February 2021 were eligible for inclusion. Patients had to be on a stable PCSK9i-containing lipid-lowering regimen for at least four weeks prior to their most recent LDL-C measurement. All LLTs were prescribed according to NICE guidelines.[2] Patients without documented LDL-C measurements before or after initiation of PCSK9i therapy were excluded.

Data extraction

Electronic patient records from the lipid clinic were reviewed for patients' demographic, clinical and biochemical data. Clinical data included cardiovascular risk factors; ASCVD and FH diagnoses; lipid-lowering regimen and dosages used at the time of the most recent LDL-C measurement; and duration, indications and side effects of PCSK9i therapy. Biochemical data included LDL-C concentration before initiation of any LLT (pre-treatment) and after initiation of PCSK9i therapy (on-treatment). All data were anonymised.

Pre-treatment LDL-C concentration was defined as either a documented untreated LDL-C concentration (i.e. before initiation of any LLT), in line with ESC/EAS guidelines,[1] or, if unavailable, as the highest documented LDL-C concentration when on a non-PCSK9i-containing lipid-lowering regimen. On-treatment LDL-C concentration was defined as the most recent LDL-C measurement whilst being on a stable PCSK9i-containing lipid-lowering regimen for at least four weeks.

Statistical analyses

All analyses were descriptive. Data were summarised for all patients and stratified by number of additional LLTs used concomitantly with PCSK9is. Patients whose on-treatment LDL-C was above target (i.e. those ***not*** achieving the LDL-C target) were also grouped by number of additional LLTs used. Continuous variables were reported as mean ± standard deviation (SD) for parametric data and median (interquartile range [IQR]) for non-parametric data. Categorical variables were reported as number (percentage) of patients within each category.

Results

Patient characteristics

Electronic patient records of 55 patients receiving PCSK9is (median duration 1.5 [IQR 0.8, 2.9] years) were extracted. Of these patients, 90.9% had ASCVD, 32.7% had FH and 30.9% had both. One patient was excluded from target attainment and side effect analyses due to unavailable data. Mean ± SD age of all patients was 60.8 ± 12.9 years, and 58.2% were male. FH patients (n=18) were younger, with a greater proportion of women and fewer cardiovascular risk factors compared with the overall PCSK9i-treated cohort, although they were more likely to have a family history of ASCVD. Pre-treatment LDL-C concentration was higher in FH patients (median 6.5 [IQR 5.3, 7.6] mmol/L; n=18) than the overall PCSK9i-treated cohort (median 5.7 [IQR 4.9, 6.9] mmol/L; n=55).

Indications for PCSK9i therapy

The main indications for PCSK9i therapy were reported intolerances to other LLTs: high-intensity statins (83.6%), ezetimibe (38.2%) and fenofibrate (27.3%; Table 2). High-intensity statin therapy led to raised creatine kinase, alanine aminotransferase or aspartate aminotransferase in 25.5% of patients. Other indications included statin aversion (9.1%) and inadequate LDL-C lowering using oral lipid-lowering therapies (9.1%). Many patients (52.7%) had multiple indications.

Current lipid-lowering regimens

Of all patients on PCSK9i therapy (n=55), 65.5% received a PCSK9i

Table 1 LDL-C treatment targets according to guideline recommendations.

Guideline	Target group	Treatment target
2019 ESC/EAS guidelines[1]	ASCVD ± FH	LDL-C <1.4 mmol/L
2016 NICE guidelines[2]	All patients	LDL-C <1.8 mmol/L
2019 ESC/EAS guidelines[1] 2019 NICE guidelines for FH[2]	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.

Table 2 Indications for PCSK9i therapy.

Indications for PCSK9i therapy	Number (%)
High-intensity statin intolerance	46 (83.6)
Ezetimibe intolerance	21 (38.2)
Fenofibrate intolerance	15 (27.3)
Averse to statin therapy	5 (9.1)
Inadequate LDL-C lowering on oral lipid-lowering therapies	5 (9.1)
Colesevalem intolerance	3 (5.5)

n=55. LDL-C=low-density cholesterol; PCSK91=proprotein convertase subtilisin/kexin type 9 inhibitor

Table 3 Numbers of lipid-lowering therapies used among PCSK9i-treated patients.

Lipid-lowering therapies	Number (%)
PCSK9i monotherapy	19 (34.5)
PCSK9i + 1 additional LLT	21 (38.2)
PCSK9i + ≥2 additional LLTs	15 (27.3)

n=55. LLT = lipid-lowering therapy; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor.

in combination with oral LLT, with 38.2% on one additional LLT and 27.3% on two or more additional LLTs, and 34.5% received PCSK9i monotherapy (Table 3). Most common combinations included PCSK9i + ezetimibe (29.1%), PCSK9i + statin + ezetimibe (20.0%) and PCSK9i + statin (7.3%) (see Appendix 1 online at www.bjd-abcd.com). All patients (100.0%) with FH (n=18) received combination therapy, the most common being PCSK9i + statin + ezetimibe (38.9%). Alirocumab was almost always used (98.2%) over evolocumab (1.8%). Most common alirocumab dosages were 150mg every 2 weeks (61.8%) and 75mg every 2 weeks (32.7%) (see Appendix 2 online at www.bjd-abcd.com).

Treatment target attainment with PCSK9i therapy

Attainment of LDL-C <1.8 mmol/L (2016 NICE guidelines)

Irrespective of lipid-lowering regimen, the LDL-C <1.8mmol/L target was achieved in 46.3% of all patients (n=54; Figure 1). Among these patients, target attainment was high in those taking a PCSK9i + two or more additional LLTs (86.7%; n=15), and lower with one additional LLT (40.0%; n=20) or monotherapy (21.1%; n=19). In FH patients on a PCSK9i + two or more additional LLTs (n=9), attainment was approximately four times higher (88.9%) than those on one additional LLT (22.2%; n=9).

Attainment of LDL-C <1.4 mmol/L (2019 ESC/EAS guidelines)

Among all patients (n=54), attainment of the LDL-C <1.4mmol/L target was 24.1%, regardless of lipid-lowering regimen (Figure 1). Target attainment was higher in those taking a PCSK9i + two or more additional LLTs (60.0%; n=15) compared to one additional LLT (15.0%; n=20) or monotherapy (5.3%; n=19). Among FH patients, target attainment was approximately five times higher in those taking a PCSK9i + two or more additional LLTs (55.6%; n=9) compared to one additional LLT (11.1%; n=9).

Attainment of ≥50% LDL-C reduction from baseline (2019 NICE and 2019 ESC/EAS guidelines)

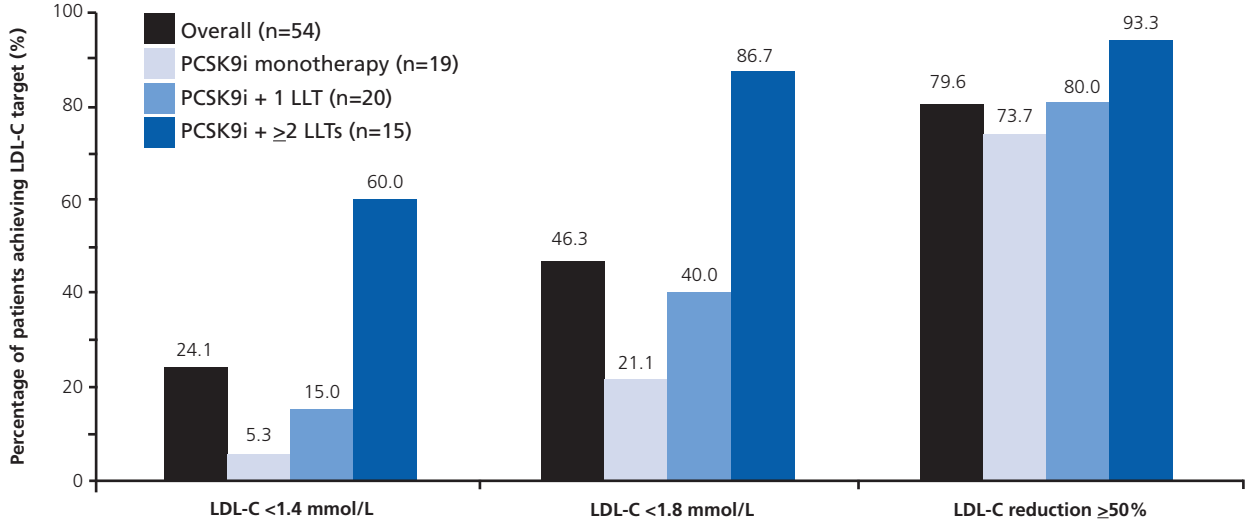
The ≥50% LDL-C reduction target was achieved in 79.6% of all patients (n=54; Figure 1), regardless of lipid-lowering regimen. Among all patients, target attainment was highest in those taking a PCSK9i + two or more additional LLTs (93.3%; n=15), followed by one additional LLT (80.0%; n=20) and monotherapy (73.7%; n=19; Figure 1).

Of the five patients (see table 2) who did not achieve adequate lipid-lowering on the maximum dose of lipid lowering therapy, four of the five achieved LDL targets of <1.8 and <1.4 mmol/L as well as >50% LDL reduction with the use of PCSK9i.

Lipid-lowering therapy use among target non-achievers

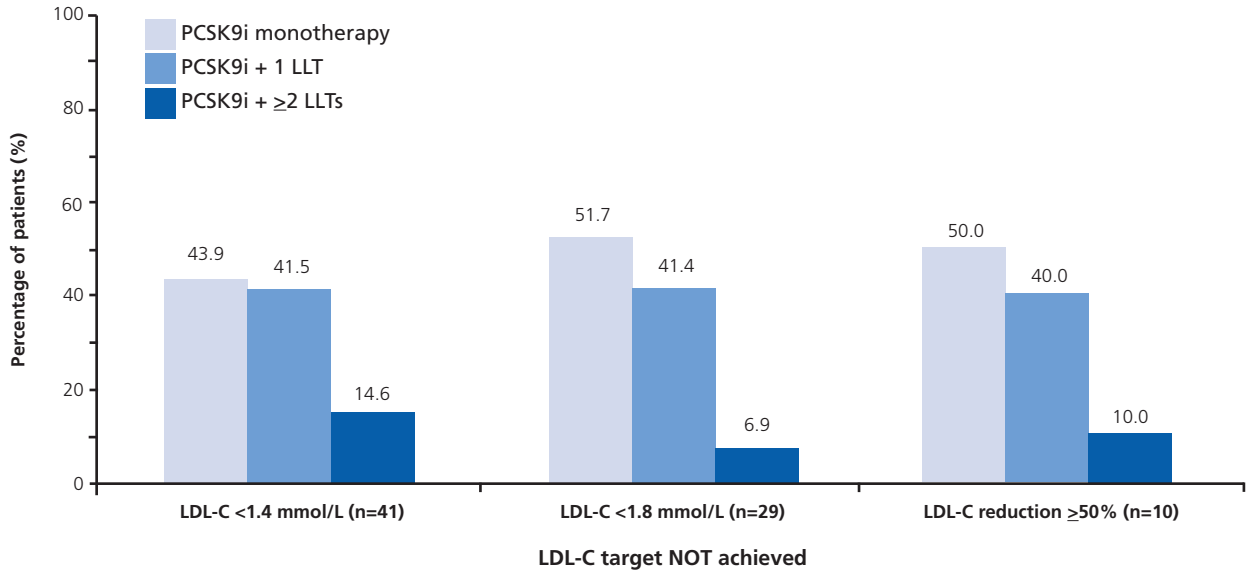
Of those patients who did not achieve the LDL-C <1.4mmol/L target (n=41), 43.9%, 41.5% and 14.6% were on PCSK9i monotherapy, one additional LLT and two or more additional LLTs, respectively (Figure 2). Similar patterns were seen for patients not achieving the LDL-C <1.8mmol/L target (n=29) and the ≥50% LDL-C reduction target (n=10).

Figure 1. LDL-C target attainment in PCSK9i-treated patients



LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor.

Figure 2. Proportion of PCSK9i monotherapy and combination therapy use among patients not achieving LDL-C treatment targets



LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor.

Table 4 PCSK9i side effects.

Side effects	Number (%)
Nasopharyngitis	4 (7.4)
Myalgia	2 (3.7)
Eczema	2 (3.7)
Gastrointestinal symptoms	1 (1.9)
Fatigue	1 (1.9)
Headache	1 (1.9)
Palpitations	1 (1.9)

n=54. PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor.

Tolerability of PCSK9i therapy

Of all patients (n=54), 14.8% experienced at least one side effect with PCSK9i therapy, and 5.6% experienced a side effect which led to a change in dosage, injection frequency or alternative PCSK9i drug choice. Side effects were mild, with none leading to permanent discontinuation of PCSK9i therapy. Most common side effects included nasopharyngitis (7.4%), myalgia (3.7%) and eczema (3.7%; Table 4).

Discussion

The present audit-based evaluation on treatment target attainment in real-world clinical practice showed that most patients attending a specialist lipid clinic with ASCVD and/or FH treated with PCSK9i therapy did not achieve the LDL-C targets recommended by current NICE and ESC/EAS guidelines. Overall, attainment of LDL-C <1.4mmol/L and LDL-C <1.8mmol/L was low, with only 24.1% and 46.3% of patients, respectively, achieving these targets. The ≥50% LDL-C reduction target, however, was achieved more often (79.6% of patients). Attainment of treatment targets increased with the number of additional, concomitant LLTs: attainment was lowest when taking PCSK9i monotherapy and greatest when taking two or more LLTs in addition to PCSK9is. Among patients not achieving targets, most were taking PCSK9i monotherapy or one additional LLT, with few taking two or more additional LLTs.

Real-world attainment of the LDL-C <1.8mmol/L target in our audit (46.3% overall) was lower than in many clinical trials,[6-8] despite comparable LDL-C-lowering efficacy (median LDL-C reduction was 65.2% overall in our audit). Differences in target attainment may result from a lower average trial baseline LDL-C (ranging from 3.2 to 4.2mmol/L)[6-8] compared to our audit (median 5.7mmol/L overall; 6.5mmol/L in FH patients) and greater use of combination therapy in these trials. ODYSSEY HIGH FH had a higher baseline LDL-C concentration (5.1 mmol/L), better reflecting the severity of dyslipidaemia in our tertiary referral lipid clinic, and showed lower (≤50%) attainment of the LDL-C <1.8mmol/L target, more consistent with our findings.[9]

Our audit is among the first to assess real-world attainment of LDL-C targets with PCSK9i therapy since the introduction of the 2019 ESC/EAS guidelines.[1] Importantly, we evaluate attainment of the more stringent LDL-C <1.4mmol/L target for patients at very high cardiovascular risk. Previous studies to do so include the DA VINCI study, which described LDL-C target attainment in 5,888 patients on LLT.[10] Among patients with very high cardiovascular risk receiving PCSK9i combination therapy (n=24), 67% and 58% achieved LDL-C targets of <1.8 and <1.4 mmol/L, respectively. This higher target attainment may be because all PCSK9i-treated patients were on combination therapy, whereas in our audit only 65.5% of

patients received PCSK9i combinations. In a retrospective analysis of PCSK9i-treated patients, attainment of LDL-C <1.8 and <1.4 mmol/L was 45.1% and 29.8%, respectively, overall (n=1,380) and 55.2% and 37.9%, respectively, in patients with ASCVD (n=855).[11] A retrospective study of 237 patients receiving PCSK9is in routine care found that 56.2%, 38.6% and 59.5% of patients achieved LDL-C targets of <1.8mmol/L, <1.4mmol/L and >50% reduction, respectively.[12] These lower levels of target attainment are similar to findings of our audit.

High baseline LDL-C concentrations in real-world practice often indicate that LDL-C targets of <1.8 and <1.4 mmol/L are unattainable using PCSK9i monotherapy. To reach these targets from a clinic median LDL-C baseline of 5.7mmol/L, reductions in LDL-C of 68.4% and 75.4%, respectively, would be needed. This would require a PCSK9i combined with a high-intensity statin, with or without ezetimibe, since PCSK9i monotherapy only results in ~60% LDL-C reduction from baseline.[1] The median 58.3% reduction observed with PCSK9i monotherapy in our audit led to low target attainment, with median on-treatment LDL-C concentrations of 2.5mmol/L. Although this reduction is comparable to high-intensity statin (atorvastatin 40/80mg, rosuvastatin 20/40mg) monotherapy, which reduces LDL-C concentrations by 48-55%,[2] it is not enough to achieve guideline-recommended targets. The additive LDL-C-lowering effects of concomitant oral LLTs may explain the higher target attainment with PCSK9i combination therapies. Hence, for patients on PCSK9i monotherapy who require further LDL-C lowering, ESC/EAS guidelines recommend PCSK9i combination therapy.[1] Our audit shows that this practice of using PCSK9i combinations with oral LLTs when above LDL-C targets was not always implemented, with ~40-55% of patients above targets still using PCSK9i monotherapy.

Several factors may contribute to ongoing use of PCSK9i monotherapy. Therapeutic inertia of physicians or reluctance of patients to take additional LLTs may be directly responsible. In real-world practice, patients miss appointments or blood tests for lipid screens (an issue exacerbated by the COVID-19 pandemic), meaning that prescribers cannot intensify or up-titrate lipid-lowering regimens. Moreover, patients may intentionally or unwittingly be non-adherent or run out of medication. The issue is further complicated by patient intolerances and aversion to oral LLTs, which restrict their concomitant use. Administrative hurdles due to strict criteria for PCSK9i eligibility[2] and monitoring costs may have made up-titration of PCSK9i dosage more difficult. By contrast, cost of adding oral LLT (statin +/- ezetimibe +/-fibrate) appears not to be a key factor, except for Omacor with a £28+ per month cost. PCSK9i monotherapy current costs are about £336-340 per month; with incremental costs of one LLT of about £2 per month and for two or more LLT about £2-4 per month.

A sustained absolute LDL-C reduction of 3.5mmol/L from a baseline of 7mmol/L can result in a 68% relative reduction in 10-year cardiovascular risk.[13] Hence, the median absolute LDL-C reduction of 3.7mmol/L (4.2mmol/L for FH patients) in our audit represents a substantial risk reduction. However, the very high baseline cardiovascular risk (10-year risk is usually >20%) in ASCVD patients means their absolute risk may still be high despite lipid modification.[12]

Key messages

- In real-world clinical practice, most patients with ASCVD and/or FH treated with PCSK9 inhibitor achieved guideline 50% LDL-C reduction, but fewer achieved guideline LDL targets <1.8 mmol/L and <1.4 mmol/L
- PCSK9 inhibitors are well-tolerated in patients previously intolerant to high-intensity statin therapy
- Patients receiving PCSK9 inhibitor +oral lipid lowering therapy combinations achieved guideline targets more often than those on PCSK9 inhibitor monotherapy
- Greater use of PCSK9 inhibitor + LLT combinations are needed in many patients to achieve guideline LDL targets

Reducing LDL-C to below 1.0mmol/L has been shown to reduce progression, and possibly induce regression, of atherosclerosis and to reduce risk of cardiovascular events.[6,7] Hence, to minimise absolute cardiovascular risk, greater LDL-C reductions to guideline-recommended targets are needed.

PCSK9i side effects were generally mild, and they occurred infrequently in our audit. Whilst 83.6% of patients were intolerant to high-intensity statin therapy, most commonly due to myalgia, only 5.6% of those prescribed PCSK9is experienced side-effects leading to a change in PCSK9i dosage, injection frequency or alternative PCSK9i drug choice, with no side effects resulting in permanent discontinuation of PCSK9i therapy. This may indicate that PCSK9is are well tolerated in patients previously intolerant to high-intensity statin therapy.

Limitations of this audit include a lack of adherence data. Some patients may have been non-adherent prior to their most recent LDL-C measurement (although it is likely patients were adherent due to strict NICE criteria for PCSK9i eligibility).[2] Furthermore, statin intensity was not quantified, despite LDL-C-lowering efficacy varying between 20-55% for different statin intensities.[2] The retrospective audit design meant that data were occasionally missing. For missing pre-treatment LDL-C values, the highest LDL-C concentration on a non-PCSK9i-containing lipid-lowering regimen was used, which may have underestimated pre-treatment concentrations.

Conclusions

In clinical practice, most patients with ASCVD and/or FH achieved LDL-C reductions of ≥50% on PCSK9i therapy. However, fewer patients achieved the LDL-C <1.8 mmol/L target, and even fewer achieved the LDL-C <1.4 mmol/L target, indicating that these absolute targets recommended by current NICE and ESC/EAS guidelines are difficult to achieve in clinical practice.

Patients on PCSK9i monotherapy were less likely to reach treatment targets compared to those taking PCSK9i combinations with other LLTs. Greater treatment target attainment occurred when taking two or more additional, concomitant LLTs versus one additional LLT. Among patients not achieving targets, around half were taking

PCSK9i monotherapy and ~40% were taking one additional LLT, with few taking two or more additional LLTs.

The current evaluation shows in routine practice that PCSK9is are well tolerated in patients previously intolerant to high-intensity statin therapy.

There needs to be greater use of combination therapies using injectable PCSK9is and additional concomitant LLTs in patients with ASCVD and/or FH who are above LDL-C target, to achieve both 2019 ESC/EAS and NICE guideline treatment targets.

Conflict of interest None.
Funding None.

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Appendix 1.

Oral lipid-lowering therapies in the PCSK9 inhibitor-treated group.

Lipid Lowering Therapies	*All patients (n=55)*
PCSK9i monotherapy	19 (34.5)
PCSK9i combination therapy	36 (65.5)
PCSK9i + 1 additional LLT	21 (38.2)
PCSK9i + statin	4 (7.3)
PCSK9i + ezetimibe	16 (29.1)
PCSK9i + Omacor	1 (1.8)
PCSK9i + ≥2 additional LLTs	15 (27.3)
PCSK9i + Ezetimibe + statin	11 (20.0)
PCSK9i + Ezetimibe + fenofibrate	1 (1.8)
PCSK9i + Ezetimibe + colesevelam	1 (1.8)
PCSK9i + Ezetimibe + Omacor	1 (1.8)
PCSK9i + Ezetimibe + statin + fenofibrate	1 (1.8)

Data presented as number (%) of patients.
Abbreviations: PCSK9= proprotein convertase subtilisin/kexin type 9; LDL-C= low-density lipoprotein cholesterol; ASCVD= atherosclerotic cardiovascular disease; FH= Familial Hypercholesterolaemia; PCSK9i =proprotein convertase subtilisin/kexin type 9 inhibitor.

Appendix 2.

Dose and type of PCSK9i used at the time of the most recent LDL-C measurement.

PCSK9i drug and dosage	*All patients (n=55)*
Alirocumab	54 (98.2)
75mg every 2 weeks	18 (32.7)
150mg every 2 weeks	34 (61.8)
150mg every 3 weeks	1 (1.8)
150mg every 4 weeks	1 (1.8)
Evolocumab	1 (1.8)
140mg every 2 weeks	1 (1.8)

Data presented as number (%) of patients.
Abbreviations: PCSK9= proprotein convertase subtilisin/kexin type 9; LDL-C= low-density lipoprotein cholesterol; PCSK9i=proprotein convertase subtilisin/kexin type 9 inhibitor; ASCVD=atherosclerotic cardiovascular disease; FH=Familial Hypercholesterolaemia.