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BRIEF REPORT

The Effect of PCSK9 Inhibitors on LDL-C Target Achievement in Patients with Homozygous Familial Hypercholesterolemia: A Retrospective Cohort Analysis

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ABSTRACT

Introduction: Achieving target low-density lipoprotein-cholesterol (LDL-C) levels remains challenging when treating homozygous familial hypercholesterolemia (HoFH). Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) are prescribed in addition to statins and ezetimibe, but patients' response varies and depends on residual low-density lipoprotein receptor (LDLR) function.

Methods: A multicenter, retrospective observational analysis evaluated LDL-C target achievement in response to PCSK9i treatment in 28 patients with HoFH from the Middle East/North Africa region. Effect of genotype was investigated. Demographic and clinical information was retrospectively obtained from medical records. Patient response to PCSK9i treatment was assessed by calculating percentage changes in lipid levels from pre-PCSK9i treatment baseline to most recent follow-up visit where patients were recorded as receiving PCSK9i on top of standard of care lipid-lowering therapies (LLTs; i.e., statins/ezetimibe) and assessing European Atherosclerosis Society (EAS) target achievement up to January 31, 2022. Lowest LDL-C level while receiving PCSK9i was identified.

Results: The cohort (n = 28) had a mean age (standard deviation; SD) of 22.8 (9.8) years (n = 28) and was 51% female (n = 27). Baseline LDL-C data were available in 24/28 (85.7%) patients (mean [SD] 14.0 [3.0] mmol/L). Median (interquartile range) duration of PCSK9i treatment was 12.0 months (4.0–19.1) months and mean (SD) % change in LDL-C after PCSK9i treatment was − 8.6% (12.1). LDL-C reduction from baseline was below 15% in 17/24 patients (70.8%). In the full cohort, mean (SD) minimum LDL-C during PCSK9i treatment was 11.9 (2.8; n = 28) mmol/L. No patient achieved EAS target LDL-C while receiving PCSK9i; genotype

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analysis suggested *LDLR*-null/null patients were most refractory to PCSK9i.
Conclusion: Response to PCSK9i was minimal in this cohort of patients with HoFH. No patients achieved EAS LDL-C targets, and most failed to reach the EAS-recommended 15% LDL-C reduction for PCSK9i therapy continuation. These results suggest additional LLTs are necessary to achieve LDL-C targets in HoFH.

Keywords: Homozygous familial hypercholesterolemia; Low-density lipoprotein; PCSK9i; Treatment targets

Key Summary Points

Why carry out this study?

Effective lipid-lowering therapy (LLT) is crucial to manage homozygous familial hypercholesterolemia (HoFH); however, achieving recommended target low-density lipoprotein-cholesterol (LDL-C) levels using commonly prescribed therapies such as statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 inhibitor(s) (PCSK9i) is challenging.

The recent 2023 European Atherosclerosis Society consensus statement for HoFH treatment recommends continual escalation of LLT to reach LDL-C target levels, but states that physicians should consider stopping PCSK9i-directed therapy if patients do not exhibit > 15% reduction in LDL-C levels after 1–2 doses of PCSK9i.

This retrospective analysis assessed the response to PCSK9i and LDL-C target achievement in a cohort of 28 patients with HoFH.

What was learned from the study?

PCSK9i provided insufficient benefit to this cohort of patients with HoFH in reducing LDL-C.

Target serum LDL-C levels were not reached and most patients failed to achieve > 15% reduction in LDL-C, particularly those with *low-density lipoprotein receptor*-null/null mutations.

INTRODUCTION

Homozygous familial hypercholesterolemia (HoFH) is characterized by substantially elevated LDL-cholesterol (LDL-C) from birth. Patients typically develop cardiovascular disease (CVD) in their second decade as aortic and supra-aortic stenosis [1–4], and their elevated cumulative total cholesterol exposure is associated with the incidence of early-onset major adverse cardiovascular events and associated death [5–7]. HoFH is rare, affecting 1 in 160,000–320,000 individuals, although prevalence is higher in countries with a founder effect and/or high consanguinity, such as those in the Middle East/North Africa region [8, 9]. The disease is commonly caused by mutations in the *LDLR* gene, affecting the function of the low-density lipoprotein receptor, LDLR [1, 4].

Reducing LDL-C levels is crucial to managing the disease. The recently updated European Atherosclerosis Society (EAS) consensus statement on HoFH states that LDL-C levels < 3.0 mmol/L (< 115 mg/dL) should be maintained for children, with thresholds of < 1.8 mmol/L (< 70 mg/dL) and < 1.4 mmol/L (< 55 mg/dL) suggested for adults and adults with atherosclerotic CVD (ASCVD), respectively [1]. The aim of treatment in HoFH is to achieve target levels of LDL-C at which atherosclerosis may be stabilized or even regress, but achieving these targets is challenging [2]. Standard-of-care pharmacotherapy for the treatment of HoFH typically involves the use of maximum dose statins and the cholesterol absorption inhibitor ezetimibe to provide an overall reduction in LDL-C of 30–40% [10–12].

Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) promote hepatic uptake of LDL-C by LDLR [13, 14], and clinical trials have shown their efficacy in reducing LDL-C levels and improving cardiovascular outcomes [15, 16]. The 2023 HoFH treatment EAS consensus statement recommends that PCSK9i are prescribed within 8 weeks of diagnosis as an add-on to statin and ezetimibe therapy [1]. However, given that their mechanism of action is dependent on LDLR function, there is evidence that PCSK9i do not lower LDL-C levels

effectively in patients with HoFH [17, 18]. In particular, the extent of residual LDL receptor activity seems to be an important determinant of PCSK9i efficacy, with a lack of effect reported in patients with HoFH who have *LDLR*-null/null mutations, in which residual LDLR function is almost completely absent [18]. As such, EAS treatment guidelines recommend physicians consider stopping PCSK9i-directed therapy if patients do not exhibit > 15% reduction in LDL-C levels after 1–2 doses of PCSK9i [1].

To date, limited data exists on LDL-C target achievement with PCSK9i in patients with HoFH. Thus, we investigated the real-world impact of PCSK9i on lipid levels and targets from a retrospective analysis of clinical cases involving patients with HoFH.

METHODS

Data Collection

This was a multicenter, observational, retrospective case series analysis of 28 patients with HoFH from the Middle East/North Africa region to assess the efficacy of PCSK9i treatment in achieving guideline-recommended LDL-C targets. Demographic and clinical information including locally measured plasma lipids were extracted from de-identified patient medical records from January 1, 2017 to January 31, 2022. Available details of concomitant lipid-lowering therapies (LLTs) were obtained, as were mutation and genotype information underlying HoFH. Mutations were assessed and classified as either *LDLR*-null or *LDLR*-defective according to information and standardized *LDLR* variant nomenclature recorded in publicly available databases, e.g., ClinVar (see Supplementary Material Tables S1 and S2 for further details).

Compliance with Ethics Guidelines

This analysis was conducted as a retrospective study of normal patient care, approved by the King Abdullah International Medical Research Center Institutional Review Board (IRB/2441/23). The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All patients provided written consent for their details to be published in the current report.

For pediatric patients, or in instances where patients died, consent was provided by patients' estates and/or living relatives.

Statistical Analysis

Descriptive statistics were employed in the conduct of this study, which were calculated using Microsoft Excel and GraphPad Prism version 9.3.1 (GraphPad Software, San Diego, California USA). No inferential statistics were necessary for this study. Changes in lipid levels attributable to PCSK9i treatment were calculated as percentage change from pre-PCSK9i treatment baseline to the most recent follow-up visit where patients were recorded as receiving a PCSK9i on top of standard of care therapy, i.e., statins/ezetimibe. Pre-PCSK9i treatment baseline levels were defined as those recorded at the last patient follow-up visit prior to PCSK9i treatment initiation. Where PCSK9i treatment was interrupted (n = 1), the lipid reading prior to the longest uninterrupted period of treatment was used as baseline. The lowest LDL-C level recorded while receiving PCSK9i was also identified. Duration of PCSK9i treatment was defined as being from PSCK9i treatment initiation to most recent follow-up visit where patients were recorded as receiving a PCSK9i without additional, non-standard of care, LLTs. As LDL-C targets differ for adult and pediatric patients with HoFH [10], patients were stratified by age into adult and pediatric cohorts, defined as aged ≥ 18 years and < 18 years at PCSK9i treatment initiation, respectively.

RESULTS

Patient Demographics

Table 1 summarizes the study population along with characteristics of the adult and pediatric patient subpopulations. The study population

Table 1 Patient characteristics

	Full cohort	Adult	Pediatric
Patients	28 (100)	16 (57)	12 (43)
Male/female	13/14* (46/51)	11/4* (69/21)	2/10 (17/83)
Body mass index, mean (standard deviation)	23.8 (6.5)	26.4 (6.6)	20.6 (5.0)
Age, years; mean (standard deviation)	22.8 (9.8)	29.3 (8.2)	14.3 (1.8)
Baseline LDL-C, mmol/L; mean (standard deviation)**	14.0 (3.0)	13.0 (2.8)	15.0 (3.0)
PCSK9i treatment duration, months; median (interquartile range)**	12.0 (4.0–19.1)	10.5 (2.9–12.5)	15.8 (10.9–24.0)
Patient genotype			
Null/null	13 (46.4)	7 (43.8)	6 (50)
Defective/defective	5 (17.9)	0 (0.0)	5 (41.6)
Unknown	10 (35.7)	9 (56.2)	1 (8.3)
Lipid-lowering therapies at PCSK9i treatment baseline			
Statin	28 (100)	16 (100)	12 (100)
Ezetimibe	28 (100)	16 (100)	12 (100)
Lipid apheresis	7 (25)	6 (37.5)	1 (8.3)

Data presented as number (percentage) unless otherwise stated

PCSK9i proprotein convertase subtilisin/kexin type 9 inhibitor, *LDL-C* low-density lipoprotein-cholesterol

*Sex of 1 patient not recorded

**Evaluated in patients where baseline data (see definition in "Methods") was available: 24/28 patients (full cohort); 12/16 adult patients and 12/12 pediatric patients. Note PCSK9i treatment duration $n = 23$ due to lack of treatment initiation data in 1 pediatric patient

comprised 28 patients, who had a mean age (SD) of 22.8 (9.8) years and was 51% female ($n = 27$). Baseline lipid measurements were available in 24/28 (85.7%) of patients. All patients were receiving statin and ezetimibe, and seven patients were receiving lipid apheresis at baseline; these treatments continued throughout the follow-up period without interruption (Table 1; see also Supplementary Material Table S1 for dosing). Mean (standard deviation, SD) LDL-C at baseline was 14.0 (3.0) mmol/L and was similarly elevated in adult and pediatric patients (Table 1). Median (interquartile range; IQR) duration of PCSK9i treatment was 12.0 (IQR 4.0–19.1) months; adult and pediatric patients received PCSK9i for a median (IQR) of 10.5 (2.9–12.5; $n = 12$) and 15.8 (10.9–24.0; $n = 11$) months, respectively. Mutation and genotype information was available for 18/28 patients (64.3%). Thirteen patients (46.4%) had an *LDLR*-null/null genotype and five patients (17.9%) had an *LDLR*-defective/defective genotype (Table 1). Detailed information regarding patient mutations is presented in Supplementary Material Table S2. A full list of patient characteristics is presented in Supplementary Material Table S1.

PCSK9i Treatment was Insufficient to Reach Recommended Treatment Targets

Figure 1a shows the percentage change from baseline in LDL-C levels after PCSK9i treatment, which was calculated for 24/28 patients for whom baseline lipid levels prior to PCSK9i initiation were available. The response to PCSK9i

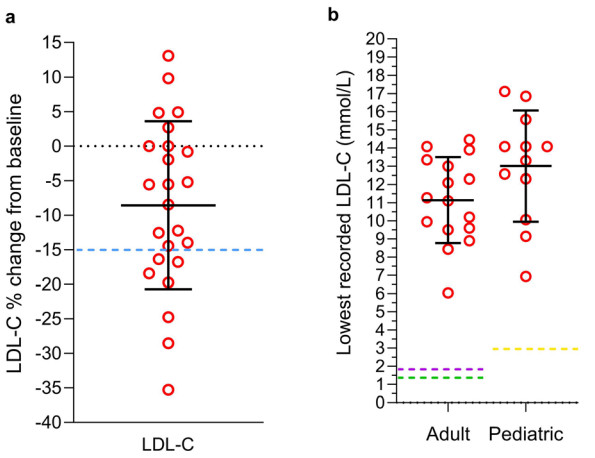

Fig. 1 Assessment of low-density lipoprotein cholesterol (LDL-C) in patients with homozygous familial hypercholesterolemia (HoFH) receiving proprotein convertase subtilisin/kexin type 9 inhibitor(s) (PCSK9i) treatment. **a** Individual % change in LDL-C from baseline in patients with HoFH receiving PCSK9i treatment (n = 24). Blue dashed line represents the European Atherosclerosis Society recommended minimum reduction in LDL-C of 15% for continuation of PCSK9i therapy. Error bars represent mean and standard deviation. **b** Lowest recorded LDL-C level in adult (n = 16) and pediatric (n = 12) patients with HoFH while receiving PCSK9i treatment. Adult and pediatric patients were defined as aged ≥ 18 and < 18 years at PCSK9i initiation, respectively. Error bars represent mean and standard deviation. Purple, green, and yellow dashed lines represent European Atherosclerosis Society guideline-recommended target LDL-C levels for adults (< 1.8 mmol/L), adults with atherosclerotic cardiovascular disease (< 1.4 mmol/L), and pediatric patients (< 3.0 mmol/L), respectively

was minimal, with a mean (SD) % change in LDL-C after PCSK9i treatment of − 8.6% (12.1; n = 24; Fig. 1a). Responses varied considerably across the cohort, with 5/24 patients (20.8%) showing increases in LDL-C from baseline while on PCSK9i and 2/24 (8.3%) showing no change from baseline (Fig. 1a).

In line with the minimal impact on LDL-C, there was only a marginal decrease in total cholesterol (mean [SD] − 7.0% [15.1]; n = 28) while the overall decrease in triglycerides approached 0% (mean [SD] − 0.9% [27.4]; n = 27). As would be expected, patients' HDL-C levels remained relatively stable (mean [SD] − 5.3% [19.4]; n = 28; Supplemental Material Fig. S1).

As recommended LDL-C targets differ for adult and pediatric patients with HoFH, we stratified the cohort into adult and pediatric subgroups (Fig. 1b). Lowest achieved LDL-C levels after PCSK9i were assessed in 16 adult patients with HoFH. No adult patient achieved the recommended LDL-C targets (2023 EAS consensus statement on HoFH guidance for management of adult patients with HoFH, < 1.8 mmol/L; or adult patients with HoFH with ASCVD, < 1.4 mmol/L) [1]. A similar trend was observed in the 12 pediatric patients, with none achieving LDL-C below the EAS-recommended target of 3.0 mmol/L. Overall, adult patients typically achieved lower LDL-C levels than pediatric patients after PCSK9i (mean [SD] 11.1 [2.4] vs. 13.0 [3.1]; Fig. 1b).

The 2023 EAS Consensus statement for HoFH recommends discontinuation of PCSK9i therapy if patients fail to achieve > 15% reduction in LDL-C after 1–2 doses of PCSK9i [1]. In this cohort, we found that 17/24 patients (70.8%) failed to achieve > 15% reduction in LDL-C after PCSK9i therapy (Fig. 1a). Interestingly, a larger proportion of adult patients failed to achieve > 15% reduction in LDL-C compared with pediatric patients (adults 10/12 [83.3%] vs. pediatric 7/12 [58.3%]).

HoFH Genotype Influences the Response to PCSK9i

Mutation and genotype information was available for 18 patients (Supplementary Material Table S2); baseline LDL-C data were available in 14 of these patients. Mean (SD) change in LDL-C in patients with *LDLR*-null/null mutations was − 4.7% (11.4; Fig. 2a), and the majority of these patients (7/9; 77.8%) failed to achieve > 15% reduction in LDL-C (Fig. 2a). Patients with defective/defective *LDLR* mutations were more responsive to PCSK9i with mean % change in LDL-C of − 19.6% (12.1; n = 5; Fig. 2a), with 2/5 (40%) failing to achieve > 15% reduction in LDL-C. In line with this, patients with *LDLR*-defective/defective mutations tended to achieve lower LDL-C levels after PCSK9i than those with *LDLR*-null/null mutations (mean [SD] lowest LDL-C: defective/defective,

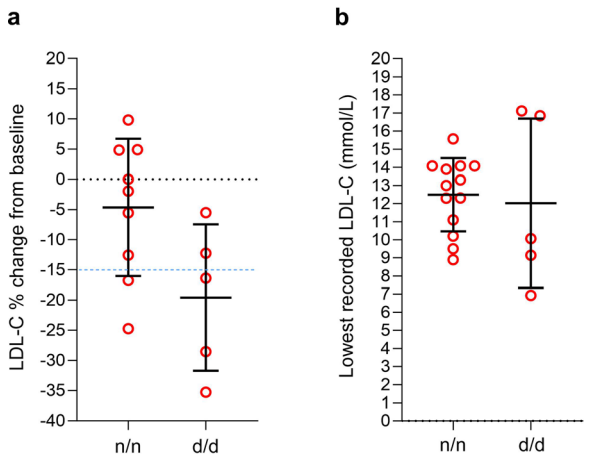

Fig. 2 Effect of patient genotype on changes in low-density lipoprotein cholesterol (LDL-C) after proprotein convertase subtilisin/kexin type 9 inhibitor(s) (PCSK9i) treatment PCSK9i. **a** Individual % change in LDL-C, calculated for 14 patients with homozygous familial hypercholesterolemia (HoFH) for whom genotype and baseline LDL-C data were available. Blue dashed line represents the European Atherosclerosis Society-recommended minimum reduction in LDL-C of 15% for continuation of PCSK9i therapy. **b** Lowest recorded LDL-C level in patients with HoFH for whom genotype data was available (null/null, $n = 13$; defective/defective, $n = 5$). Error bars represent mean and standard deviation. *n/n* null/null, *d/d* defective/defective

12.0 mmol/L [4.7]; null/null, 12.5 mmol/L [2.0]; Fig. 2b). Moreover, 3/9 and 1/9 patients (33.3% and 11.1%) with *LDLR*-null/null mutations recorded increases or no change in LDL-C from baseline, respectively, further suggesting that these patients are refractory to PCSK9i treatment.

DISCUSSION

This analysis showed that addition of PCSK9i elicited a marginal improvement in LDL-C levels in a cohort of patients with HoFH from the Middle East/North Africa region receiving statin and ezetimibe treatment. Patients with *LDLR*-null/null mutations were most refractory to PCSK9i, with a mean LDL-C reduction of around 5% from baseline. Reduction of LDL-C to within EAS guideline-recommended levels was not observed after PCSK9i in any of the patients in the cohort, and only a small proportion of patients achieved the > 15% reduction from baseline in LDL-C recommended by the current EAS guidelines for continuation of PCSK9i therapy.

The marginal response to PCSK9i observed in this real-world dataset (mean reduction from baseline in LDL-C of − 8.6%) is in contrast to the approximate average 20% reduction reported in patients with HoFH enrolled in the TAUSSIG trial, who were treated with evolocumab on top of conventional statin and ezetimibe therapy [17]. Given that response to PCSK9i is linked to patients' residual LDLR activity and previous studies have shown that patients with *LDLR*-null/null mutations show limited response to PCSK9i [18–21], a potential explanation for this is the high proportion (46.4%; 13/28) of patients in this analysis with *LDLR*-null/null mutations. In line with this, we found that patients with *LDLR*-null/null mutations were most refractory to PCSK9i, with either no change or increases in LDL-C observed in just under half (4/9; 44%) of these patients for whom baseline LDL-C data was available. Eight of these nine patients (and 11/13 [85%] of those with mutation data) had the c.2027delG: p.G676fs *LDLR* mutation (see Supplementary Material Table S2), which leads to a recurrent frameshift and truncation of the LDLR protein [22]. This variant has been reported previously in several unrelated individuals from Saudi Arabia and its presence in this Saudi-predominant patient cohort supports that it is a variant of high prevalence in this region [22]. The variant has also previously been reported as linked to statin resistance [23], supporting its potential role in PCSK9i resistance. However, it should be noted that we observed considerable heterogeneity in response to PCSK9i even within *LDLR*-null/null patients, with percentage change in LDL-C ranging from a reduction of − 24.8% to an increase of 9.8% from baseline (see Fig. 2). Of note, the best response to PCSK9i (− 24.8%) was recorded in a patient who did not possess the c.2027delG:p.G676fs *LDLR* mutation, which further suggests patients with this mutation could be more refractory to PCSK9i treatment. A previous study by Thedrez et al. [19] has also reported considerable

variability in LDLR cell-surface expression among patients with identical genetic defects.

The present study is timely, given the recent update from the EAS on the treatment of HoFH [1]. In a new recommendation, the 2023 EAS statement suggests that PCSK9i should be the first adjunctive treatment trialed in patients with HoFH if LDL-C treatment goals are not achieved with statins plus ezetimibe [1]. In the present study, the patients' treatment was in-line with this recommendation, and it is noteworthy that the duration of PCSK9i treatment was relatively lengthy (median 12.0 months; IQR 4.0–19.1). The updated guidelines also recognize the variable efficacy of PCSK9i in HoFH by recommending that treatment be discontinued if at least a 15% reduction in LDL-C is not observed after 1–2 doses, with addition of LDLR-independent therapies such as lomitapide or angiopoietin-like 3 (ANGPTL-3)-directed therapy (e.g., evinacumab) suggested should patients fail to reach LDL-C goals on PCSK9i. Lomitapide has been shown to reduce patients' LDL-C by 50–68.2.% [24–26] and evinacumab can reduce it by 47.1% [27]. Moreover, achieving LDL-C targets with these treatments has been documented in their respective phase 3 studies; 28% of patients achieved target LDL-C < 70 mg/dL (< 1.8 mmol/L) while receiving evinacumab [27], as did 28% and 58% of patients receiving lomitapide at week 26 and up to week 256, respectively [28]. More recently in a large real-world pan-European retrospective study, 29% of patients receiving lomitapide achieved LDL-C < 70 mg/dL (< 1.8 mmol/L) [26].

The present study adds support to the pragmatic approach outlined in the recent EAS statement given that PCSK9 inhibitors are widely available but of variable effect in HoFH. Moreover, since no patients achieved LDL-C levels within the EAS-recommended targets, our data support the addition of lomitapide or ANGPTL3-directed therapy to attempt to push LDL-C levels within targets. Of note, the lack of EAS target level achievement in the present study is similar to a previous study of 66 patients with FH from China, including 26 patients with HoFH, where less than 5% of patients with HoFH achieved treatment goals [21]. Similarly, a recent retrospective review of patients from the Middle East/North Africa with HoFH revealed that the majority of patients fail to reach LDL-C targets despite receiving LLTs such as statins, ezetimibe, PCSK9i, and apheresis [3].

HoFH remains an underdiagnosed and undertreated condition, which makes early initiation (preferably in childhood) of effective LLTs crucial [1]. Despite this, a recent registry study by Tromp et al. [29] reported that diagnosis typically occurs after the first decade, highlighting the need for improved initiatives to diagnose the condition. Tromp et al. [29] also reported that LDL-C target achievement was attained in 53% of patients who were receiving five LLTS, which decreased to 18.9% and 16.7% of patients who were receiving four and three LLTS, respectively. Our data reflects these observations, where the addition of PCSK9i to the treatment regimen of patients with HoFH is insufficient to bring LDL-C levels within the EAS-recommended targets [2], and highlights that addition of LLTs other than PCSK9i to the treatment regimen of such patients may be necessary to push LDL-C levels within targets.

This analysis has some limitations. First, the follow-up time was not standardized, meaning patients received PCSK9i for different durations. Second, several patients received concomitant LLTs such as plasma apheresis and the effect of these on the results cannot be excluded. Finally, the retrospective nature of the analysis and the small cohort size limited the study to reporting descriptive statistics and necessitates that the data should be interpreted with caution.

CONCLUSION

This analysis suggests that addition of PCSK9i to the treatment regimen of patients with HoFH results in only marginal improvements in LDL-C levels that are insufficient to achieve recommended targets. There is a need to escalate LLT to effectively manage HoFH. Adjunctive LLTs that act independent of LDLR and robustly reduce LDL-C levels are needed to bring LDL-C within target levels for the majority of patients with HoFH.

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Data Availability. The datasets generated during and/or analyzed during the current analysis are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Awad Alshahrani has no competing interests to declare. Mutaz Al-Khnifsawi has received honoraria from Amryt. Moeber Mahzari has no competing interests to declare. Naji Kholaif has received honorarium from Amryt, Novartis and Amgen. Hawazen Zarif has received honoraria from Amryt.

Ethical Approval. This analysis was conducted as a retrospective study of normal patient care, approved by the King Abdullah International Medical Research Center Institutional Review Board (IRB/2441/23). The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All patients provided written consent for their details to be published in the current report. For pediatric patients, or in instances where patients died, consent was provided by patients' estates and/or living relatives.

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