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# Real-world lipid outcomes after switching PCSK9-targeting therapies in heterozygous familial hypercholesterolemia: the SHIFT-FH study

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**Real-world lipid outcomes after switching PCSK9-targeting therapies in heterozygous familial hypercholesterolemia: the SHIFT-FH study**

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**ABSTRACT**

**Background** Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition represents a cornerstone of lipid-lowering therapy in heterozygous familial hypercholesterolemia (HeFH). Monoclonal antibodies (mAbs) and small interfering RNA (siRNA) targeting PCSK9 provide complementary therapeutic strategies; however, real-world data comparing lipid outcomes and target achievement after switching between these treatments remain limited.

**Methods** The SHIFT-FH study was a retrospective real-world cohort study including genetically confirmed HeFH patients receiving maximally tolerated lipid-lowering therapy and stable PCSK9 monoclonal antibody treatment for ≥6 months. According to routine clinical practice, patients either switched to siRNA therapy (inclisiran; Group 1) or continued monoclonal antibody therapy (Group 2). The primary outcome was achievement of guideline-recommended LDL-C targets at 6 and 12 months. Secondary outcomes included changes in lipid parameters and hepatic safety.

**Results** Forty-eight patients were included (22 in Group 1 and 26 in Group 2; mean age 59.3 ± 12.8 years). At baseline, LDL-C target achievement was lower in patients subsequently switched to siRNA therapy (36.4% vs 80.8%; $p = 0.002$). At 12 months, target attainment remained lower in Group 1 (22.7% vs 53.8%). Switching to siRNA therapy was associated with a moderate increase in LDL-C levels (Δ +29.6 ± 37.4 mg/dL; $p = 0.003$), whereas lipid levels remained stable in patients continuing monoclonal antibody therapy. Exploratory analysis suggested a trend toward an inverse association between baseline LDL-C levels and target achievement at follow-up. Liver enzymes remained within the normal range in both groups.

**Conclusions** In this real-world cohort of genetically confirmed HeFH patients, LDL-C target achievement was strongly influenced by baseline lipid burden and differed across therapeutic pathways. Switching between PCSK9-targeting strategies may influence long-term lipid control, highlighting the importance of individualized, target-oriented lipid management.

## 1. Introduction

Heterozygous familial hypercholesterolemia (HeFH) is a genetic disorder characterized by lifelong elevation of low-density lipoprotein cholesterol (LDL-C), leading to a markedly increased risk of premature atherosclerotic cardiovascular disease (ASCVD) (1) with a prevalence of 1 in 220 individuals worldwide, recognized as the most common hereditary lipid disorder (2), that often remains underdiagnosed and undertreated (3). Despite maximally standard lipid lowering therapy (LLT) with statins and ezetimibe, a significant percentage of HeFH patients fail to achieve recommended LDL-C goal (4). The 2025 ESC/EAS Guidelines for the management of dyslipidaemias highlight the need for early and intensive LDL-C lowering in HeFH classified as high-risk patients, advocating the stepwise combination of high-intensity statins, ezetimibe, and PCSK9 inhibitors (5). Two clinically validated pharmacologic strategies targeting PCSK9 are currently available: monoclonal antibodies (mAb), which neutralize circulating PCSK9, and small interfering RNA (siRNA), which suppress hepatic PCSK9 synthesis (6). Both approaches have demonstrated substantial LDL-C reductions and cardiovascular benefit in randomized trials (7-12); however, real-world comparative evidence remain limited. In clinical practice, treatment selection relies on both patient preferences and clinician judgment, the latter being primarily informed by the patient's adherence, overall compliance, and quality of life, with the additional aim of minimizing dosing frequency whenever appropriate.

Early observational studies have explored inclisiran use in mixed cardiovascular populations, reporting consistent LDL-C reductions but variable results when compared indirectly with mAb therapy (13, 14). Nevertheless, these investigations did not specifically target individuals with HeFH and offered only a limited appraisal of hepatic safety. In addition, the preponderance of available evidence stems from short-duration studies or methodologically heterogeneous cohorts, without

addressing treatment persistence or switching behaviours within real-world clinical practice settings.

To the best of our knowledge, no prior investigation has specifically described lipid outcomes and hepatic safety in real-world HeFH patients undergoing to different PCSK9 inhibition strategies, including treatment switching. Accordingly, the present study was aimed to provide pragmatic real-world data on lipid profile evolution and hepatic safety in HeFH patients managed with different PCSK9 inhibition strategies in routine clinical practice.

## 2. Methods

The SHIFT-FH study (SwItcHing between pcSk9-targeting Therapies in Familial Hypercholesterolemia) was designed as a retrospective real-world cohort study, conducted and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist (15). Between 2023 and 2025, within the framework of the LIPIGEN network, a national project on familial dyslipidaemia (16), medical records of patients attending the lipid clinic of Federico II University Hospital were retrospectively reviewed to identify individuals with very high levels of LDL-C (above the 95th percentile compared with a sex- and age-matched general population), normal triglyceride (TG) levels, and presumed autosomal dominant transmission of hypercholesterolemia (Dutch Lipid Clinic Network score >6).

### 2.1 Study population

The major inclusion criteria were: genetically confirmed diagnosis of HeFH (presence of a single pathogenic variant in FH-causative genes) and stable treatment with a PCSK9 monoclonal antibody (alirocumab or evolocumab) for at least six months prior to data review, on top of LLT. Genetic confirmation of HeFH was obtained through molecular testing performed by analyzing the main genes associated with familial hypercholesterolemia (*LDLR*, *APOB*, *PCSK*9, LDLRAP1 and *APOE*) by next-generation sequencing using the Devyser FH v2 kit (Devyser, Sweden) for target enrichment as previously described (16, 17). Exclusion criteria included: age <18 years; inability to understand or provide informed consent; moderate hypertriglyceridemia (TG>300 mg/dL); active hepatic or inflammatory disease; history of liver enzyme elevation >3× the upper limit of normal (ULN); end-stage kidney disease (estimated filtration rate <15 mL/min/m²); secondary causes of hypercholesterolemia (e.g., hypothyroidism, hormone therapy, corticosteroid use); diabetes mellitus with HbA1c >7.0% (18), discontinuation of LLT during the observation period; incomplete follow-up data; and clinical or familial evidence of familial combined hyperlipidaemia. Due to the

retrospective nature of the study and the real-world setting, the sample size was not predetermined; all consecutive eligible patients attending the lipid clinic during the study period were included.

**2.2 Study Protocol**

Following the acquisition of informed consent, comprehensive medical history was obtained from existing clinical records for each patient. Retrospective data encompassed demographic variables (age, sex), vascular risk factors (smoking status, hypertension, diabetes mellitus), concomitant clinical conditions, and both last follow-up and prior LLT data.

Biochemical data on lipid parameters [total cholesterol (TC); LDL-C; high density lipoprotein cholesterol (HDL-c); TG] and hepatic necrosis markers [aspartate aminotransferase (AST), and alanine aminotransferase (ALT)] were retrospectively retrieved at baseline (T0), 6 months (T1) and 12 months (T2), when available. Analyses at each follow-up timepoint were conducted exclusively on the available paired measurements; consequently, the number of patients included in the evaluations differed across timepoints.

Given the retrospective nature of the study, patients were classified according to the therapeutic pathway followed in routine clinical practice. One group switched to PCSK9-targeting siRNA therapy (inclisiran 284 mg, following the standard dosing schedule at day 1, month 3, and every 6 months thereafter), whereas the other continued treatment with PCSK9 monoclonal antibodies (alirocumab 150 mg or evolocumab 140 mg was administered every 14 days according to approved dosing schedules). Following eligibility screening, enrolled patients were classified into two groups according to the therapeutic pathway observed in routine clinical practice. Group 1 (G1) included patients who switched from PCSK9 monoclonal antibody therapy (alirocumab or evolocumab) to small interfering RNA therapy (inclisiran), while Group 2 (G2) included patients who continued

PCSK9 monoclonal antibody treatment. Baseline (T0) was defined as the last available clinical and biochemical assessment preceding treatment switching for G1, or the corresponding timepoint during ongoing PCSK9 monoclonal antibody therapy for G2. Treatment allocation was not randomized. The decision to switch was based on clinician judgment and patient preference, primarily aimed at reducing treatment burden and improving long-term adherence. Accordingly, differences in baseline lipid control between groups were expected and were considered in the interpretation of follow-up findings.

**2.3 Outcomes and statistical analysis**

The primary outcome was the proportion of patients achieving LDL-C targets according to the 2025 ESC/EAS Guidelines at 6 and 12 months (T1 and T2) (19). In accordance with guideline recommendations, LDL-C targets were defined as <55 mg/dL for very high-risk patients and <70 mg/dL for high-risk patients (19). Patients were classified according to their individual cardiovascular risk profile as defined by the ESC/EAS guidelines (19). Secondary outcomes included changes in lipid parameters (LDL-C, HDL-C, TC, TG) and hepatic safety based on variations in AST and ALT. All data were retrospectively extracted from electronic medical and laboratory records. Continuous variables were summarized as mean ± standard deviation (SD) or median (interquartile range, IQR), and categorical variables as counts and percentages. Normality was assessed using the Shapiro–Wilk test. Between-group comparisons were performed with Student's t-test or Mann–Whitney U test, as proper. Within-group comparisons used paired t-test or Wilcoxon signed-rank test. Categorical variables were analysed using chi-square or Fisher's exact test. A two-tailed p-value <0.05 was considered statistically significant. No imputation of missing data was performed. Given the retrospective real-world design, analyses at each follow-up timepoint were conducted using a complete-case approach including only patients with available paired biochemical measurements. Comparisons of target achievement between groups were conducted using tests

for independent proportions, as treatment allocation defined the groups rather than paired observations. Changes in target status over follow-up were assessed by examining the proportion of patients transitioning between categories and illustrated through a Sankey diagram representing these variations. Due to the small sample size, the retrospective design and the clinically driven treatment allocation, no propensity score-based adjustment was applied, as it was deemed inappropriate for the study objectives. An exploratory univariate logistic regression analysis was performed to assess the association between baseline LDL-C levels and LDL-C target achievement at T2 for G1. All statistical analyses and graphical representations were performed using R software (R Foundation for Statistical Computing, Vienna, Austria; version 4.5.2) within the RStudio environment.

## 3. RESULTS

A total of 228 patients were screened for eligibility for inclusion in the SHIFT-FH study cohort. Of these, patients were excluded according to predefined criteria: 73 for Dutch Lipid Clinic Network score <6, 18 for diabetes mellitus with HbA1C > 7%, 48 for combined hyperlipidaemia with hypertriglyceridemia, 29 for secondary hypercholesterolemia, and 12 for a history of malignant neoplasia within the previous two years. Forty-eight patients met the inclusion criteria and constituted the final SHIFT-FH study cohort (**Supplementary figure 1**). Enrolled patients were classified into two groups: G1 included 22 patients who switched from PCSK9 monoclonal antibody therapy to siRNA (inclisiran), and G2 included 26 patients who continued PCSK9 monoclonal antibody therapy.

### 3.1 Clinical and Biochemical Profile at Baseline

Baseline clinical and biochemical characteristics of the SHIFT-FH study cohort are reported in **Table 1**. All patients included in the study were heterozygous carriers of pathogenic *LDLR* variants (100%, 48) (**Table 1**). The proportion of patients achieving the therapeutic LDL-C target was significantly lower in G1 than in G2 (36.4% vs. 80.8%, p = 0.002), indicating a marked imbalance in baseline lipid control between the two groups. No significant differences were observed between groups with respect to age, sex, cardiovascular risk factors (arterial hypertension, smoking habits, diabetes mellitus), DUTCH score, TC, HDL-C, TG and LDL-C. In contrast, AST levels were significantly higher in Group 2 compared with Group 1 [22.5 (20.2;23.7) vs 25 (23.2;25.7) U/L, p = 0.013), although values remained within the normal range in both groups.

### 3.2 Clinical and Biochemical Profile at T1

The number of patients with available paired biochemical measurements remained stable across follow-up, except for a single missing laboratory assessment in G1. At T1, 84.6% of patients in G2

and 45.5% of those in G1 achieved LDL-C targets, with no significant changes compared with baseline (p = 0.414 for G1 and p = 0.564 for G2). No statistically significant within-group variations in lipid parameters or liver enzymes were observed in either cohort at this timepoint (**Table 2**). In G1, mean TC at T1 was 173.2 ± 55.1 mg/dL, median TG were 73 [58–97] mg/dL, HDL-C was 60.2 ± 17.9 mg/dL, and LDL-C was 95.2 ± 48.4 mg/dL, with median AST and ALT levels of 23 [21–24] U/L and 20 [19–21] U/L, respectively. In G2, mean TC was 125.9 ± 33.5 mg/dL, TG 87 [70–106.5] mg/dL, HDL-C 53.4 ± 7.8 mg/dL, and LDL-C 53.6 ± 31.8 mg/dL (**Figure 1**); AST and ALT values were 23.5 [23–25] U/L and 19 [19–20] U/L, respectively. A modest, non-significant increase in TC and LDL-C was observed in G1, whereas lipid parameters in G2 remained stable throughout follow-up (**Table 2**).

### 3.3 Clinical and Biochemical Profile at T2

At the 12-month follow-up (T2), paired biochemical measurements were available for 19 patients in G1 and 21 patients in G2. The proportion of patients achieving LDL-C targets remained unchanged over time, with 22.7% in G1 and 53.8% in G2 (**Figure 2**). In G1, mean TC was 181.3 ± 47.8 mg/dL, TG were 73 [61.5–107] mg/dL, HDL-C was 60.0 ± 19.7 mg/dL, and LDL-C was 103.5 ± 36.1 mg/dL. Median AST and ALT levels were 22 [24–24] U/L and 19 [18–20] U/L, respectively. In G2, mean TC was 134.6 ± 32.0 mg/dL, median TG were 103 [68.8–145.3] mg/dL, HDL-C was 50.4 ± 10.6 mg/dL, and LDL-C was 62.1 ± 27.0 mg/dL, with corresponding median AST and ALT levels of 22 [19.5–23.5] U/L and 19 [19–20] U/L. In G1, a significant increase in TC and LDL-C was observed compared with baseline (Δ = 31.2 ± 41.9 mg/dL, p = 0.004; and Δ = 29.6 ± 37.4 mg/dL, p = 0.003), whereas no significant changes were detected in TG, HDL-C, or liver enzyme levels. At 12 months of follow-up, divergent trends were observed between the two treatment groups, while a statistically significant reduction in AST values was noted, all measurements consistently remained within the normal range throughout the study period (**Table**

**3**). The individual LDL-C trajectories across the study time points are illustrated in **Supplementary Figure 2**, highlighting the variability of lipid responses within each treatment group.

### 3.4 Changes in target status during follow-up

Among patients with available data, 47.4% (18/38) were classified as never target, while 14.6% (6/41) experienced a loss of target during follow-up. The proportion of never target patients differed significantly between treatment groups (difference 42.1%, p = 0.009), whereas the difference in loss of target was not statistically significant (difference 17.5%, p = 0.115) (**Figure 3**).

### 3.5 Exploratory Analysis of Predictors of LDL-C Response

In the exploratory univariate logistic regression analysis, higher baseline LDL-C levels showed a trend toward a lower likelihood of achieving LDL-C targets at T2 (OR = 0.96 per 1 mg/dL increase; 95% CI 0.91–1.00; p = 0.068).

## 4. Discussion

In the SHIFT-FH study cohort, we assessed LDL-C target achievement, lipid profile evolution, and hepatic safety over 12 months in genetically confirmed HeFH patients treated with two PCSK9 inhibition strategies (siRNA vs mabs).

LDL-C target achievement differed substantially between groups already at baseline, with a markedly lower proportion of patients at goal in those subsequently switched to inclisiran, with a higher proportion of patients on continued mAbs therapy meeting guideline-recommended targets compared with those later switched to siRNA, and this imbalance persisted over follow-up. This pattern is consistent with the well-described gap between recommended LDL-C goals and real-world attainment in high/very-high-risk populations, even in contemporary European settings (20).

The marked imbalance in LDL-C target achievement observed at baseline deserves careful consideration when interpreting between-group differences. Because treatment allocation was clinician-driven rather than randomized, patients switched to inclisiran may have represented a subgroup with less satisfactory lipid control, greater residual LDL-C burden, or specific management needs in routine practice. This potential selection bias likely contributed, at least in part, to the different lipid trajectories observed during follow-up and limits any causal interpretation of the comparison between treatment strategies.

Exploratory regression analysis suggested a trend toward an inverse relationship between baseline LDL-C levels and the likelihood of achieving LDL-C targets at 12 months. This observation aligns with recent real-world evidence identifying baseline LDL-C as a major determinant of target non-achievement in PCSK9 inhibitor treatment pathways (21). Clinically, this relationship is intuitive within a target-based framework: markedly elevated baseline LDL-C requires a larger absolute reduction to meet stringent guideline thresholds, making residual above-target values

more likely even when relative LDL-C lowering is substantial. Furthermore, evidence suggests that baseline LDL-C influences the percentage reduction observed across multiple lipid-lowering drug classes, including PCSK9 inhibitors, reinforcing its role as a key driver of treatment response and goal attainment (22).

When examining lipid profile trajectories, patients who continued monoclonal antibody therapy maintained stable LDL-C levels throughout follow-up, whereas those who switched to siRNA therapy showed a progressive increase in LDL-C and TC at 12 months. Although the LDL-C increase observed after switching reached statistical significance, its magnitude remained relatively modest and should be interpreted within the context of baseline lipid burden and pharmacological differences between treatment strategies. This pattern aligns with real-world evidence on inclisiran, which while generally supporting meaningful LDL-C reductions also reports variability related to background LLT and, notably, prior treatment with PCSK9 mAbs (23). Consistently, other observational cohorts have documented that patients transitioning from mAbs to siRNA may show an LDL-C increase, mirroring the trend observed in our study (13).

A plausible explanation for these divergent lipid trajectories lies in the distinct pharmacodynamic mechanisms of the two therapeutic strategies. MAbs (evolocumab and alirocumab) act extracellularly by binding circulating PCSK9, thereby preventing PCSK9-mediated degradation of the LDL receptor (LDLR) and enhancing hepatic LDLR recycling and LDL clearance. Because they directly neutralize circulating PCSK9, their onset of action is rapid and their lipid-lowering effect reflects sustained antibody availability in the circulation (24). In contrast, inclisiran is a GalNAc-conjugated siRNA selectively internalized by hepatocytes, where it silences PCSK9 synthesis via RNA interference (RISC-mediated mRNA degradation). This mechanism reduces hepatic PCSK9 production and progressively decreases circulating PCSK9 levels over time, without binding or inactivating existing extracellular PCSK9 molecules (25). Conceptually, this

“inside-the-hepatocyte” approach depends on intracellular delivery and sustained gene silencing rather than immediate extracellular neutralization. As a result, switching from mAbs to siRNA represents a pharmacodynamic shift that, in real-world transitions without therapeutic overlap, may transiently alter circulating PCSK9 dynamics and contribute to LDL-C variations observed during follow-up.

Across randomized clinical trials, mAbs generally achieve slightly greater mean LDL-C reductions than inclisiran (approximately 55–60% vs. 45–50%), although both strategies provide clinically meaningful lipid lowering (7-12), suggesting that a relative decrease in pharmacologic potency may become clinically evident when switching from mAb to siRNA therapy. This effect is particularly relevant in patients who are already near guideline-recommended thresholds or those with higher baseline LDL-C values, who require larger absolute reductions to remain on target (24). Supporting this interpretation, comparative real-world analyses indicate higher rates of LDL-C target attainment with monoclonal antibodies than with inclisiran among patients starting from elevated baseline LDL-C levels (26).

Considering hepatic safety, both strategies showed an excellent tolerability profile. Transaminases remained within the normal range throughout follow-up and no clinically relevant elevations were observed. This is consistent with the broader evidence base indicating a favourable hepatic safety profile for both monoclonal antibody PCSK9 inhibitors and inclisiran in clinical development and real-world settings (24).

The comparison between treatment strategies should be interpreted with caution, as treatment allocation was clinician- and patient-driven rather than randomized. In routine clinical practice, switching from PCSK9 mAbs to siRNA is often prompted by the desire to simplify the therapeutic regimen and potentially improve long-term adherence. Therefore, the LDL-C increase observed after switching should not be interpreted as evidence of reduced drug efficacy, but rather as the

combined result of baseline lipid burden, pharmacological differences between treatment strategies, and real-world treatment allocation.

This study has limitations inherent to its retrospective, single-centre design and modest sample size, which restrict causal inference and limit generalizability. Treatment allocation was non-randomized, adherence could not be objectively quantified, and cardiovascular outcomes were not assessed. Notably, the lower proportion of patients achieving LDL-C targets in the switching group should be interpreted considering the markedly lower target attainment already present at baseline. This pattern may reflect a subgroup of patients with more difficult-to-control lipid profiles or reduced responsiveness to PCSK9-targeting therapies. In such contexts, additional lipid-lowering strategies, including emerging third-line treatments such as angiopoietin-like protein 3 (ANGPTL3) inhibitors, may represent a potential therapeutic option (26). Nevertheless, the focus on a genetically confirmed HeFH cohort and the pragmatic observation of real-world switching behaviour provide clinically relevant insights into target attainment, lipid trajectories, and hepatic tolerability in routine practice.

**5. Conclusions**

In conclusion, in the SHIFT-FH study cohort, LDL-C target achievement was strongly influenced by baseline lipid burden and differed across therapeutic pathways. Patients who continued mAbs therapy maintained stable lipid control, whereas those who switched to siRNA therapy showed a moderate increase in LDL-C levels at 12 months, while maintaining an excellent hepatic safety profile. These findings highlight the importance of individualized, target-oriented lipid management when considering therapeutic switching between PCSK9-targeting strategies. Future prospective multicentre studies including cardiovascular outcomes are warranted to better define the optimal positioning of these therapies in routine clinical practice.

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**Ethics approval**

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the local Ethics Committee of the University of Naples Federico II. All participants provided written informed consent for the use of their clinical data for research purposes.

**Author contributions**

Conceptualization: ILC, CDL, MNDM; Data curation: ILC, CDL, LJV, GDE; Clinical investigation: ILC, CDL, LJV, GDE, GI, AT; Genetic analyses: MDT, GF, MF, GC; Formal statistical analysis: ILC, CDL; Writing – original draft preparation: ILC, CDL; Writing – review and editing: ILC, CDL, LJV, GDE, MF, GC, MDT, GF, GI, AT, MNDM; Supervision: MNDM, AT, GF.

All authors have read and approved the final version of the manuscript.

**Conflict of interest**

The authors declare that they have no conflict of interest related to this work.

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**Declaration of AI-assisted writing**

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) to assist in improving the language, structure, and clarity of the text. The AI tool was used exclusively for language polishing and editorial refinement. No scientific content, data analysis, or interpretation was generated by the AI. All outputs were carefully reviewed, edited, and validated by the authors, who take full responsibility for the integrity and accuracy of the final manuscript.

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**Tables and Figures**

**Table 1. Baseline clinical and biochemical characteristics of the study population.**

| | Total (48) | Group 1 (22) | Group 2 (26) | p-value |
|---|---|---|---|---|
| **Age (n)** | 59.3±12.8 | 58.9±13 | 61.4±12.5 | 0.228 |
| **Male (%, n)** | 54.2% (26) | 54.5% (12) | 53.8% (14) | 0.961 |
| **Smoking habits (%, n)** | 45.8% (22) | 36.4% (8) | 53.8% (14) | 0.226 |
| **Arterial Hypertension (%, n)** | 50.0% (24) | 40.9% (9) | 57.7% (15) | 0.247 |
| ***LDLR* causative variants (%,n)** | 100% (48) | 100% (22) | 100% (26) | N.A. |
| **DUTCH score** | 15.0±4.0 | 16±3.7 | 14.0±4.1 | 0.86 |
| **Diabetes Mellitus (%, n)** | 10.4% (5) | 9.1% (2) | 11.5% (3) | 0.782 |
| **Secondary Prevention (%, n)** | 50.0% (24) | 45.5% (10) | 53.8% (14) | 0.562 |
| **Total cholesterol (mg/dl)** | 139.2±43.5 | 150.9±47.5 | 129.3±37.9 | 0.088 |
| **Triglycerides (mg/dl)** [a] | 87.5 [61.7-107.7] | 83 [61.5–108] | 95.5 [63.5–106] | 0.992 |
| **HDL-C (mg/dl)** | 55.6±13.3 | 55.1±14.8 | 56.0±12.2 | 0.824 |
| **LDL-C (mg/dl)** | 67.0±43.8 | 76.2+42 | 59.2±44.6 | 0.184 |
| **AST (U/dl)** [a] | 24.0 [22.7;25.0] | 22.5 [20.2;23.7] | 25 [23.2;25.7] | 0.013 |
| **ALT (U/dl)** [a] | 19.0 [18.0;20.0] | 20.0 [18.2;20] | 19.0 [18.0;20.0] | 0.432 |
| **Therapeutic LDL-CTarget (%, n)** | 60.4% (29) | 36.4% (8) | 80.8% (21) | 0.002 |

[a] reported as median [IQR]

Continuous variables are expressed as mean ± standard deviation or median [interquartile range], as appropriate. Categorical variables are reported as percentages and absolute numbers. Comparisons between groups were performed using Student's *t*-test or Mann–Whitney *U* test for continuous variables, and $\chi^2$ test for categorical variables. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N.A. not applicable.

**Table 2. Six-month follow-up lipid profile and liver enzyme levels according to treatment group.**

| | G1 (21) | | G2 (26) | |
|---|---|---|---|---|
| | **Δ vs baseline** | **p-value** | **Δ vs baseline** | **p-value** |
| **CT (mg/dl)** | 21.1 ± 48.0 | 0.057 | −3.4 ± 38.5 | 0.654 |
| **TG (mg/dl)** | −12.8 ± 44.7 | 0.204 | 0.3 ± 48.8 | 0.971 |
| **HDL-C (mg/dl)** | 5.1 ± 14.9 | 0.129 | −2.6 ± 12.1 | 0.286 |
| **LDL-C (mg/dl)** | 18.1 ± 42.6 | **0.065** | −5.6 ± 42.2 | **0.504** |
| **AST (U/dl)** | 1.1 ± 5.0 | 0.334 | −1.2 ± 4.1 | 0.159 |
| **ALT (U/dl)** | 1.3 ± 4.2 | 0.195 | −0.3 ± 2.2 | 0.424 |
| **LDL-C Target (%, n)** | **45.5% (10)** | **0.414** | **84.6% (22)** | **0.564** |

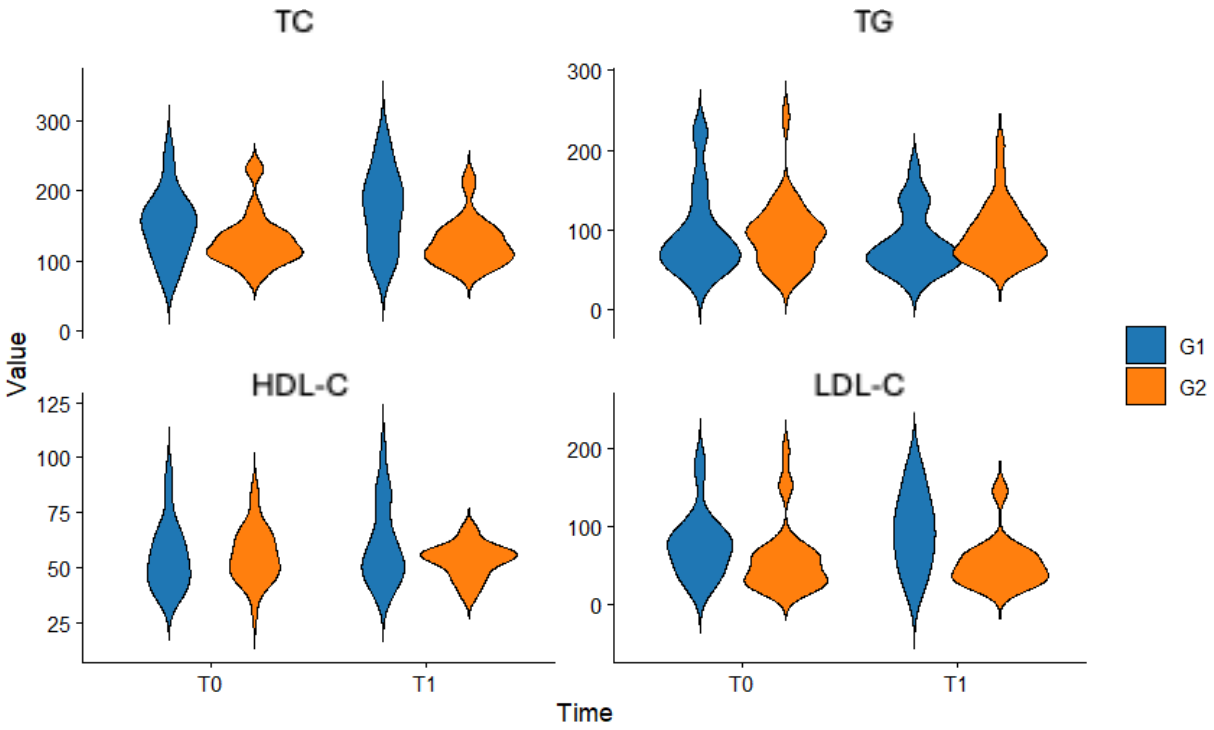
Changes from baseline (Δ) and corresponding two-sided *p* values for within-group comparisons are reported for both groups. Continuous variables are expressed as mean ± standard deviation. Within-group comparisons were performed using paired tests, as appropriate. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

**Table 3. Twelve-month follow-up outcomes and changes from baseline according to treatment group.**

| | G1 (19) | | G2 (21) | |
|---|---|---|---|---|
| | **Δ vs baseline** | **p-value** | **Δ vs baseline** | **p-value** |
| **CT (mg/dl)** | 31.2±41.9 | 0.004 | 1.4±44.2 | 0.894 |
| **TG (mg/dl)** | 0.3±39.8 | 0.973 | 18.9±43.5 | 0.074 |
| **HDL-C (mg/dl)** | 4.5±15.6 | 0.227 | -6.9±14.1 | 0.46 |
| **LDL-C (mg/dl)** | **29.6±37.4** | **0.003** | **-2.4±50** | **0.839** |
| **AST (U/dl)** | 0.21±3.5 | 0.796 | -3.21±3.3 | <0.001 |
| **ALT (U/dl)** | -0.21±2.5 | 0.719 | 0.6±2.2 | 0.22 |
| **LDL-C Target (%, n)** | **22.7% (5)** | **0.257** | **53.8% (14)** | **1.00** |

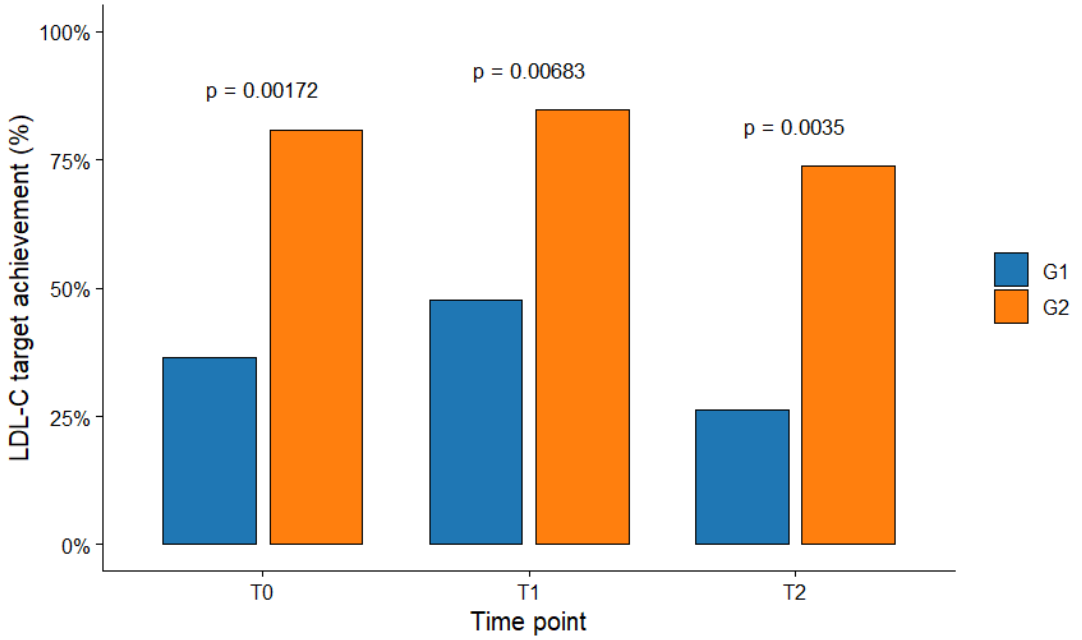
Changes from baseline (Δ) and corresponding two-sided *p* values are reported for Group 1 and Group 2. Continuous variables are expressed as mean ± standard deviation. Within-group comparisons were performed using paired tests, as appropriate. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

**Figure 1. Distribution of lipid parameters at baseline (T0) and follow-up (T1) according to study group.**



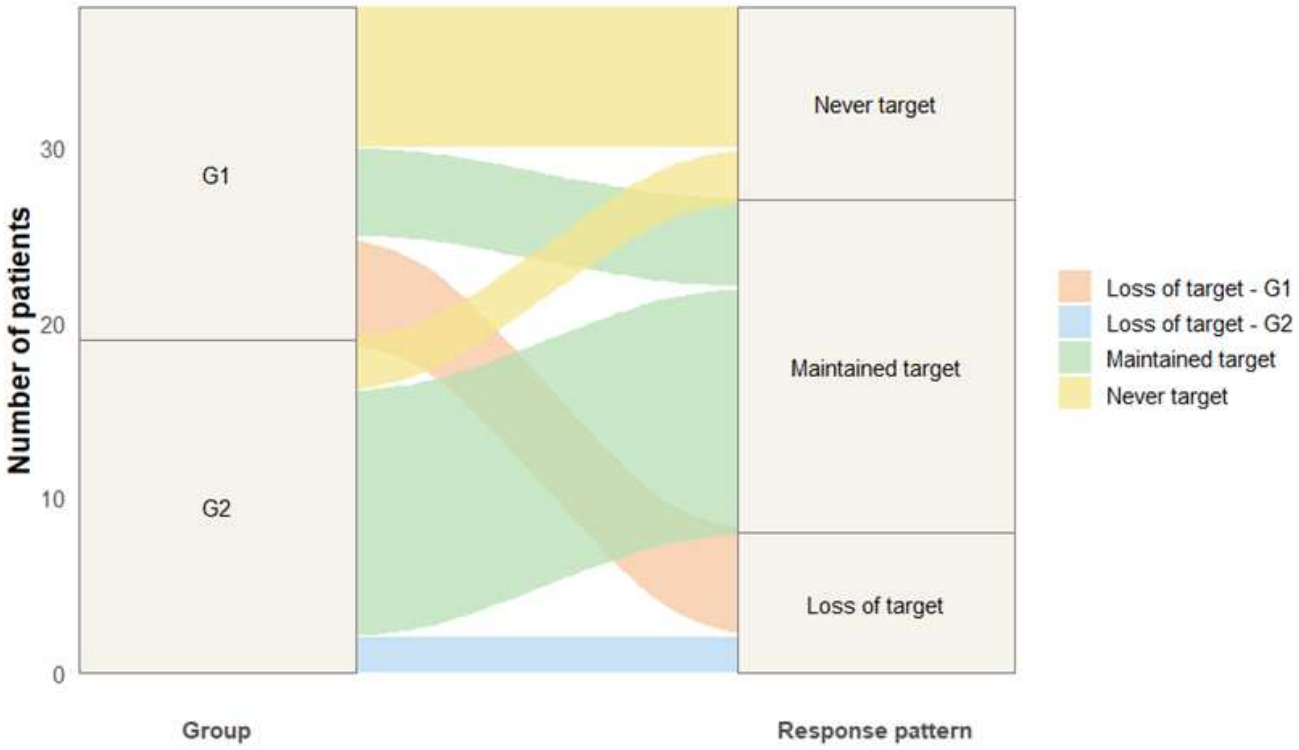

Violin plots show the distribution of total cholesterol (TC), triglycerides (TG), HDL-C and LDL-C in group G1 (blue) and group G2 (orange). P-values refer to within-group comparisons between T0 and T1 and were calculated using paired Wilcoxon signed-rank test, including only subjects with complete paired measurements.

**Figure 2. LDL-C target achievement over time in the two study groups.**




Proportion of patients achieving the therapeutic LDL-C target at baseline (T0), 6 months (T1), and 12 months (T2) in G1 and G2. P-values refer to between-group comparisons at each time point (independent proportions test).

**Figure 3. Sankey diagram showing patterns of therapeutic target achievement according to treatment group.**




Patients from each treatment group (G1 and G2) were classified according to target attainment over time (T0, T1, and T2) into three response patterns: never target (no target attainment at any time point), maintained target (target achieved at T1 and maintained at T2), and loss of target (transition from target attainment to loss of control during follow-up). The width of each flow is proportional to the number of patients in each trajectory.

## Supplementary Files

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