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# Real-world effectiveness and cardiovascular outcomes of PCSK9 inhibitor therapy: a prospective registry study

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## Abstract

**Background and aims** Randomized trials showed efficacious lipid-lowering with PCSK9 inhibitors (PCSK9i), but real-world treatment is often limited by statin-associated side effects (SASE). We quantified the effectiveness, safety and cardiovascular outcomes of alirocumab, evolocumab and inclisiran in a national prospective registry.

**Methods** This was a prospective registry-based study of patients initiating a PCSK9i. Lipid trajectories were assessed at 0, 3, 9, 21, and 33 months. The average treatment effect of PCSK9i on lipid trajectories and cardiovascular outcomes was estimated by inverse probability of treatment weighting (IPTW) using covariate balancing propensity scores.

**Results** One thousand three hundred eighty five patients (median age 64 years; 52% women; median baseline low-density lipoprotein cholesterol [LDL-C] 4 mmol/L, 57% SASE) were included and followed for 2459 patient-years. In patients on alirocumab ($N=598$), evolocumab ($N=693$), or inclisiran ($N=94$), mean unadjusted LDL-C reductions were −58.2% (−1.98 mmol/L), −58.9% (−2.09 mmol/L), and −33.2% (−1.17 mmol/L), respectively ($p<0.001$). IPTW-adjusted LDL-C reductions remained numerically greater for monoclonal antibodies but were no longer significantly different long-term. Predictors of greater LDL-C reduction were longer treatment duration, male sex, higher age, statin co-therapy and first-line use ($p<0.001$). Adverse events occurred in 31% of patients. Major adverse cardiovascular events were infrequent (2.6 per 100 person-years) with no significant between-drug differences after IPTW.

**Conclusions** PCSK9i are safe in real-world practice. Alirocumab and evolocumab achieve trial-like LDL-C reductions, while inclisiran shows attenuated effectiveness without statins. Meaningful residual risk persists despite therapy.

**Keywords** PCSK9 inhibitors, Monoclonal antibodies, siRNA, Real-world study, Inclisiran, Evolocumab, Alirocumab, LDL-C, Statin intolerance, Cardiovascular outcomes

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## Introduction

Despite therapeutic progress, coronary artery disease remains a major cause of death globally [1]. Elevated low-density lipoprotein cholesterol (LDL-C) is a well-established, causal risk factor for atherosclerosis, contributing directly to the development of major cardiovascular events and associated mortality [2]. Robust evidence from both randomized trials and genetic studies has consistently demonstrated that lowering LDL-C reduces the risk of cardiovascular events and improves survival [3, 4].

The introduction of statins represented the first major breakthrough in lipid-lowering therapy, enabling substantial reductions in LDL-C levels and significantly improving clinical outcomes [5, 6]. The addition of ezetimibe provided a further incremental LDL-C reduction. However, even with the combination of high-intensity statin and ezetimibe therapy, the maximal achievable LDL-C reduction is typically up to 65%, which is frequently insufficient for high-risk patients [7, 8]. According to current European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines, LDL-C levels below 1.4 mmol/L are recommended for patients at very high cardiovascular risk [9]. Achieving these targets remains challenging in many patients, particularly in real-world settings [10].

An additional challenge in clinical practice is statin-associated side effects (SASE). Albeit relatively uncommon in randomized controlled trials, SASE occur more frequently in routine care and may significantly limit effective lipid-lowering therapy [11, 12]. The development of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors marked a second major advance in lipid-lowering management, offering potent additional LDL-C reductions of approximately 50–60% beyond statin therapy. The first approved agents, the monoclonal antibodies alirocumab and evolocumab, were subsequently joined by inclisiran, a small interfering RNA (siRNA) therapeutic targeting hepatic PCSK9 synthesis. All three agents have demonstrated robust LDL-C lowering and excellent tolerability, while the monoclonal antibodies have additionally shown significant reduction of cardiovascular events [13–15].

However, it is important to recognize that >90% of patients enrolled in pivotal PCSK9 inhibitor trials were also receiving background statin therapy [13–15]. This differs substantially from real-world clinical practice, where a significant proportion of patients receiving PCSK9 inhibitors are unable to tolerate statins or receive them only intermittently. Real-world data indicate that treatment patterns, adherence, and response profiles in clinical practice may differ considerably from those observed in randomized trials [16–18].

In the present study, we aimed to assess the real-world effectiveness of PCSK9 inhibitors in clinical practice, evaluating LDL-C response, tolerability, adverse effects, and long-term cardiovascular outcomes. In addition, we sought to explore potential differences between the available PCSK9 inhibitors—alirocumab, evolocumab, and inclisiran—within the limitations of observational registry data, as direct comparative data remain limited.

## Methods

This prospective registry-based study was approved by the National Ethics Committee and conducted at the University Medical Centre Ljubljana (UMCLJ) in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion, including consent for genetic analyses and publication of anonymized data. Study reporting adheres to the STROBE guidelines.

### PCSK9 inhibitor registry and study population

A prospective PCSK9 inhibitor registry has been maintained at UMCLJ since May 2016 in accordance with national requirements. By February 20, 2025, 1,556 patients were screened, of whom 1,385 met inclusion criteria, contributing 2,459.2 patient-years of follow-up and receiving alirocumab, evolocumab, or inclisiran. Patient selection is shown in Fig. 1, annual inclusions in Supplemental Fig. 1, and detailed registry methodology and eligibility criteria in the Supplemental Materials.

### Initial assessment and therapy initiation protocol

Patients with uncontrolled LDL-C despite maximally tolerated statins and ezetimibe or documented SASE are referred to the Centre for Preventive Cardiology, UMCLJ. At baseline, clinical and family history, cardiovascular risk factors, and standard laboratory and anthropometric measurements are obtained. Eligibility for PCSK9 inhibitor therapy is confirmed by a multidisciplinary lipid team, after which patients are entered into the national registry, receive structured education, and initiate treatment (alirocumab/evolocumab self-administered; inclisiran administered in healthcare settings). All patients provide informed consent and continue background lipid-lowering therapy and lifestyle measures. The full protocol is provided in the Supplemental Materials.

### Follow-up protocol

Follow-up visits were scheduled at 3 months, 6–8 months, and annually thereafter for ≥2 years. At each visit, lipid response, tolerability, adherence, co-therapy, and cardiovascular risk factors were assessed. Therapy continuation or switching was guided by LDL-C response and adverse effects, with a two-dose washout for suspected intolerance. Cardiovascular events

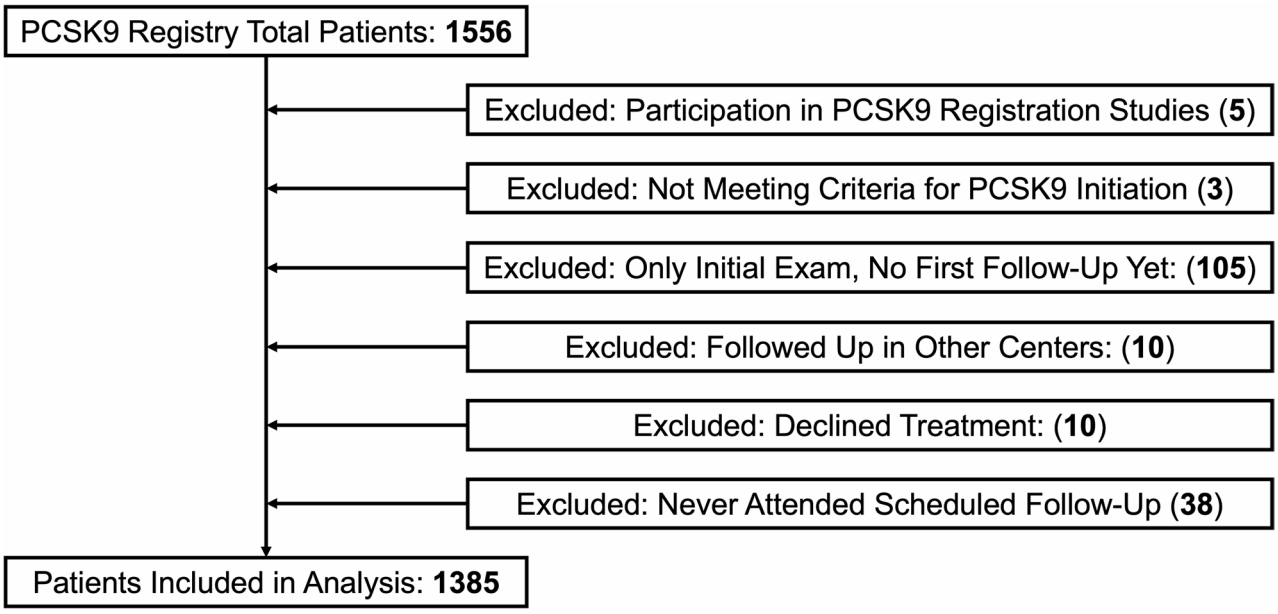


**Fig. 1** Flowchart of patient selection for inclusion in the PCSK9 inhibitor registry study

were ascertained through structured interviews, medical record review, and linkage to the Central Registry of Patient Data, enabling comprehensive outcome capture. The full follow-up protocol is provided in the Supplemental Materials.

#### Laboratory measurements and familial hypercholesterolemia assessment

All laboratory and genetic analyses were performed at the accredited laboratory of the UMCLJ following standardized protocols. Venous blood samples were collected after an overnight fast.

To assess the clinical probability of familial hypercholesterolemia (FH), the Dutch Lipid Clinic Network (DLCN) score was calculated for all patients and used to categorize individuals as having unlikely, possible, probable, or definite FH [19]. To help guide FH diagnosis in childhood and adolescence, the recently developed FH Pediatric Diagnostic Score (FH-PeDS) is used in our center to supplement genetic testing and clinical assessment [20]. Genetic testing was performed in a subset of patients, with detailed methodology described elsewhere [21, 22]. FH was considered genetically confirmed if a pathogenic or likely pathogenic variant was identified in one of the three major FH-related genes: *LDLR*, *APOB*, *or PCSK9*, with interpretation based on American College of Medical Genetics and Genomics guidelines [9, 23, 24].

#### Statistical analysis

Continuous variables are reported as medians (IQR) and categorical variables as counts (%). Group comparisons used Kruskal–Wallis and $\chi^2$ tests, with two-sided $p < 0.05$ considered statistically significant. Longitudinal lipid trajectories (primary: LDL-C) were analysed at prespecified visits using log-transformed data and summarized as geometric means with 95% confidence intervals. LDL-C changes over time were assessed using mixed-effects models with random patient intercepts, modelling therapy as a time-varying exposure and adjusting for baseline covariates.

Comparative treatment effects were estimated using inverse probability of treatment weighting (IPTW) based on covariate-balancing propensity scores. Exploratory time-to-event analyses for major adverse cardiovascular events were performed using Kaplan–Meier methods and Cox proportional-hazards models in both intention-to-treat and IPTW-adjusted populations. All analyses were performed in R (version 4.4.1). Detailed methods are provided in the Supplemental Materials.

## Results

#### Baseline characteristics

Baseline characteristics are summarized in Table 1. We included 1,385 patients: the median age was 64 years, and 52% were women. The most common inclusion diagnoses were preclinical atherosclerotic cardiovascular disease (ASCVD) (32%), defined as the presence of atherosclerotic plaques on carotid or femoral ultrasonography or asymptomatic coronary artery disease identified by coronary artery calcium scoring or computed tomography angiography, and myocardial infarction (31%). The median LDL-C at inclusion was 4.0 mmol/L.

At baseline, 43% of patients were receiving statin therapy (65% on high-intensity regimens), while 64% had documented SASE, and 46% were treated with ezetimibe (23% as monotherapy). Significant differences in

**Table 1** Baseline demographic, clinical, and biochemical characteristics of patients by PCSK9 inhibitor therapy (alirocumab, evolocumab, inclisiran)

| Characteristic | Overall, (*N* = 1,385) | Alirocumab, (*N* = 598) | Evolocumab, (*N* = 693) | Inclisiran, (*N* = 94) | *p*-value |
|---|---|---|---|---|---|
| Age at inclusion | 64 (56, 70) | 64 (56, 70) | 65 (56, 70) | 65 (57, 73) | 0.382 |
| Sex (Female) | 714 (51.6%) | 289 (48.3%) | 374 (53.9%) | 51 (54.2%) | 0.112 |
| Index diagnosis | | | | | |
| FH | 33 (2.4%) | 16 (2.7%) | 12 (1.7%) | 5 (5.3%) | * |
| Myocardial infarction | 427 (30.8%) | 204 (34.1%) | 198 (28.6%) | 25 (26.6%) | |
| Peripheral Artery Disease | 29 (2.1%) | 11 (1.8%) | 16 (2.3%) | 2 (2.1%) | |
| Subclinical ASCVD | 441 (31.8%) | 172 (28.7%) | 234 (33.8%) | 35 (37.2%) | |
| Revascularization (PCI/CABG) | 172 (12.4%) | 78 (13.0%) | 87 (12.6%) | 7 (7.4%) | |
| Stroke | 45 (3.2%) | 16 (2.7%) | 25 (3.6%) | 4 (4.3%) | |
| Hypercholesterolemia | 238 (17.2%) | 101 (16.9%) | 121 (17.5%) | 16 (17.0%) | |
| Risk Factors | | | | | |
| Arterial hypertension | 753 (54.4%) | 325 (54.3%) | 373 (53.8%) | 55 (58.5%) | 0.693 |
| Diabetes mellitus | 130 (13.7%) | 80 (13.3%) | 101 (14.6%) | 9 (9.6%) | 0.396 |
| Smoking | | | | | 0.265 |
| Current | 178 (12.9%) | 89 (14.9%) | 80 (11.5%) | 9 (9.6%) | |
| Never | 861 (62.2%) | 362 (60.5%) | 432 (62.3%) | 67 (71.3%) | |
| Quit ≥ 2 years before event | 210 (15.2%) | 88 (14.7%) | 109 (15.7%) | 13 (13.8%) | |
| Quit at event | 136 (9.8%) | 59 (9.9%) | 72 (10.4%) | 5 (5.3%) | |
| Body mass index [kg/m2] | 27.4 (24.7, 30.4) | 27.1 (24.5, 30.4) | 27.6 (25.0, 30.3) | 26.6 (24.2, 30.8) | 0.318 |
| Lipid profile | | | | | |
| Total cholesterol [mmol/L] | 5.90 (4.58, 7.30) | 5.84 (4.35, 7.38) | 6.10 (4.70, 7.32) | 5.80 (4.74, 6.88) | 0.142 |
| HDL-C [mmol/L] | 1.31 (1.10, 1.60) | 1.30 (1.09, 1.60) | 1.34 (1.12, 1.60) | 1.40 (1.10, 1.60) | 0.531 |
| LDL-C [mmol/L] | 4.00 (2.60, 5.03) | 3.90 (2.40, 5.00) | 4.10 (2.72, 5.14) | 4.00 (2.83, 4.90) | 0.172 |
| Triglycerides [mmol/L] | 1.56 (1.11, 2.20) | 1.51 (1.10, 2.20) | 1.59 (1.17, 2.23) | 1.61 (1.10, 2.13) | 0.657 |
| Apolipoprotein A1 [g/L] | 1.48 (1.31, 1.64) | 1.49 (1.32, 1.68) | 1.46 (1.30, 1.63) | 1.46 (1.27, 1.63) | 0.594 |
| Apolipoprotein B [g/L] | 1.28 (1.02, 1.55) | 1.27 (1.00, 1.55) | 1.29 (1.03, 1.57) | 1.23 (0.99, 1.46) | 0.386 |
| DLCN Score Category | | | | | |
| Definite FH | 200 (14.4%) | 96 (16.1%) | 94 (13.6%) | 10 (10.6%) | 0.547 |
| Probable FH | 207 (14.9%) | 93 (15.6%) | 97 (14.0%) | 17 (18.1%) | |
| Possible FH | 520 (37.5%) | 213 (35.6%) | 273 (39.4%) | 34 (36.2%) | |
| Unlikely FH | 458 (33.1%) | 196 (32.8%) | 229 (33.0%) | 33 (35.1%) | |
| Genetically confirmed FH | | | | | |
| *APOB* | 11 (0.8%) | 3 (0.5%) | 6 (0.9%) | 2 (2.1%) | 0.108 |
| *LDLR* | 31 (2.2%) | 14 (2.3%) | 14 (2.0%) | 3 (3.2%) | |
| Negative | 44 (3.2%) | 25 (4.2%) | 19 (2.7%) | 0 (0.0%) | |
| Other | 2 (0.1%) | 1 (0.2%) | 1 (0.1%) | 0 (0.0%) | |
| No genetic testing | 1297 (93.6%) | 555 (92.8%) | 653 (94.2%) | 89 (94.7%) | |
| Statin | | | | | |
| Atorvastatin | 63 (4.5%) | 25 (4.2%) | 35 (5.1%) | 3 (3.2%) | 0.010 |
| Fluvastatin | 5 (0.4%) | 4 (0.7%) | 1 (0.1%) | 0 (0%) | |
| Pravastatin | 28 (2.0%) | 14 (2.3%) | 13 (1.9%) | 1 (1.1%) | |
| Rosuvastatin | 478 (34.5%) | 228 (38.1%) | 220 (31.7%) | 30 (31.9%) | |
| Simvastatin | 19 (1.4%) | 9 (1.5%) | 5 (0.7%) | 5 (5.3%) | |
| None | 792 (57.2%) | 318 (53.2%) | 419 (60.5%) | 55 (58.5%) | |
| Statin therapy intensity[a] | | | | | |
| High | 385 (27.8%) | 186 (31.1%) | 177 (25.5%) | 22 (23.4%) | 0.010 |
| Intermediate | 198 (14.2%) | 89 (14.9%) | 95 (13.7%) | 14 (14.9%) | |
| Low | 10 (0.7%) | 5 (0.8%) | 2 (0.3%) | 3 (3.2%) | |
| None | 792 (57.2%) | 318 (53.2%) | 419 (60.5%) | 55 (58.5%) | |
| SASE[b] | 880 (63.5%) | 361 (60.4%) | 454 (65.5%) | 65 (69.1%) | 0.078 |

**Table 1** (continued)

| Characteristic | Overall, (*N* = 1,385) | Alirocumab, (*N* = 598) | Evolocumab, (*N* = 693) | Inclisiran, (*N* = 94) | *p*-value |
|---|---|---|---|---|---|
| Ezetimibe | 641 (46.2%) | 286 (47.8%) | 303 (43.7%) | 52 (55.3%) | 0.053 |
| Fibrate | 67 (4.8%) | 22 (3.7%) | 40 (5.8%) | 5 (5.3%) | 0.207 |

Categorical data are n (%); continuous data are median (Q1–Q3). Group comparisons used Kruskal–Wallis (continuous) and $\chi^2$ or Fisher's exact tests (categorical). $p < 0.050$

*N* Number of patients, *FH* Familial hypercholesterolemia, *ASCVD* Atherosclerotic cardiovascular disease, *PC*I Percutaneous coronary intervention, *CABG* Coronary artery bypass grafting, *HDL-C* High-density lipoprotein cholesterol, *LDL-C* Low-density lipoprotein cholesterol, *DLCN* Dutch Lipid Clinic Network, *APOB* Apolipoprotein B gene, LDLR Low-density lipoprotein receptor gene, *SASE* Statin-associated side effects, *NA* Data not available

Missing values: Body mass index 73, Total cholesterol 2, HDL-C 3, LDL-C 5, Triglycerides 5, Apolipoprotein A1 797, Apolipoprotein B 451, SASE 3, Ezetimibe 9

[a]Statin intensity per ESC/EAS guidelines [9]

[b]SASE: adverse effects with ≥ 2 statins

[*]No p-value for sparse multi-category variables

background statin therapy were observed across PCSK9 inhibitor groups, both for statin type and statin intensity (overall $p = 0.010$ for both). Rosuvastatin was the most frequently prescribed statin, followed by atorvastatin (Table 1), and was predominantly used at high doses; approximately 74% of rosuvastatin users received 40 mg, and ~ 72% of atorvastatin users received ≥ 40 mg. High-intensity statin therapy was most common among alirocumab-treated patients (31.1%), compared with evolocumab- (25.5%) and inclisiran-treated patients (23.4%), while evolocumab-treated patients were more frequently statin-free at baseline (60.5% vs. 53.2% for alirocumab and 58.5% for inclisiran). Pairwise comparisons showed significant differences in statin use and intensity between alirocumab and evolocumab ($p = 0.035$ for both) and between evolocumab and inclisiran ($p = 0.018$ and $p = 0.019$, respectively), whereas differences between alirocumab and inclisiran were not significant. Over follow-up, baseline differences in statin exposure attenuated: although statin use differed at inclusion (46.8%, 39.5%, and 41.5% for alirocumab, evolocumab, and inclisiran, respectively; $p = 0.030$), no significant differences were observed at 3, 9, or 21 months (all $p \geq 0.18$), indicating convergence of background lipid-lowering therapy across treatment groups.

### Initial PCSK9 inhibitor therapy and switching patterns during follow-up

Of the 1,385 patients included in the study, 598 (43%) were initially treated with alirocumab, 693 (50%) with evolocumab, and 94 (7%) with inclisiran. Overall, 90% of patients remained on their first-line PCSK9 inhibitor throughout the study. The proportions of patients receiving alirocumab and evolocumab declined slightly over time (to 42% and 47%, respectively), whereas inclisiran use increased to 10.5%—as illustrated in Supplemental Fig. 2.

### Adverse effects and therapy discontinuation

Adverse effects were reported in 31% of patients. Local injection-site reactions were uncommon (4%) but led to therapy discontinuation in 46% of those affected. Systemic adverse effects were more frequent (30%) and prompted discontinuation in 33%. Musculoskeletal symptoms (12%) and flu-like symptoms (7%) were the most commonly reported adverse effects (Supplemental Table 1). Adverse-effect incidence was assessed at each follow-up visit, separately for first- and second-line therapy. Overall, incidence declined over time, with first-line inclisiran recipients reporting the lowest rate (12% at 3 months) and virtually no reports beyond the first year (Fig. 2). First-line alirocumab and evolocumab users reported adverse-effect rates of 19% and 20%, respectively, persisting at just above 10% after one year. As expected, patients switched to second-line PCSK9 inhibitors exhibited higher adverse-event rates (52% with alirocumab, 32% with evolocumab, 28% with inclisiran), depicted in Supplemental Fig. 3. Discontinuation patterns (Supplemental Fig. 4) mirrored these trends, peaking at 3 months and stabilizing thereafter, with less than 3% discontinuing beyond the first year. Early discontinuation was slightly more frequent with first-line inclisiran (13% at 3 months) compared to alirocumab (8.2%) and evolocumab (7.6%), driven primarily by suboptimal LDL-C reduction or failure to achieve treatment goals rather than adverse effects.

### Effectiveness

#### *Unadjusted LDL-C reductions*

Figure 3 illustrates the unadjusted geometric mean LDL-C levels over time for each therapy. Both alirocumab and evolocumab achieved substantial LDL-C reductions at 3 months: − 58.2% (1.98 mmol/L; 95% CI: 1.88–2.07) and − 58.9% (2.09 mmol/L; 95% CI: 2.00–2.18), respectively—and maintained similar reductions at 9 months: − 58.9% (2.00 mmol/L; 95% CI: 1.90–2.10) and − 56.9% (2.02 mmol/L; 95% CI: 1.91–2.13), respectively. The response rate, defined as a ≥ 25% LDL-C reduction, remained approximately 85% for both monoclonal antibodies at these timepoints, with no statistically significant difference between them ($p > 0.050$). In contrast, inclisiran showed a more modest and variable

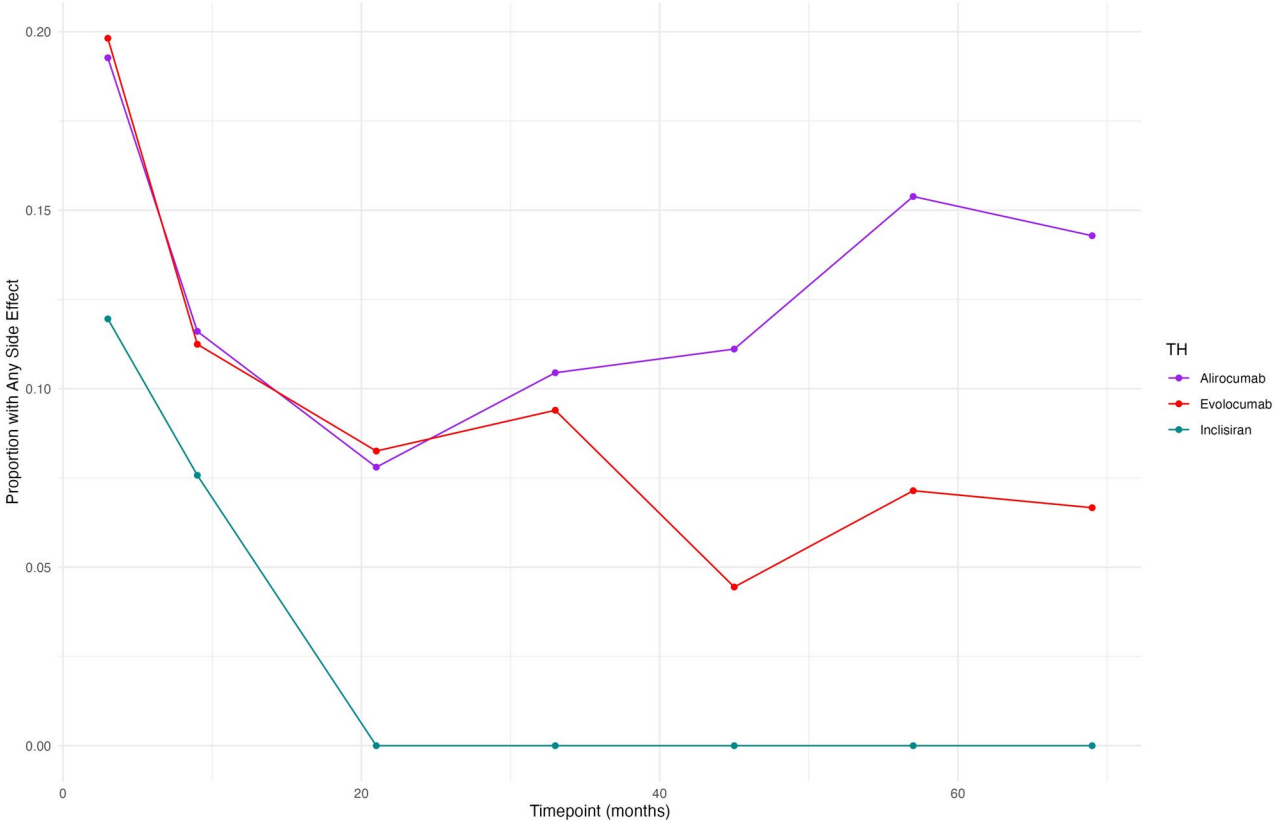


**Fig. 2** Incidence of any reported adverse effect over time by PCSK9 inhibitor for first line therapy. The figure shows the proportion of patients reporting any adverse effect over time for alirocumab, evolocumab, and inclisiran

LDL-C–lowering effect, with reductions of −33.2% (1.17 mmol/L; 95% CI: 0.93–1.39) at 3 months and −24.7% (0.87 mmol/L; 95% CI: 0.51–1.19) at 9 months. Response rates for inclisiran were 64.3% and 52.8% at 3 and 9 months, respectively. Compared with both monoclonal antibodies, these reductions were significantly smaller at both timepoints ($p < 0.001$), highlighting lower efficacy and greater inter-individual variability. Supplemental Fig. 5 further illustrates that second-line therapy was associated with higher baseline LDL-C and wider confidence intervals, suggesting more complex clinical backgrounds. Nonetheless, LDL-C reductions remained evident across therapies, though attenuated for inclisiran in this context.

At baseline, only a minority of patients met the ESC/EAS LDL-C target of ≤1.4 mmol/L.[9] The highest goal attainment was observed among statin-treated alirocumab users (12.2%), followed by those on inclisiran (10.3%) and evolocumab (9.6%). Among non-statin users, target attainment was <2% across all therapies. No significant baseline differences were observed between treatment groups. Following initiation of PCSK9 inhibitors, LDL-C goal attainment improved substantially. Among statin-treated patients, 78.5% of alirocumab users achieved target at 3 months and 76.8% at 9 months, while 77.7% and 67.9% of evolocumab users did so at the same timepoints. In contrast, non-statin users had considerably lower goal attainment with monoclonal antibodies—generally ≤21.5%, except at the first follow-up in the evolocumab group (27.1%). Inclisiran was associated with the lowest overall goal attainment:<3% during the first two years and 5.1% at 33 months in the absence of statins. When combined with statin therapy, inclisiran users achieved target levels in 52.6% at 3 months and 53.6% at the last available follow-up. Importantly, similar patterns were observed for the less stringent LDL-C thresholds of ≤1.8 mmol/L and ≤2.6 mmol/L, with consistently higher target attainment among statin-treated patients across all therapies and follow-up visits. These patterns are illustrated in Fig. 4. LDL-C goal attainment should be interpreted in the context of Slovenian eligibility criteria for PCSK9 inhibitor therapy, which typically require failure to reach target levels despite maximally tolerated lipid-lowering treatment—reflected by a median baseline LDL-C of 4 mmol/L.

### *Predictors of LDL-C response*

Statin therapy was the strongest predictor of LDL-C response. Compared with high-intensity statin therapy, no statin therapy, low-intensity therapy, and

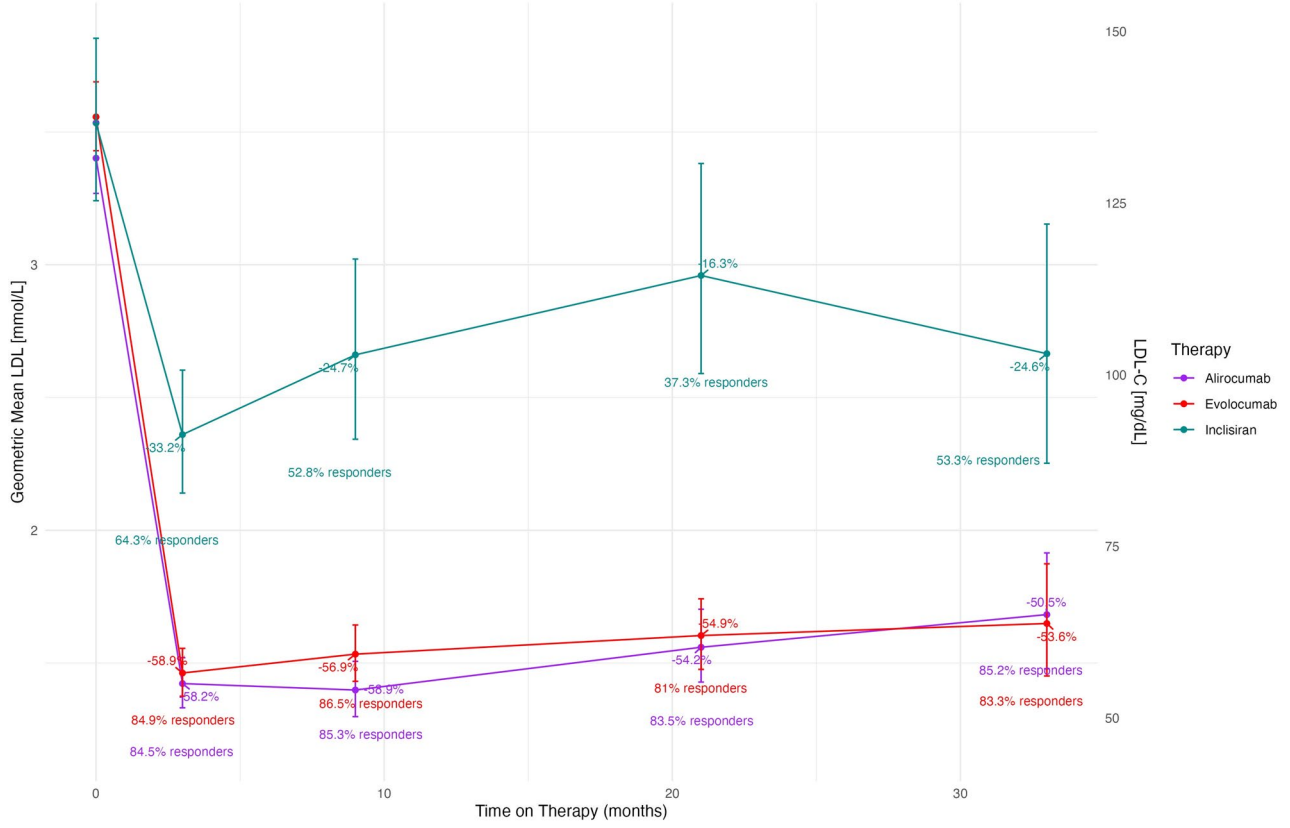


**Fig. 3** Unadjusted Geometric Mean LDL-C Over Time by PCSK9 Inhibitor Therapy. Geometric mean LDL-C levels over time for alirocumab, evolocumab, and inclisiran, with percent change from baseline and proportion of responders (defined as ≥ 25% LDL-C reduction) shown at each timepoint (0, 3, 9, 21, 33 months). Error bars represent 95% confidence intervals. Note: Baseline: Evolocumab vs. Alirocumab: $p = 0.240$, Inclisiran vs. Alirocumab: $p = 0.681$, Inclisiran vs. Evolocumab: $p = 0.989$; Control 1: Evolocumab vs. Alirocumab: $p = 0.813$, Inclisiran vs. Alirocumab: $p < 0.001$, Inclisiran vs. Evolocumab: $p < 0.001$; Control 2: Evolocumab vs. Alirocumab: $p = 0.166$, Inclisiran vs. Alirocumab: $p < 0.001$, Inclisiran vs. Evolocumab: $p < 0.001$; Control 3: Evolocumab vs. Alirocumab: $p = 0.888$, Inclisiran vs. Alirocumab: $p < 0.001$, Inclisiran vs. Evolocumab: $p < 0.001$; Control 4: Evolocumab vs. Alirocumab: $p = 0.973$, Inclisiran vs. Alirocumab: $p = 0.009$, Inclisiran vs. Evolocumab: $p = 0.005$

intermediate-intensity therapy were associated with 0.73, 0.38, and 0.16 mmol/L smaller LDL-C reductions, respectively (Supplemental Table 2). Additionally, male sex and older age were linked to greater LDL-C reductions, whereas second-line therapy predicted lower effectiveness. Compared with alirocumab, inclisiran was associated with 0.12 mmol/L less LDL-C lowering ($p < 0.001$); there was no significant difference between evolocumab and alirocumab (mean difference 0.01 mmol/L; $p = 0.588$).

### *Adjusted LDL-C reductions*

After IPTW weighting, adjusted LDL-C reductions were maintained across all therapies (Fig. 5). Initial differences in LDL-C reduction (-42% for inclisiran, -60% for alirocumab, and – 59% for evolocumab, respectively) diminished over time (-42%, -50%, and 51% reduction, respectively, by the last LDL-C measurement) and were no longer significant by the last timepoint ($p > 0.050$).

### *Effect on other lipid parameters*

Supplemental Fig. 6 shows unadjusted geometric mean trajectories of additional lipid markers by therapy. Alirocumab and evolocumab consistently lowered TC (– 32% to – 36%) and apolipoprotein B (– 40% to – 45%), reflecting their potent effect on atherogenic particles. Inclisiran produced milder but directionally similar reductions (TC – 11% to – 20%, apolipoprotein B – 13.6% to – 23.9%). Triglycerides declined modestly across all therapies, with early reductions most pronounced for alirocumab (– 20.2%) and evolocumab (– 18.5%), though these effects waned over time. Inclisiran showed smaller, more variable triglyceride reductions (– 5.3% to – 7.8%). HDL-C and apolipoprotein A1 remained largely unchanged.

### Survival analysis

During a median follow-up of 912 days (IQR: 476–1,630), we observed 108 events—an incidence rate of 2.6 per 100 patient-years. Of these events, 25 patients died; 12 experienced myocardial infarction; 9 suffered a transient

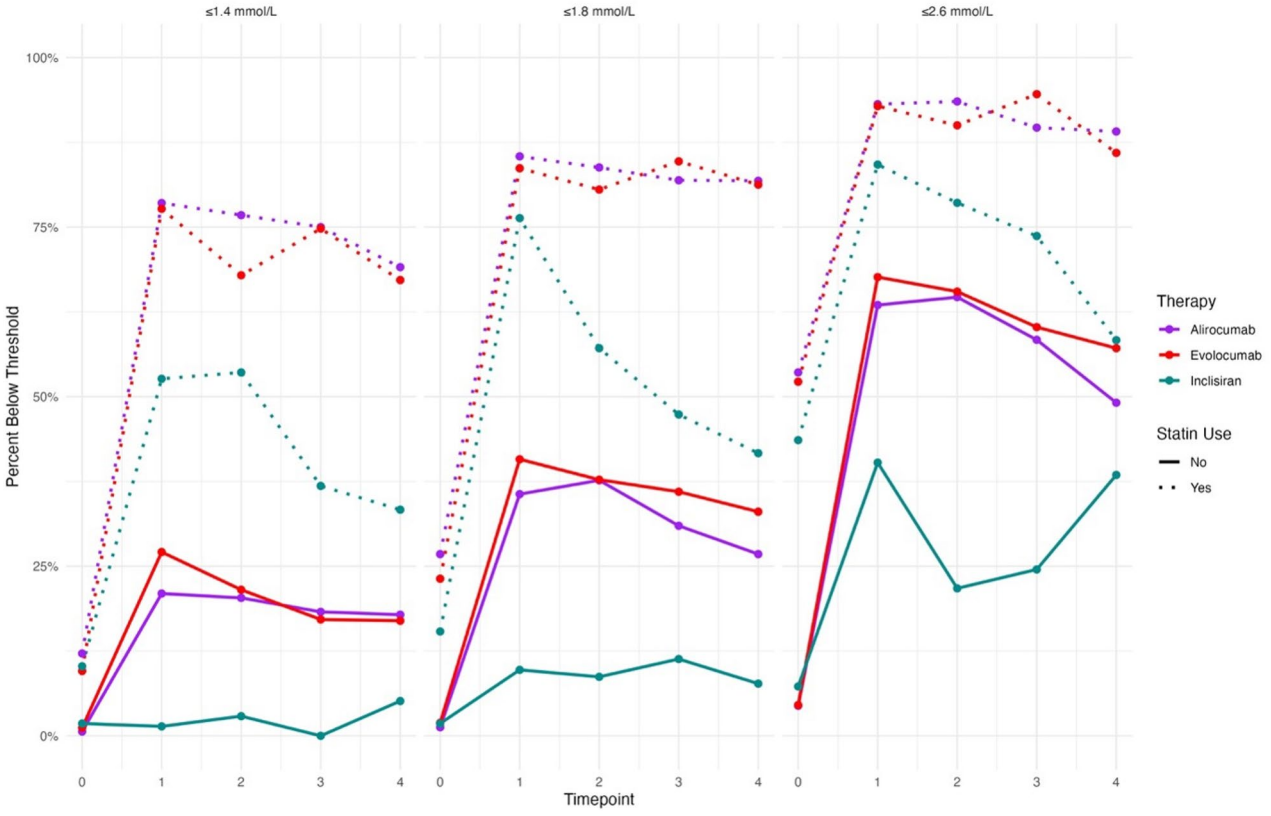


**Fig. 4** LDL-C Target Attainment Over Time According to Therapy and Statin Use. Percentage of patients achieving LDL-C target (≤ 1.4 mmol/L, ≤ 1.8 mmol/L and ≤ 2.6 mmol/L) over time for Alirocumab, Evolocumab, and Inclisiran, stratified by concomitant statin use. Time is expressed as mean days from first visit (Visit 0: initial visit; Visit 1: 3 months; Visit 2: 9 months; Visit 3: 21 months; Visit 4: 33 months). Statin co-medication consistently resulted in higher target attainment across therapies and visits, with the highest proportion observed for Alirocumab and Evolocumab in combination with statins. Inclisiran showed lower target attainment overall, particularly in the no-statin subgroup

ischemic attack or stroke; 43 underwent unplanned coronary revascularization; and 19 underwent unplanned peripheral or carotid revascularization.

#### *Intention-to-treat survival analysis*

No significant differences in event rates were observed among patients treated with alirocumab, evolocumab, or inclisiran (Fig. 6). Using alirocumab as the reference, the hazard ratios for evolocumab and inclisiran were 0.78 (95% CI, 0.42–1.45; $p = 0.426$) and 0.98 (95% CI, 0.13–7.55; $p = 0.987$), respectively. Age and diabetes emerged as significant predictors of major adverse cardiovascular event (Supplemental Table 3).

#### *Propensity score–weighted analysis*

In the IPTW-weighted pseudocohort (Supplemental Fig. 7), estimated event rates did not differ significantly among alirocumab, evolocumab, and inclisiran (Fig. 7). Compared with alirocumab, the hazard ratio was 0.64 (95% CI, 0.44–0.92; $p = 0.104$) for evolocumab and 0.66 (95% CI, 0.40–1.09; $p = 0.681$) for inclisiran.

## Discussion

Our prospective registry is the first to compare the real-world effectiveness of alirocumab, evolocumab, and inclisiran. All three agents achieved clinically meaningful LDL-C reductions: alirocumab and evolocumab lowered LDL-C by 58% and 59%, respectively, while inclisiran produced a 33% reduction. After propensity-score adjustment, estimated reductions were the same or greater—59% for alirocumab, 60% for evolocumab, and 42% for inclisiran. Background statin therapy substantially modified treatment response, with greater LDL-C lowering and higher response rates among statin-treated patients; over half of these individuals achieved LDL-C < 1.4 mmol/L on combination therapy. All inhibitors were well tolerated, with low discontinuation rates, and cardiovascular event rates remained low and did not differ significantly between therapies.

Our real-world cohort differed substantially from patients enrolled in PCSK9 inhibitor trials. Whereas trial populations were predominantly male (70–75%), our registry was balanced by sex (52% women, 48% men). Background lipid-lowering therapy and baseline LDL-C levels also diverged markedly: nearly two-thirds of our

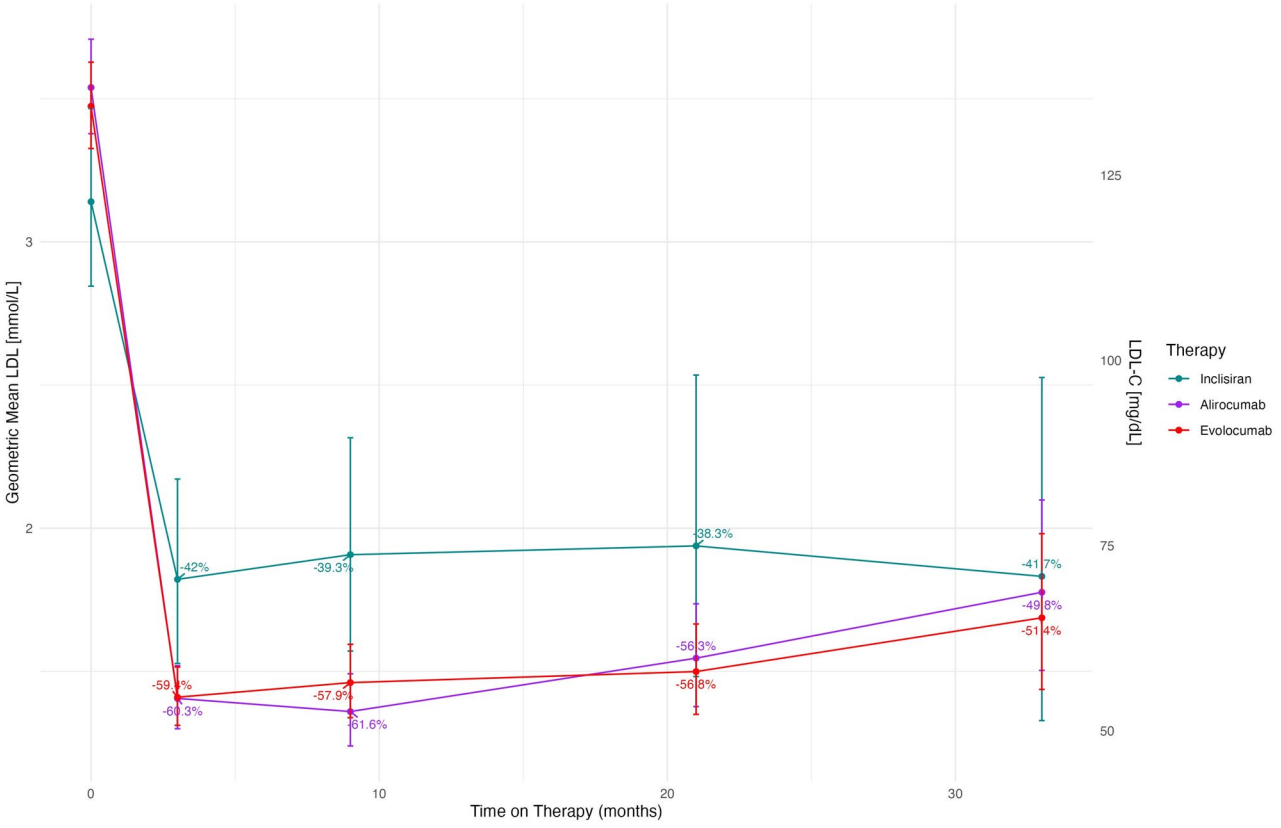


**Fig. 5** Adjusted LDL-C Over Time by Therapy. Adjusted geometric mean LDL-C levels (with 95% confidence intervals) over time for inclisiran, alirocumab, and evolocumab, weighted using inverse probability of treatment based on covariate balancing propensity scores. Adjustments were made for age, sex, BMI, hypertension, diabetes, smoking status, statin intensity, and index cardiovascular diagnosis

patients had SASE, and only 43% received concomitant statins, compared with 90% of trial participants on high-intensity statin regimens per protocol. These factors—together with stricter reimbursement criteria (including prior treatment failures)—likely drove higher baseline LDL-C in our cohort (4.0 mmol/L) versus pivotal trials: ODYSSEY OUTCOMES (alirocumab) and FOURIER (evolocumab) both enrolled patients with LDL-C ≈ 2.4 mmol/L, and ORION-10/11 (inclisiran) enrolled patients with LDL-C ≈ 2.7 mmol/L [13–15]. Although a substantial proportion of our patients fulfilled clinical criteria for FH, genetic testing was only performed in a limited subset, making direct comparison with trial cohorts less meaningful. Collectively, these differences highlight that real-world cohorts often include a more heterogeneous and complex patient population than those enrolled in highly selected randomized controlled trials.

Reductions in LDL-C were clinically meaningful with all three PCSK9 inhibitors. The effect of both monoclonal antibodies on LDL-C reduction was large and comparable to that seen in clinical trials and observational studies. Alirocumab and evolocumab each reduced LDL-C by almost 60%, aligning with the 50–60% reductions reported in ODYSSEY OUTCOMES and FOURIER, as well as in several real-world observational cohorts [13, 15, 17, 25–27]. Recent large real-world registry studies have further confirmed the effectiveness, safety, and long-term persistence of monoclonal PCSK9 inhibitors in routine clinical practice, extending randomized trial findings to broader and more heterogeneous patient populations [28, 29]. Conversely, LDL-C reductions with inclisiran were less pronounced, particularly when compared with trial results. While the ORION-10/11 trial reported a 50% LDL-C reduction with inclisiran, our findings indicate a smaller, albeit still meaningful, 33% reduction [14]. This difference likely reflects our patient population's more complex lipid-lowering histories and lower rates of statin tolerance. Inclisiran lowers LDL-C by up-regulating LDL receptor expression via hepatic PCSK9 inhibition; its efficacy therefore appears highly dependent on background statin therapy, which increases LDL receptor availability [30]. In this respect, our results align with other observational data. The German Inclisiran Network study reported median LDL-C reductions of 41% and 28% at 3 and 9 months, respectively, despite only one-third of patients receiving statins [31]. Data from the Erasmus University Medical Center lipid registry showed 38% and 34% reductions at 3 and 9 months,

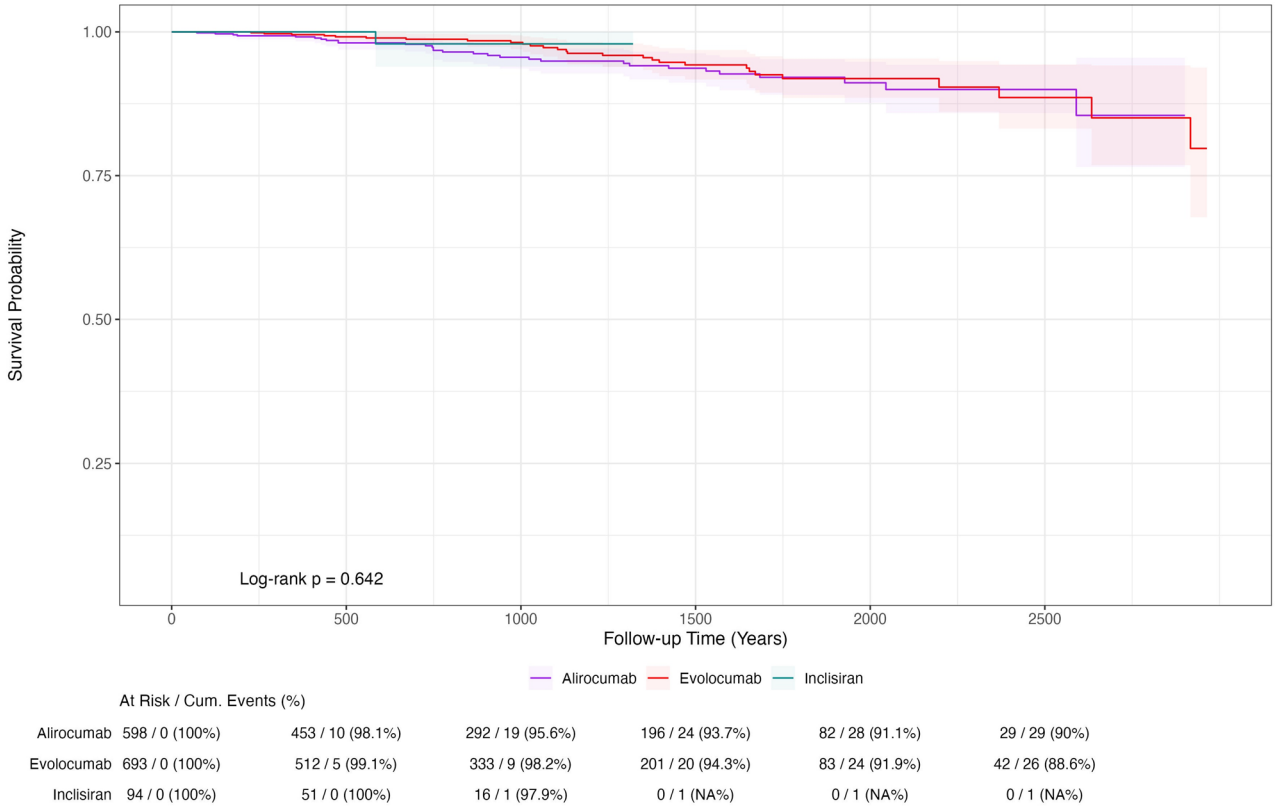


**Fig. 6** Kaplan-Meier survival curves for time to first major adverse cardiovascular event (MACE) by baseline PCSK9 inhibitor therapy (intention-to-treat analysis [ITT]). Survival probability is shown over time for patients initiated on alirocumab, evolocumab, or inclisiran. The ITT approach retains baseline therapy assignment throughout follow-up. Shaded areas represent 95% confidence intervals. The number at risk and cumulative events per group are displayed below the x-axis

respectively, with greater declines among statin-treated patients [18]. Likewise, the largest healthcare organization in Israel reported a 42% LDL-C reduction overall—46% with statin co-therapy and 40% without [16]. Finally, the Italian CHOLINET registry observed a 51% reduction overall—58% with statin and 42% without—although its baseline LDL-C was lower (2.7 mmol/L) and over 70% of patients were on statins [32]. Overall, real-world data—including ours—suggest variable effectiveness of inclisiran depending on patient characteristics and, especially, background statin therapy. These findings should not be interpreted as evidence of intrinsic inferiority of inclisiran, but rather as reflecting real-world differences in treatment context, background statin use, and timing of LDL-C assessment. Notably, ours is the first study to compare all three PCSK9 inhibitors head-to-head. Although baseline characteristics did not differ significantly among patients receiving alirocumab, evolocumab, or inclisiran, the magnitude of LDL-C lowering remained greater with the monoclonal antibodies.

LDL-C target attainment reflects both drug efficacy and our cohort's characteristics, which included many patients who failed to achieve target levels despite adherence to maximally tolerated statin and ezetimibe therapy. At baseline, only about 10% of statin-treated patients reached the ESC/EAS goal of ≤1.4 mmol/L [9]. After PCSK9 inhibitor initiation,>75% of those on alirocumab or evolocumab with statins hit the ≤1.4 mmol/L target at 3 months—on par with ODYSSEY OUTCOMES and FOURIER—while inclisiran plus statin exceeded 50% attainment. In statin-free patients, attainment was low across all agents, especially with inclisiran [13, 15]. These findings mirror other real-world studies showing attenuated inclisiran responses without statins and consistent monoclonal antibody performance regardless of statin use [16–18, 25, 26, 32]. Nevertheless, over 25% of patients on combined PCSK9 inhibitor and statin therapy still missed LDL-C goals, highlighting persistent residual risk and the need for additional strategies. Importantly, the persistence of LDL-C levels above guideline-recommended targets should not be interpreted as treatment failure, but rather as a reflection of real-world implementation gaps. Delayed treatment escalation, limitations in long-term adherence, and the reliance of current lipid-lowering strategies on statin-based combinations substantially restrict achievable LDL-C reduction in patients with SASE. These findings highlight the need for earlier intervention, improved adherence-support strategies,

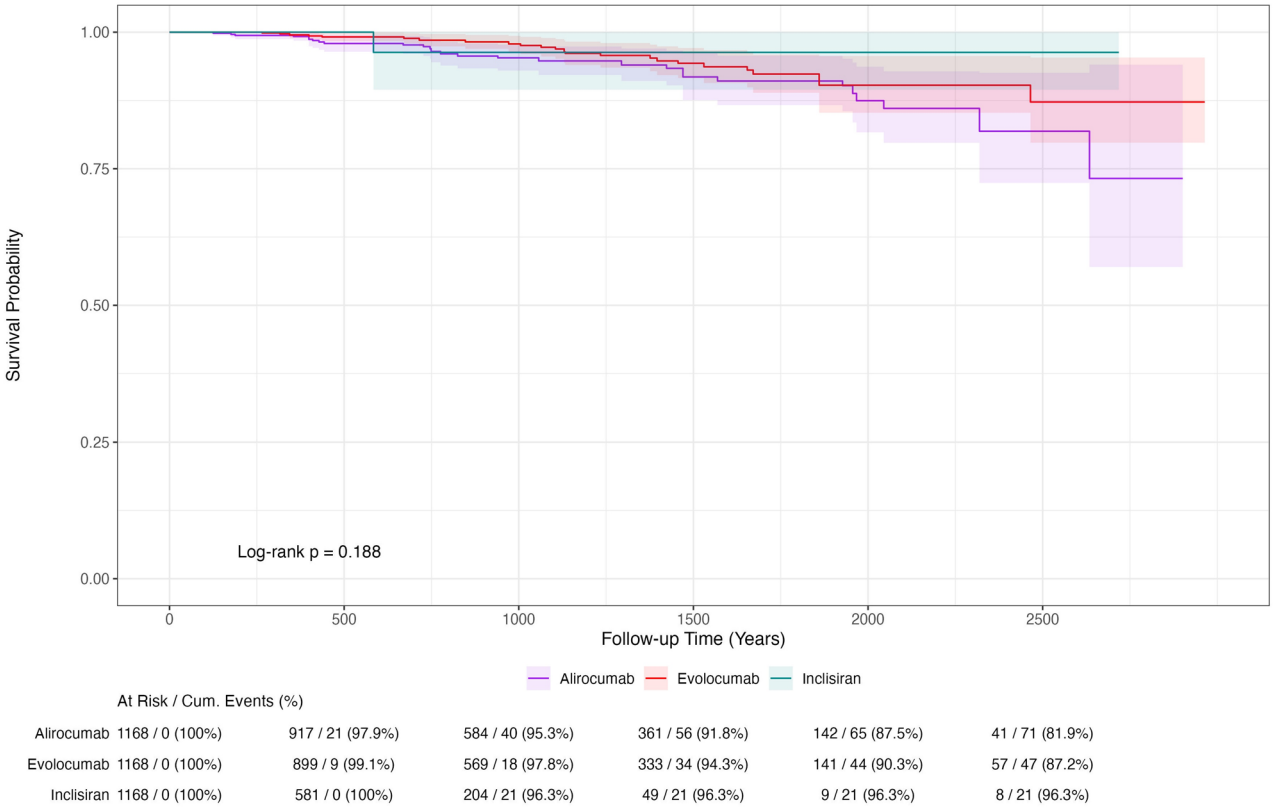


**Fig. 7** Kaplan–Meier curves for inverse probability of treatment weighting (IPTW) survival analysis by therapy. Weighted Kaplan–Meier estimates of time to first major adverse cardiovascular event (MACE) across PCSK9 inhibitor therapies using IPTW derived from covariate balancing propensity scores. The curves represent marginal survival probabilities for inclisiran, alirocumab, and evolocumab. Shaded areas indicate 95% confidence intervals

and the development of additional non-statin lipid-lowering therapies to enable more effective combination regimens and reduce residual cardiovascular risk.

Statin therapy—especially high-intensity regimens—was the most important predictor of LDL-C reduction trajectories after multivariate adjustment, underscoring the additive, pivotal role of combination lipid-lowering therapy. Patients receiving PCSK9 inhibitors following myocardial infarction or revascularization experienced larger adjusted LDL-C reductions than those with other index diagnoses, likely reflecting a stronger commitment by both patients and providers to LDL-C lowering after a major cardiac event. Male sex and increasing age also predicted greater LDL-C reduction, further highlighting the need for outcomes research in diverse, real-world populations. As expected, second-line therapy yielded smaller LDL-C reductions, since first-line non-responders are more prone to treatment failure with a subsequent PCSK9 inhibitor. Importantly, after propensity-score adjustment, LDL-C levels declined significantly over time with all three agents, and inter-therapy differences were no longer statistically significant at later follow-up points. This may reflect treatment-effect stabilization over time and potentially better long-term adherence with inclisiran [33]. However, there are conflicting reports on long-term monoclonal antibody adherence: the European HEYMANS registry reported only an 8% discontinuation rate for evolocumab at 30 months [27].

Adverse effects and therapy-discontinuation rates demonstrate favorable real-world safety profiles for all three PCSK9 inhibitors. Adverse events were reported by 31% of patients across all time points, with the highest incidence immediately after therapy initiation and declining thereafter. This compares favorably with registration trials, in which 70–80% of participants experienced adverse events—most of which were mild and comparable to placebo. The incidence of adverse effects was slightly higher among second-line therapy recipients, reflecting cross-therapy intolerance. Inclisiran exhibited the lowest overall adverse-event burden in our cohort. Although early discontinuation rates exceeded 10% in some subgroups—particularly during the initial months—dropout on first-line therapy remained low (< 3%). This pattern mirrors discontinuation rates observed in major PCSK9 trials, including FOURIER (12–13%) and ODYSSEY OUTCOMES (14–16%), highlighting the challenges of long-term adherence in both trial and real-world settings and underscoring the need for sustained follow-up and support strategies [13–15].

No differences were observed in event-free survival among patients treated with alirocumab, evolocumab, or inclisiran. However, these survival analyses were exploratory and underpowered to detect modest between-group differences, particularly for inclisiran due to its later introduction and smaller sample size. Accordingly, the present findings should be considered hypothesis-generating with respect to comparative cardiovascular outcomes rather than definitive evidence of equivalence across PCSK9 inhibitor therapies. Notably, event rates in our cohort (2.6 per 100 patient-years) were lower than those reported in trial populations (4.5 per 100 patient-years in FOURIER and 3.4 per 100 patient-years in the ODYSSEY OUTCOMES intervention arms) [13, 15]. Despite higher baseline LDL-C levels, our cohort reflects a lower-risk case mix, including patients without prior events or clinically detectable ASCVD. Although our survival analysis was exploratory and underpowered to detect small intergroup differences, it provides valuable real-world insights into PCSK9-inhibitor effectiveness in the absence of randomized head-to-head trials. Most notably, substantial residual cardiovascular risk persisted despite optimal lipid-lowering management.

Several limitations of our study should be acknowledged, although important contextual strengths also apply. First, this observational registry–based study provides measures of association—not causation—between PCSK9-inhibitor therapies and long-term lipid trajectories; nevertheless, our participants reflect real-world clinical populations often underrepresented in randomized trials. Second, the study was conducted at a single centre, which serves as the national referral centre for lipid disorders and had exclusive access to PCSK9 inhibitors during the first two years after their introduction. Third, the inclisiran subgroup was smaller due to its later market availability, and lipid measurements in inclisiran-treated patients were obtained at scheduled follow-up visits corresponding to planned drug administration, without systematic interim assessments. Consequently, LDL-C levels could not be evaluated at fixed intervals after the last injection or as time-averaged reductions, which may have attenuated observed LDL-C lowering and should be considered when comparing inclisiran with monoclonal antibodies. Finally, the survival analysis was underpowered, underscoring the need for future outcomes research in larger, multinational real-world cohorts.

## Conclusions

In this real-world registry, alirocumab, evolocumab, and inclisiran all achieved meaningful LDL-C reductions with good tolerability. Monoclonal antibodies yielded almost 60% unadjusted reductions, whereas reductions with inclisiran were less pronounced yet still clinically significant. Background statin therapy was the single most important independent predictor of LDL-C trajectories, underscoring the role of combination lipid-lowering therapy in achieving LDL-C targets. Despite combination therapy, many patients—especially those with SASE—remained above target, reflecting residual risk. After adjustment for baseline characteristics, long-term LDL-C reductions and cardiovascular event rates were comparable across all three therapies, suggesting similar real-world effectiveness for alirocumab, evolocumab, and inclisiran.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-026-02897-3.

Supplementary Material 1.

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### Use of AI and AI-assisted technologies statement

We acknowledge the use of artificial intelligence (AI)-based natural language processing tools for language editing and minor assistance with coding and data processing. These tools were used to improve clarity and readability and to facilitate certain computational tasks. No AI tool was involved in generating original scientific content, analysis, or interpretation.

### Originality of content

We confirm all information and materials in the manuscript are original.

### Authors' contributions

Conceptualization: J.K., Z.F., M.N. and B.J.; Methodology: J.K., Z.F., M.N., U.G. and B.J.; Validation: M.N., L.S.S., M.C., B.K., and U.G.; Formal analysis: J.K. and B.J.; Investigation: J.K., M.N., M.C., B.K., L.K., A.K., K.K., K.V., and M.S.; Data Curation: J.K., M.N., M.C., B.K., L.K., A.K., K.K., K.V., and M.S.; Writing - Original Draft: J.K. and B.J.; Writing - Review & Editing: Z.F., L.S.S., M.N., M.C., B.K., L.K., A.K., K.K., K.V., M.S., and U.G.; Visualization: B.J.; Supervision: : Z.F., L.S.S., U.G., B.J.; Funding acquisition: Z.F., U.G., B.J.

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### Data availability

Data are available from the corresponding author upon reasonable request.

## Declarations

### Ethics approval and consent to participate

The study was approved by the Slovenian National Medical Ethics Committee (No. 22/01/2017; 0120 – 14/2017-2; 0120 – 14/2017-5). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the dyslipidemia registry.

### Competing interests

J.K. received speaking honoraria from Medison Pharma. Z.F. received speaker honoraria / consultancy fees from Novo Nordisk, Swixx Biopharma and

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## References

1. Mensah GA, Fuster V, Murray CJL, et al. Global burden of cardiovascular diseases and Risks, 1990–2022. J Am Coll Cardiol. 2023;82:2350–473. https://doi.org/10.1016/j.jacc.2023.11.007.
2. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European atherosclerosis society consensus panel. Eur Heart J. 2017;38:2459–72. https://doi.org/10.1093/eurheartj/ehx144.
3. Heart Protection Study Collaborative G. Effects on 11-year mortality and morbidity of Lowering LDL cholesterol with Simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. Lancet. 2011;378:2013–20. https://doi.org/10.1016/S0140-6736(11)61125-2.
4. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab. 2012;97:3956–64. https://doi.org/10.1210/jc.2012-1563.
5. Scandinavian Simvastatin Survival Study G. Randomised trial of cholesterol Lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin survival study (4S). Lancet. 1994;344:1383–9. https://doi.org/10.1016/S0140-6736(94)90566-5.
6. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195–207. https://doi.org/10.1056/NEJMoa0807646.
7. Writing C, Lloyd-Jones DM, Morris PB, et al. ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2022;80:1366–418. https://doi.org/10.1016/j.jacc.2022.07.006
8. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to Statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–97. https://doi.org/10.1056/NEJMoa1410489.
9. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41:111–88. https://doi.org/10.1093/eurheartj/ehz455.
10. Ray KK, Molemans B, Schoonen WM, et al. EU-Wide Cross-Sectional observational study of Lipid-Modifying therapy use in secondary and primary care: the DA VINCI study. Eur J Prev Cardiol. 2021;28:1279–89. https://doi.org/10.1093/eurjpc/zwaa047.
11. Bytyci I, Penson PE, Mikhailidis DP, et al. Prevalence of Statin intolerance: a meta-analysis. Eur Heart J. 2022;43:3213–23. https://doi.org/10.1093/eurheartj/ehac015.
12. Banach M, Rizzo M, Toth PP, et al. Statin intolerance - an attempt at a unified definition. Position paper from an international lipid expert panel. Arch Med Sci. 2015;11:1–23. https://doi.org/10.5114/aoms.2015.49807.
13. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018;379:2097–107. https://doi.org/10.1056/NEJMoa1801174.
14. Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020;382:1507–19. https://doi.org/10.1056/NEJMoa1912387.
15. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376:1713–22. https://doi.org/10.1056/NEJMoa1615664.
16. Naoum I, Saliba W, Aker A, Zafrir B. Lipid-lowering therapy with inclisiran in the real-world setting: initial data from a National health care service. J Clin Lipidol. 2024;18:e809–16. https://doi.org/10.1016/j.jacl.2024.05.003.
17. Gupta M, Mancini GBJ, Wani RJ, et al. Real-World insights into Evolocumab use in patients with hyperlipidemia: Canadian analysis from the ZERBINI study. CJC Open. 2022;4:558–67. https://doi.org/10.1016/j.cjco.2022.03.003.
18. Mulder J, Galema-Boers AMH, van Roeters JE. First clinical experiences with inclisiran in a real-world setting. J Clin Lipidol. 2023;17:818–27. https://doi.org/10.1016/j.jacl.2023.09.005.
19. Programme WHOHG. Familial hypercholesterolaemia (FH): report of a second WHO consultation, Geneva, 4 September 1998. In. Geneva: World Health Organization; 1999.
20. Kafol J, Miranda B, Sikonja R, et al. Proposal of a Familial hypercholesterolemia pediatric diagnostic score (FH-PeDS). Eur J Prev Cardiol. 2025. https://doi.org/10.1093/eurjpc/zwaf352.
21. Sustar U, Kordonouri O, Mlinaric M, et al. Universal screening for Familial hypercholesterolemia in 2 populations. Genet Med. 2022;24:2103–11. https://doi.org/10.1016/j.gim.2022.06.010.
22. Ain Q, Sikonja J, Sadiq F, et al. Cascade screening of a Pakistani consanguineous Familial hypercholesterolemia cohort: identification of seven new homozygous patients. Atherosclerosis. 2025;402:119118. https://doi.org/10.1016/j.atherosclerosis.2025.119118.
23. Chora JR, Iacocca MA, Tichy L, et al. The clinical genome resource (ClinGen) Familial hypercholesterolemia variant curation expert panel consensus guidelines for LDLR variant classification. Genet Med. 2022;24:293–306. https://doi.org/10.1016/j.gim.2021.09.012.
24. Chora JR, Medeiros AM, Alves AC, Bourbon M. Analysis of publicly available LDLR, APOB, and PCSK9 variants associated with Familial hypercholesterolemia: application of ACMG guidelines and implications for Familial hypercholesterolemia diagnosis. Genet Med. 2018;20:591–8. https://doi.org/10.1038/gim.2017.151.
25. Ebenbichler C, Drexel H, Hanusch U, et al. Evolocumab effectiveness in the real-world setting: Austrian data from the pan-European observational HEYMANS study. Wien Klin Wochenschr. 2024;136:77–86. https://doi.org/10.1007/s00508-023-02245-w.
26. Leitner DR, Toplak H, Kedenko L, et al. Efficacy and tolerability of Alirocumab in Austrian clinical practice - results of the non-interventional PEARL-AT study. Curr Med Res Opin. 2020;36:1419–25. https://doi.org/10.1080/03007995.2020.1786678.
27. Ray KK, Bruckert E, Peronne-Filardi P, et al. Long-term persistence with Evolocumab treatment and sustained reductions in LDL-cholesterol levels over 30 months: final results from the European observational HEYMANS study. Atherosclerosis. 2023;366:14–21. https://doi.org/10.1016/j.atherosclerosis.2023.01.002.
28. Gargiulo P, Basile C, Galasso G, et al. Strike early-strike strong lipid-lowering strategy with proprotein convertase subtilisin/kexin type 9 inhibitors in acute coronary syndrome patients: real-world evidence from the AT-TARGET-IT registry. Eur J Prev Cardiol. 2024;31:1806–16. https://doi.org/10.1093/eurjpc/zwae170.
29. Gargiulo P, Basile C, Cesaro A, et al. Efficacy, safety, adherence and persistence of PCSK9 inhibitors in clinical practice: A single country, multicenter, observational study (AT-TARGET-IT). Atherosclerosis. 2023;366:32–9. https://doi.org/10.1016/j.atherosclerosis.2023.01.001.
30. Lagace TA. PCSK9 and LDLR degradation: regulatory mechanisms in circulation and in cells. Curr Opin Lipidol. 2014;25:387–93. https://doi.org/10.1097/MOL.0000000000000114.
31. Makhmudova U, Schatz U, Perakakis N, et al. High interindividual variability in LDL-cholesterol reductions after inclisiran administration in a real-world multicenter setting in Germany. Clin Res Cardiol. 2023;112:1639–49. https://doi.org/10.1007/s00392-023-02247-8.
32. Gargiulo P, Marzano F, Crisci M, et al. Real-World efficacy and safety of inclisiran: A Single-Country, Multicenter, observational study (CHOLINET Registry). J Am Coll Cardiol. 2025;85:536–40. https://doi.org/10.1016/j.jacc.2024.10.106.
33. Popadic L, Ma X, Ali Y, et al. Treatment patterns among early inclisiran vs Anti–PCSK9 mAbs users: A retrospective analysis of US claims databases. J Clin Lipidol. 2024;18:e515–6. https://doi.org/10.1016/j.jacl.2024.04.045.

## Publisher's Note