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Original Research

Reduction of visit-to-visit LDL-C intraindividual variability in patients treated with PCSK9 inhibitors and inclisiran vs standard lipid-lowering therapy

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BACKGROUND: Recent evidence suggests that visit-to-visit low-density lipoprotein cholesterol (LDL-C) variability—a measure of intraindividual lipid fluctuation over time—may independently influence cardiovascular risk. This study evaluated the impact of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) and inclisiran on LDL-C variability compared to standard lipid-lowering therapy (LLT) in a real-world population of very high-risk patients.

METHODS: We conducted a longitudinal, observational study including 618 patients at very high cardiovascular risk, treated at a single tertiary center. Patients were stratified into 3 groups: standard LLT (statins ± ezetimibe), PCSK9i, or inclisiran. LDL-C variability was assessed at 4 follow-up time points using both SD and coefficient of variation (CV), excluding the first lipid measurement to minimize early

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response bias. High variability was defined as SD or CV above the population median. Major adverse cardiovascular events (MACE) were collected as exploratory outcomes.

RESULTS: Patients receiving PCSK9i or inclisiran had significantly lower LDL-C variability compared to those on standard LLT (mean SD: 8.2 and 8.5 vs. 20.5 mg/dL; $P < .001$; mean CV: 0.17 and 0.16 vs. 0.31; $P < .001$). High variability in both SD and CV was observed in 77.3% of patients on standard LLT, but only in 17.2% and 17.1% of patients on PCSK9i and inclisiran, respectively. MACE incidence was higher in patients with high variability (12.5% vs. 6.1%, $P = .012$). Multivariate analysis confirmed that treatment with PCSK9i or inclisiran was independently associated with lower LDL-C variability.

CONCLUSIONS: In patients at very high cardiovascular risk, PCSK9i and inclisiran therapies are associated with significantly lower visit-to-visit LDL-C variability compared to standard statin-based regimens. These findings support the importance of not only achieving LDL-C targets but also maintaining lipid stability over time, which may contribute to improved cardiovascular outcomes.

Introduction

Over the past several decades, extensive research has established that elevated levels of low-density lipoprotein cholesterol (LDL-C) significantly contribute to the pathogenesis of atherosclerosis and its clinical outcomes.[1,2] Achieving consistent and stable LDL-C levels is crucial for reducing the risk of atherosclerotic cardiovascular events.[2] Traditional lipid-lowering strategies have primarily focused on reducing the mean concentrations of LDL-C to decrease cardiovascular risk. While statins have long been the cornerstone of lipid-lowering therapy (LLT), newer therapeutic agents, such as proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) and inclisiran, have emerged as powerful alternatives, particularly for patients with high cardiovascular risk or statin intolerance.[3–8] However, emerging evidence highlights the importance of lipid stability over time, or lipid variability, in influencing cardiovascular health. Fluctuations in lipid levels may lead to transient periods of increased atherogenic burden, which, over time, could cause vascular damage and accelerate the progression of atherosclerosis.[9,10]

Notably, high visit-to-visit variability in LDL-C has been identified as an independent predictor of major adverse cardiovascular events (MACE), as shown in the Treating to New Target (TNT) trial.[11] Further supporting this, data from the Coronary Artery Risk Development in Young Adults (CARDIA) study have emphasized the crucial role of lipid variability in the development of coronary artery calcium (CAC).[12] The results demonstrated that a 1-SD increase in lipid variability, independent of the mean, was strongly linked to a higher risk of CAC.[12]

These findings suggest that not only the mean levels of lipids but also their fluctuations over time should be considered in atherosclerosis progression.

This study aims to evaluate the impact of PCSK9i and inclisiran therapies on the reduction of visit-to-visit LDL-C variability compared to standard LLT in patients at very high cardiovascular risk. Understanding how these newer therapies affect LDL-C variability is crucial for determining their role in improving long-term cardiovascular outcomes and refining treatment strategies for high-risk patients.

Methods

Study design and population

This longitudinal study included patients attending the Cardiology Outpatient Clinic of the S. Anna and S. Sebastiano Hospital in Caserta, Italy, between January 2022 and December 2022. All patients included in the study had a history of cardiovascular events (eg, myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, or stroke) or were classified as very high cardiovascular risk based on their clinical characteristics and profiles, in accordance with current risk stratification scores (SCORE 2 and SCORE 2 OP) as recommended by the European Society of Cardiology (ESC).

Patients were prescribed the most appropriate LLT according to current ESC guidelines, which considered their risk profiles, baseline lipid levels, distance to LDL-C target, and national reimbursement rules for lipid-lowering medications. Based on their prescribed therapies, patients were categorized into 3 groups: "standard LLT," "PCSK9i," and "inclisiran." The standard LLT therapy was defined as statins alone or in combination with ezetimibe. LLT was prescribed based on each patient's risk and current lipid profile, with adjustments made to achieve target LDL-C levels according to established ESC guidelines. Notably, both PCSK9i and inclisiran were prescribed as add-on therapies on top of standard LLT (statins ± ezetimibe), except in cases of documented statin or ezetimibe intolerance.

At the time of enrollment, a complete lipid profile was assessed for each patient. Follow-up assessments were carried out at 4 time points, every 6 months, to monitor lipid levels, with a primary focus on LDL-C levels. Clinical measurements followed standardized protocols to ensure consistency across visits.

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Table 1. Baseline characteristics of the study population stratified by lipid-lowering therapy group.

	Overall population ($n = 618$)	Standard LLT ($n = 274$)	PCSK9i ($n = 192$)	Inclisiran ($n = 152$)	*P*-value
Age - yrs, mean (SD)	63 (11.19)	67.5 (10.64)	61.1 (10.44)	60 (10.95)	<.001
Male gender, n (%)	399 (64.6)	196 (71.5)	118 (61.5)	85 (55.9)	.003
Hypertension, n (%)	472 (76.4)	222 (81)	140 (72.9)	110 (72.3)	.052
Diabetes, n (%)	148 (23.9)	76 (27.7)	40 (20.8)	32 (21)	.144
Familial history of ASCVD, n (%)	137 (22.2)	36 (13.1)	56 (29.2)	45 (29.6)	<.001
Previous MI, n (%)	286 (46.2)	72 (26.3)	126 (65.6)	88 (57.9)	<.001
Previous PCI, n (%)	306 (49.5)	98 (35.8)	118 (61.5)	90 (59.2)	<.001
Previous CABG, n (%)	29 (4.7)	12 (4.4)	10 (5.2)	7 (4.6)	.915
Previous stroke, n (%)	30 (4.9)	6 (2.2)	12 (6.3)	12 (7.9)	.018
Peripheral artery disease, n (%)	37 (6)	8 (2.9)	16 (8.3)	13 (8.5)	.016
Statins, n (%)	510 (82.5)	274 (100)	128 (66.7)	108 (71)	<.001
Ezetimibe, n (%)	468 (75.7)	128 (46.7)	190 (98.9)	150 (98.7)	<.001
Total cholesterol - mg/dL, mean (SD)	198.82 (62.87)	151.39 (41.09)	231.33 (52.36)	232.43 (55.33)	<.001
HDL-C - mg/dL, mean (SD)	45.43 (12.29)	44.89 (12.23)	45.77 (12.06)	45.78 (12.73)	.708
LDL-C - mg/dL, mean (SD)	120.26 (43.63)	83.08 (35.88)	145.05 (29.94)	142.27 (28.74)	<.001
Triglycerides - mg/dL, mean (SD)	140.88 (61.84)	127.69 (59.32)	152.59 (62.89)	147.24 (60.86)	<.001

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; MI, myocardial infarction; PCI, percutaneous coronary intervention; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors; yrs, years.

Lipid profile and variability assessment

The primary outcome of this study was the visit-to-visit variability of LDL-C. At each time point, LDL-C was measured, and the variability across visits was assessed using 2 statistical indices: the SD and the coefficient of variation (CV). The SD was calculated as the square root of the variance of LDL-C values over the course of the study, while the CV was calculated as the ratio of the SD to the mean LDL-C, expressed as a percentage. To avoid bias from an initial large drop in LDL-C values—observed particularly in the PCSK9i and inclisiran groups—the first measurement was excluded, and variability was assessed starting from the second time point onward.

Patients were categorized into 2 groups based on LDL-C variability: those with high variability (above the median SD or CV) and those with low variability (below the median). To identify patients with the highest variability, the study combined both SD and CV measurements, with patients above the median for both indices classified as having the highest variability.

An exploratory analysis was performed to assess the occurrence of MACE in patients with high and low LDL-C variability during 24 months follow-up. MACE were defined as a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and urgent coronary revascularization.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics and lipid profiles. Continuous variables were presented as mean ± SD or median with IQR, depending on the data distribution. The normal distribution of data was evaluated using the Kolmogorov–Smirnov goodness-of-fit test. Comparisons between the 3 therapy groups (standard LLT, PCSK9i, and inclisiran) were conducted using analysis of variance (ANOVA) for normally distributed data, or the Kruskal–Wallis test for non-normally distributed data. Categorical variables were expressed as frequencies and percentages, with comparisons made using the Pearson chi-square test. Multivariate analysis was performed to assess the impact of lipid-lowering therapy type (standard LLT, PCSK9i, inclisiran) on LDL-C variability, adjusting for potential confounders such as age, gender, and baseline lipid levels. We included variables that were significant in univariate analyses using a threshold of $P < .1$, along with those considered clinically relevant based on prior evidence and their potential impact on the outcomes. A *P*-value of less than .05 was considered statistically significant. All statistical analyses were conducted using SPSS version 29 (IBM) and R software (CRAN 3.3.4).

Results

A total of 727 patients were enrolled in the study, with 618 completing the analysis and follow-up. The study population consisted of 399 males (63.6%) with a mean age of 63.7 years (±11.2). The PCSK9i and inclisiran groups were slightly younger than the standard LLT group. The baseline characteristics of patients are shown in Table 1. There were no significant differences in comorbidities between the 3 groups. However, patients treated with PCSK9i and inclisiran had a higher cardiovascular risk profile as they were more likely to have a family history of cardiovascular disease and a history

Table 2. LDL-C variability indices (SD and coefficient of variation) by treatment group.

	Overall population ($n = 618$)	Standard LLT ($n = 274$)	PCSK9i ($n = 192$)	Inclisiran ($n = 152$)	*P*-value
SD, mean (SD)	13.74 (9.45)	20.53 (8.68)	8.22 (5.97)	8.45 (5.77)	<.001
CV, mean (SD)	0.23 (0.14)	0.31 (0.13)	0.17 (0.11)	0.16 (0.11)	<.001
High variability - SD, n (%)	309 (50)	234 (85.4)	41 (21.4)	34 (22.4)	<.001
High variability - CV, n (%)	309 (50)	216 (78.8)	53 (27.6)	40 (26.3)	<.001
High variability - CV + SD, n (%)	271 (43.9)	212 (77.4)	33 (17.2)	26 (17.1)	<.001

Abbreviations: CV, coefficient of variation; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors.

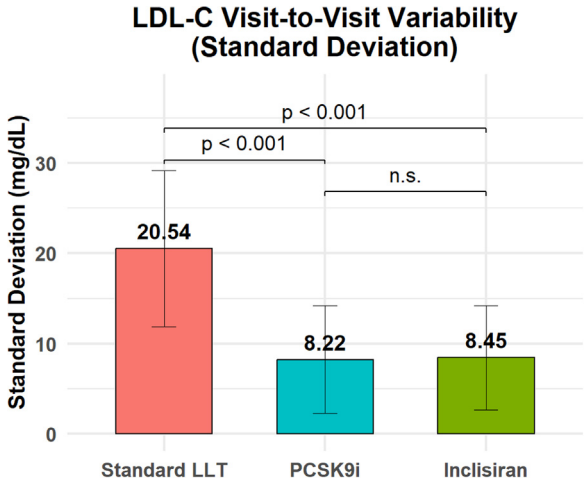

Figure 1. Bar graph showing mean LDL-C variability (SD) by treatment group. "High variability" is defined as patients exhibiting SD of LDL-C values above the median of the study population. Specifically, SD: Variation in LDL-C values across visits measured as the SD above the population median. Abbreviations: LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors.

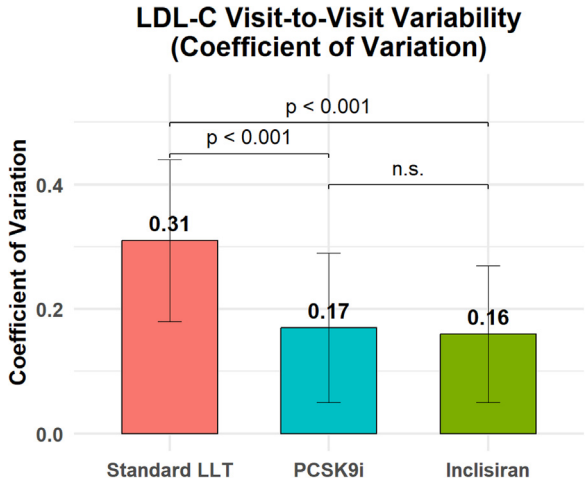

Figure 2. Bar graph showing mean LDL-C variability (coefficient of variation) by treatment group. "High variability" is defined as patients exhibiting a coefficient of variation (CV) of LDL-C values above the median of the study population. Specifically, CV: The ratio of the SD to the mean LDL-C, expressed as a percentage, above the population median. Abbreviations: CV, coefficient of variation; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors.

of previous cardiovascular events or revascularization procedures.

The mean baseline LDL-C for the entire cohort was 120.26 mg/dL (±43.63), with patients in the PCSK9i and inclisiran groups showing significantly higher levels compared to those in the standard LLT group (145.05 [±29.94], 142.27 [±28.74], and 83.08 [±35.88], respectively), with a greater distance from the recommended LDL-C targets.

The overall SD for LDL-C variability was 13.74 mg/dL (±9.45) (Table 2). The standard LLT group exhibited the highest variability, with an SD of 20.53 mg/dL (±8.68), while the PCSK9i and inclisiran groups showed lower variability, with an SD of 8.22 mg/dL (±5.97) and 8.45 mg/dL (±5.77), respectively ($P < .001$). Similarly, the overall CV for LDL-C variability was 0.23 (±0.14) (Fig 1). The standard LLT group had a significantly higher CV (0.31 ± 0.13) compared to the PCSK9i (0.17 ± 0.12) and inclisiran (0.16 ± .11) groups ($P < .001$) (Fig 2).

The percentage of patients with high LDL-C variability, defined as SD or CV above the median, was significantly different between the groups. In the standard LLT group, 85.4% of patients exhibited high variability in LDL-C measured by SD, compared to 21.4% in the PCSK9i group and 22.4% in the inclisiran group ($P < .001$). Similarly, 78.8% of patients in the standard LLT group had high CV variability, while only 27.6% of patients in the PCSK9i group and 26.3% in the inclisiran group exhibited high variability ($P < .001$). When both SD and CV were considered simultaneously, 77.3% of patients in the standard LLT group showed high variability in both indices, compared to 17.2% in the PCSK9i group and 17.1% in the inclisiran group (Fig 3).

The incidence of MACE was significantly different across the treatment groups. In the standard LLT group, 12.4% of patients experienced a MACE, compared to 5.7% in the PCSK9i group ($P = .017$) and 7.9% in the inclisiran group ($P = .192$). Among patients with high variability in both SD and CV, the incidence of MACE was 12.5%, compared to 6.1% in patients with low variability ($P = .012$) (Fig 4).

The multivariate logistic regression analysis revealed that patients receiving statin therapy alone, without adding

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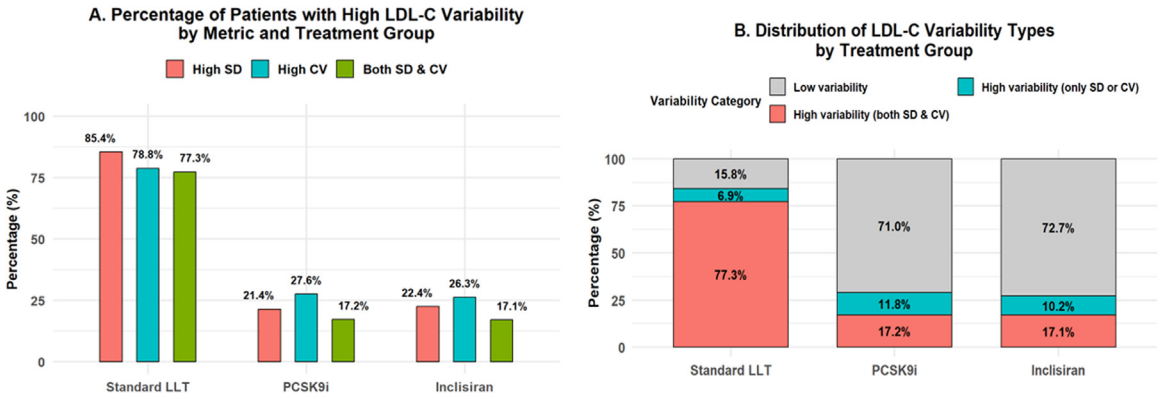

Figure 3. Distribution of patients with high LDL-C variability across treatment groups. Patients meeting criteria for both SD and CV above the median were classified as having high LDL-C visit-to-visit variability, indicating greater fluctuations in LDL-C levels over time. Abbreviations: CV, coefficient of variation; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors.

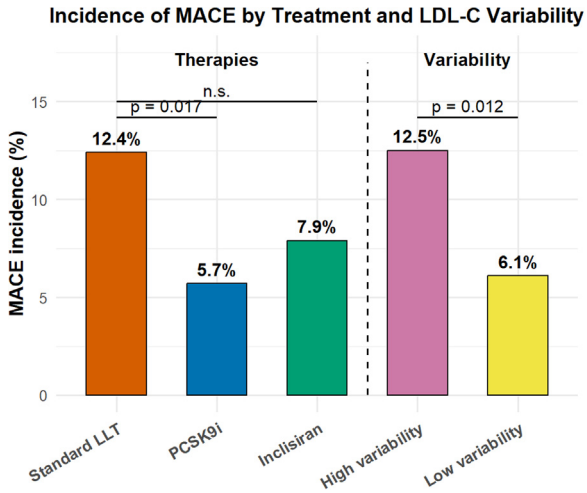

Figure 4. Incidence of MACE according to treatment group and LDL-C variability. Abbreviations: LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; MACE, major cardiovascular events; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors.

PCSK9i or inclisiran, had significantly higher LDL-C variability ($P < .001$). In contrast, treatment with PCSK9i and inclisiran was associated with lower LDL-C variability, highlighting the potential benefits of these therapies in reducing LDL-C fluctuations over time (Table 3).

Discussion

The main findings of the current study can be summarized as follows. First, LDL-C variability was significantly higher in patients receiving standard LLT than in those treated with PCSK9i or inclisiran. Specifically, the SD and CV were markedly elevated in the standard LLT group, suggesting a greater degree of fluctuation in LDL-C levels over time. Second, multivariate analysis confirmed that treatment with PCSK9i and inclisiran was independently associated with lower LDL-C variability, while statin therapy alone was a significant predictor of greater variability. Third, patients with higher LDL-C variability exhibited an increased incidence of MACE. Notably, among patients with high variability (SD and CV above the median), the incidence of MACE was significantly higher (12.5%) compared to those with lower variability (6.1%). These findings highlight the potential clinical relevance of LDL-C variability as a significant factor influencing cardiovascular outcomes, suggesting that novel lipid-lowering strategies may confer additional benefits beyond LDL-C reduction by promoting lipid stability.

In the context of lipid management, it is important to distinguish between intraindividual and interindividual variability. While interindividual variability reflects differences in treatment response due to genetic, demographic, and phenotypic factors, intraindividual variability refers to fluctuations in LDL-C levels within the same patient over time. The latter has been shown to be a significant predictor of cardiovascular events, as inconsistent LDL-C control may increase the risk of atherosclerotic progression and adverse outcomes. A real-world retrospective study in 3398 patients with stable coronary artery disease demonstrated that greater LDL-C variability is associated with increased risk of all-cause mortality and cardiovascular hospitalizations. Over a median follow-up of 56 months, only 31.9% of patients achieved LDL-C <70 mg/dL despite statin therapy, and each 20 mg/dL increase in LDL-C at the last visit was linked to a 6% higher risk of adverse events (hazard ratio [HR]: 1.06; 95% CI, 1.03-1.09).[13]

It is well known that there is significant interindividual variability in response to LLT.[14] A recent study employing a waterfall plot approach illustrated the broad heterogeneity in individual LDL-C responses to lipid-lowering therapies in a real-world setting, highlighting that a substantial proportion of patients fail to reach guideline-recommended targets despite treatment intensification.[15] Patient response to statin treatment is heterogeneous, leading to a broad range of LDL-C reductions even with a fixed-dose approach. Data from the VOYAGER [16] meta-analysis, which included 32,258 pa-

Table 3. Multivariate logistic regression analysis of predictors of high LDL-C variability.

High Variability by SD			High Variability by CV			High Variability by SD & CV		
Variables	OR [CI, 95%]	*P*-value	Variables	OR [CI, 95%]	*P*-value	Variables	OR [CI, 95%]	*P*-value
Age	1.02 [0.99-1.04]	.197	Age	1.01 [0.99-1.03]	.427	Age	1.01 [0.98-1.03]	.552
Gender, Male	1.36 [0.85-2.16]	.192	Gender, Male	1.46 [0.95-2.23]	.081	Gender, Male	1.10 [0.70-1.74]	.672
Arterial hypertension	1.27 [0.75-2.16]	.377	Family History of ASCVD	0.96 [0.57-1.61]	.874	Arterial hypertension	1.59 [0.94-2.70]	.083
Family history of ASCVD	1.15 [0.64-2.07]	.643	Previous stroke	5.83 [2.38-14.24]	<.001	Family History of ASCVD	1.17 [0.67-2.07]	.582
Previous MI	1.27 [0.74-2.19]	.393	Previous MI	0.80 [0.50-1.29]	.359	Previous MI	0.89 [0.53-1.50]	.064
Previous PCI	1.48 [0.88-2.47]	.136	Previous PCI	1.23 [0.77-1.97]	.382	Previous PCI	1.25 [0.75-2.08]	.386
Statin intolerance	1.51 [0.87-2.62]	.143	LDL-C	1.00 [0.99-1.01]	.552	LDL-C	0.99 [0.99-1.01]	.789
LDL-C	1.00 [0.99-1.01]	.973	**Standard LLT**	10.19 [5.49-18.89]	<.001	**Standard LLT**	16.73 [8.69-32-22]	<.001
Standard LLT	**31.57 [14.21-70.12]**	**<.001**						

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CV, coefficient of variation; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention.

tients treated with atorvastatin, rosuvastatin, or simvastatin, demonstrated that the SD of LDL-C reduction for these statins ranged from 12.8% to 17.9%. Moreover, interindividual variability has also been reported with PCSK9i and inclisiran, indicating that response to these therapies is not uniform across patients.[17,18] In an analysis of the FOURIER trial, Qamar et al. reported that over 90% of patients treated with evolocumab achieved an LDL-C reduction of ≥50% at 4 weeks, and >99% achieved a reduction of ≥30%, demonstrating minimal interindividual response variability.[19] Beyond the well-known interindividual variability in response to statins, PCSK9i, and inclisiran, there is the intraindividual variability in LDL-C levels over time, which appears to have an even greater prognostic impact.[10,11] Significant fluctuations in LDL-C within the same individual have been associated with an increased cardiovascular risk, independent of average LDL-C levels, suggesting that maintaining lipid stability could be a crucial therapeutic target to improve clinical outcomes.[9–11]

Recent findings from the SWEDEHEART registry reinforce the concept that lipid-lowering goals should be achieved not only promptly but also maintained over time. In a cohort of over 56,000 patients with myocardial infarction, those who attained non-HDL-C targets within 2 months and sustained them at 1 year had the lowest incidence of adverse cardiovascular outcomes (HR: 0.80, 95% CI, 0.74-0.86), compared to those who reached the target either early or late. These results highlight that the prognostic benefit of lipid-lowering therapy depends not only on achieving targets but on achieving them early and durably, challenging the traditional stepwise approach that may delay optimal risk reduction.[20]

Our data confirm that LDL-C variability is significantly higher in patients receiving standard LLT compared to those treated with PCSK9i or inclisiran. In particular, LDL-C fluctuations were more pronounced in the standard LLT group, with an SD more than twice as high as in the PCSK9i and inclisiran groups. Similarly, a significantly larger proportion of patients on statin therapy alone exhibited high LDL-C variability, with over 85% showing elevated SD values, compared to approximately 22% in the PCSK9i and inclisiran groups. When considering both SD and CV together, nearly 77% of patients in the standard LLT group had high variability in both indices, whereas this was observed in only about 17% of those receiving PCSK9i or inclisiran.

The reduction of LDL-C is dose-dependent and varies between statins, with considerable differences in response observed among individuals receiving the same dose. This variability has been linked to demographic, phenotypic, and genetic factors. A study in Spain, which analyzed data from the SEA Dyslipidaemia Registry, explored the effectiveness of statins in managing primary hypercholesterolemia. Among the 1004 patients included, rosuvastatin 40 mg showed the greatest reduction in LDL-C, achieving a mean reduction of 58.7%. In contrast, simvastatin 10 mg resulted in the lowest reduction, at 32.5%.[21] The combination therapy of statins and ezetimibe was associated with less variability in LDL-C reduction, suggesting a more consistent therapeutic response.[21] Recent large-scale studies have demonstrated that combining ezetimibe with statins yields a more stable reduction in LDL-C levels compared to statin therapy alone, reducing variability in treatment responses. A pooled analysis from 27 clinical trials involving over 21,000 patients showed that the variability in LDL-C reduction was significantly lower in the combination therapy group (ezetimibe + statins) than in those treated with statins alone.[22] The reduced variability observed with combination therapy can be attributed to the larger mean LDL-C reductions achieved by combining these 2 therapies. These findings suggest that combination therapy with ezetimibe and statins offers a more predictable response, which could improve the ability to meet LDL-C targets.

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In this context, it is appropriate to focus on therapeutic adherence. A limitation of our study is the lack of direct measurement of adherence to oral background therapies such as statins and ezetimibe. No validated adherence scales or indices were used, thus, adherence levels remain unknown. Nevertheless, it is reasonable to hypothesize that nonadherence and patient self-discontinuation represent key contributors to the elevated LDL-C variability observed, particularly in the standard oral therapy group. Moreover, it is plausible that some patients receiving injectable therapies (PCSK9i or inclisiran) may discontinue their oral background therapy independently while maintaining the injectable treatment, potentially leading to LDL-C fluctuations even within these groups. Regarding this, our previous real-world data indicate that patients treated with PCSK9i exhibit higher adherence to both the injectable therapy and the oral background therapy compared to patients receiving oral LLT alone.[8] Medication adherence often influences intraindividual or visit-to-visit variability in LDL-C levels, particularly in patients receiving statin therapy.[23] This variability poses a challenge in assessing adherence across a broad spectrum of patients, and inconsistent adherence to statin therapy can lead to fluctuations in LDL-C levels. A retrospective analysis of 782 statin-treated patients from the Boston Medical Center Health Plan revealed that higher visit-to-visit variability of LDL-C—quantified as the within-patient SD—was strongly associated with statin nonadherence. The proportion of nonadherent patients increased progressively across variability quintiles, reaching over 90% in the highest quintiles. In multivariate analysis, patients in the highest variability quintile had 3.4 times the odds of nonadherence compared to those in the lowest quintile.[23] Notably, an LDL-C variability–based model incorporating demographic and lipid parameters demonstrated good discrimination in predicting nonadherence (C-statistic 0.75), outperforming models based solely on age and gender. These findings support the use of LDL-C variability as a practical surrogate marker of adherence in routine clinical settings, particularly when pharmacy refill data are unavailable.[23]

Injectable agents such as PCSK9 monoclonal antibodies, administered every 2 or 4 weeks, and inclisiran, with its twice-yearly dosing regimen, may offer substantial adherence advantages over daily oral therapies.[17] This improved adherence profile likely contributes to the observed reduction in LDL-C variability and may translate into more consistent cardiovascular risk reduction. Real-world data have shown that long-acting injectable agents can reduce therapeutic inertia and improve long-term persistence with treatment.[6,24,25]

The pharmacodynamic consistency shown by PCSK9i may help explain the lower visit-to-visit LDL-C fluctuations observed in our cohort, particularly compared to standard statin-based regimens. These data further reinforce the potential clinical advantages of PCSK9i and inclisiran, not only in achieving LDL-C targets but also in maintaining lipid stability over time, which may represent an underappreciated mechanism contributing to cardiovascular risk reduction. The almost uniform efficacy of evolocumab reported in the FOURIER subanalysis suggests that biological resistance or nonresponse is exceedingly rare, especially when compared to the heterogeneity frequently seen with statins. While PCSK9i are typically associated with robust and predictable LDL-C reductions, some reports highlight that intraindividual variability may still occur, particularly depending on the timing of lipid assessment. In a case study, LDL-C levels in a patient treated with alirocumab 75 mg every 2 weeks fluctuated markedly—from 37 mg/dL (1 day after injection) to 90 mg/dL (13 days postinjection, just before the next dose).[26] These observations suggest that LDL-C levels rebound as drug concentrations wane, likely due to reactivation of PCSK9-mediated LDL receptor degradation.

In RUTHERFORD-2, the intraindividual CV for LDL-C response to evolocumab was 4.5% when measured at day 71 and day 78 of therapy, indicating extremely low within-patient variability during steady-state dosing.[27] Pharmacokinetic modeling and data from 4 ODYSSEY phase 3 trials have shown that LDL-C levels fluctuate meaningfully within the 14-day dosing cycle of alirocumab. LDL-C reaches its nadir around day 7 postinjection, followed by a progressive rebound of up to 30–40% by day 14, associated with a concomitant rise in free circulating PCSK9.[28] This cyclical behavior introduces intraindividual variability in LDL-C, which may complicate clinical interpretation if LDL-C measurements are not taken at an appropriate time.

Our findings are consistent with these pharmacodynamic data. Notably, longer-acting agents such as inclisiran, which achieve sustained PCSK9 suppression without peak–trough fluctuations, may offer enhanced lipid stability.

Although specific intraindividual LDL–C variability metrics (such as SD or CV between visits) are not yet published for inclisiran, the dosing regimen (initial dose, 3–month second, then every 6 months) and pharmacodynamic data from ORION–10/11 suggest a stable and durable LDL–C reduction, with minimal peak-trough fluctuations compared to PCSK9 antibodies.[29] Real-world data indicate some interindividual variability,[25] but the lack of measured within-patient fluctuations strengthens the hypothesis that inclisiran provides consistent lipid control over time and may therefore offer advantages in lipid stability beyond absolute LDL–C lowering.

Limitations

This study has several limitations. First, its observational and retrospective design precludes the establishment of causal relationships between LDL-C variability and clinical outcomes. Although multivariate analyses were performed to adjust for potential confounders, residual confounding cannot be entirely excluded. Second, treatment adherence was not objectively measured, particularly in the statin-based group, where poor adherence may partially explain the greater LDL-C variability observed. Although visit-to-visit monitoring provides some indirect assessment, tools such as pharmacy refill data, electronic monitoring, or drug

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levels were not employed. Third, the sample size was relatively small in the inclisiran subgroup compared to the standard LLT and PCSK9i groups, which may reduce the statistical power to detect differences in this cohort and increase the risk of type II error. Fourth, the analysis was limited to a single-center cohort, which may affect the generalizability of our findings to broader or more diverse populations. Fifth, we assessed LDL-C variability using 4 time points, which, while sufficient to capture meaningful trends, may not reflect long-term fluctuations or changes beyond this timeframe. Finally, the analysis of MACE was exploratory due to the limited number of patients and events, and event adjudication was not performed by a blinded independent committee, which may introduce potential bias in outcome classification. Despite these limitations, the consistency of findings across both SD and CV measures, and the concordant reduction in MACE in patients with lower LDL-C variability, supports the observed associations.

Conclusions

In this real-world analysis of patients at very high cardiovascular risk, treatment with PCSK9i and inclisiran was associated with significantly lower visit-to-visit variability in LDL-C levels compared to standard LLT. This reduced variability was consistently observed across both SD and CV metrics and associated with a lower incidence of MACE.

Our findings suggest that, beyond achieving LDL-C targets, maintaining lipid stability over time may be a key therapeutic goal to optimize cardiovascular risk reduction. Given the strong association between LDL-C variability and outcomes, newer lipid-lowering agents with more stable pharmacokinetics—such as PCSK9 monoclonal antibodies and inclisiran—may provide clinical advantages by minimizing fluctuations and enhancing long-term lipid control.

CRediT authorship contribution statement

Arturo Cesaro: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Vincenzo Acerbo:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Francesco Scialla:** Writing – review & editing, Data curation. **Andrea Zito:** Writing – review & editing, Data curation. **Gennaro Porcelli:** Writing – review & editing, Data curation. **Domenico Panico:** Writing – review & editing, Data curation. **Giovanni Argenziano:** Writing – review & editing, Data curation. **Demetrio Iaria:** Writing – review & editing, Data curation. **Maria Grazia Monaco:** Writing – review & editing, Visualization, Formal analysis, Data curation. **Vincenzo De Sio:** Writing – review & editing, Methodology, Data curation. **Felice Gragnano:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation. **Michele Golino:** Writing – review & editing, Visualization, Methodology, Data curation. **Massimiliano Ruscica:** Writing – review & editing, Visualization, Validation. **Stefano Carugo:** Writing – review & editing, Validation, Supervision. **Alberto Corsini:** Writing – review & editing, Visualization, Validation, Supervision. **Paolo Calabrò:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Conceptualization.

Ethical approval

The study protocol complied with the Declaration of Helsinki and was approved by the local institutional ethics committee (AORN "Sant'Anna e San Sebastiano", protocol no 486 29-Apr-2025). Informed consent was obtained from all partecipants.

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Declarations of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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