Clinical Epidemiology

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Real-World Assessment of the Association Between PCSK9i Adherence and LDL Reduction and Variability in a Chinese Clinical Practice

Xiaomin Ye[1,2,*], Shaozhao Zhang[1,2,*], Xiangbin Zhong[1,2], Miaohong Li[1,2], Menghui Liu[1,2], Xiaodong Zhuang[1,2], Xinxue Liao[1,2]

[1]Cardiology Department, First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, People's Republic of China; [2]NHC Key Laboratory of Assisted Circulation, Sun Yat-Sen University, Guangzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xinxue Liao; Xiaodong Zhuang, Cardiology Department, First Affiliated Hospital, Sun Yat-Sen University, 58 Zhongshan 2nd Road, Guangzhou, 510080, People's Republic of China, Tel +86-13903063724; +86-13760755035, Fax +86-020-28823388, Email liaoxinx@mail.sysu.edu.cn; zhuangxd3@mail.sysu.edu.cn

Background: Real-world evidence about adherence to proprotein convertase subtilisin/kexin type-9 inhibition (PCSK9i) is needed in Chinese population.

Objective: We aimed to evaluate the adherence patterns using anti-PCSK9 monoclonal antibody in Chinese clinical practice and explored the association between adherence to PCSK9i and low-density lipoprotein cholesterol (LDL-C) reduction ratio and variability.

Methods: A total of 5373 patients initiating PCSK9i in the First Affiliated Hospital of Sun Yat-sen University were included as sub-analysis of the RED-CARPET registry. Adherence to PCSK9i was measured by proportion of days covered (PDC), calculated for treatment covered days divided by 365 days during a one-year period. Reduction ratio (percentage points, range 0–100) was calculated as the ratio of reduction degree (difference between baseline value and the lowest value) to the baseline value. LDL-C variability was measured as standard deviation of three LDL-C measurement 2 weeks after medication initiation. We used linear regression to measure the association between PCSK9i PDC and the reduction ratio and variability of LDL-C. PDC (range 0–1) was scaled by 10 in the model.

Results: At 12 months, the mean PDC was 0.09 ± 0.10. PCSK9i PDC was positively associated with LDL-C reduction ratio after adjustment for traditional risk factors (Adjusted β 4.05, 95% CI [2.61, 5.50]), p<0.001), which means for every 0.1-unit increase in PDC, the LDL-C reduction ratio increases by 4.05 percentage points. PCSK9i PDC was negatively associated with LDL-C standard deviation after fully adjustment (Adjusted β −0.042, 95% CI [−0.066, −0.018]), p=0.001). For every 0.1-unit increase in PDC, the LDL-C standard deviation decreased by 0.042 units, indicating improved lipid stability with higher adherence.

Conclusion: The adherence to PCSK9i presented as a skewed distribution, most people only received one injection, which did not reach the ideal adherence goal. Unsatisfactory adherence to PCSK9i reduce the lipid-lowering effect of PCSK9i.

Keywords: medicine adherence, visit-to-visit variability, LDL-C reduction

Introduction

Low-density lipoprotein cholesterol (LDL-C) is a major causative factor in atherosclerotic cardiovascular disease (ASCVD).[1] Greater the reduction in LDL-C, the lower ASCVD risk,[2] even below 1 mmol/L.[3] However, despite lipids controlled according very-high risk criteria, residual risk persists.[4] In addition to focusing on absolute LDL-C reduction, clinical practice needs to explore new lipid-lowering targets. LDL-C variability, independent of levels, predicts cardiovascular events and atherosclerosis progression.[5–8] Unstable lipid levels may increase plaque vulnerability and rupture

Received: 21 November 2024
Accepted: 3 May 2025
Published: 9 June 2025

risk by preventing lipid efflux from plaques.[9,10] Higher LDL-C variability is associated with vascular endothelial dysfunction.[11] Therefore, ASCVD risk reduction requires both lowering LDL-C and stabilizing its levels.

Lipid variability is highly correlated with treatment adherence to lipid-lowering drugs.[12–14] Traditional small-molecule oral lipid-lowering drugs, such as statins, have short half-lives and require daily use. Proprotein convertase subtilisin/kexin 9 inhibition (PCSK9i), an important tool in the treatment of hyperlipidemia, can reduce LDL-C levels by 50%–70% and effectively reduce the risk of ASCVD.[3,15,16] PCSK9i has a longer treatment cycle (1 injection every 2 or 4 weeks), which theoretically improves patients' adherence to treatment. Previously randomized controlled studies showed higher mean treatment adherence of 98% in patients who self-inject PCSK9i.[17] However, randomized controlled trials are usually conducted in selective populations and do not necessarily represent the real situation in routine clinical practice. In an Israeli clinical practice, patients using PCSK9i discontinued halfway and reinjected after discontinuation accounted for the majority of cases, and only 30% of patients could adhere to PCSK9i therapy for 80% of the first year.[18] Data on PCSK9i treatment adherence outside the framework of clinical trials remain limited in Chinese population, and its effect on lipid variability is unclear. It is clinically important to explore the relationship to guide clinicians to identify and intervene early in patients with inadequate treatment adherence.

Therefore, this study intends to conduct a prospective observational study in China to investigate the relationship between PCSK9i treatment adherence and lipid variability and reduction.

Materials and Methods

Study Population

The population enrolled was from the "REal-world Data of CARdiometabolicProtEcTion", referred to as the "RED-CARPET" study. RED-CARPET is a single-center, historical prospective cohort study conducted by the Department of Cardiovascular Medicine of the First Affiliated Hospital of Sun Yat-sen University. In the study population, hospitalized patients were diagnosed with metabolic cardiovascular diseases. Through long-term follow-up and real-world data analysis of the study population, it searches for risk factors associated with metabolic cardiovascular diseases and explores their relationship with long-term cardiovascular endpoints. Registry number: ChiCTR2000039901. This study is a sub-study of the RED-CARPET, which collects patients who were diagnosed with coronary artery disease or hyperlipidemia from April 2019 to May 2023 in the First Affiliated Hospital of Sun Yat-sen University. A total of 5373 patients received their first PCSK9 inhibitor (Evolocumab or Alirocumab) treatment in an outpatient or inpatient unit at our hospital for medication adherence analysis. Follow-up time was 12 months. Patients with baseline and at least 1 reviewed lipid measurement during follow-up time were available for LDL-C reduction analysis. Patients with at least 3 reviewed lipid measurement during follow-up time were included for LDL-C visit-to-visit variability analysis. Based on the efficacy of PCSK9i in previous studies, we required that the analyzed lipid measurements needed to be taken 2 weeks after initiating PCSK9i, with one of the measurements to be taken within 4 weeks after PCSK9i administration, as well as one of the measurements to be taken within 2 weeks before and after the set time point. The clinical data, including medication information for this study, were gathered through electronic medical record. Study process and number of participants included in each analysis were presented in flow-chart (Figure 1). The study was approved by Ethics Review Committee of the First Affiliated Hospital of Sun Yat-Sen University, in accordance with the Declaration of Helsinki, with waiving of the need for individual patient consent due to the retrospective design of the study. To preserve patient privacy and data confidentiality, patient data have been deidentified before analysis. All analyses in this retrospective study were performed based on the data from anonymized patients.

Study Variables and Definition of Terms

Self-reporting clinical data by patients include age, sex, and current prescription usage at the time of administration or outpatient visits. Medication adherence was assessed by three methods: (1) Proportion of days covered (PDC), measured by number of days with treatment divided by follow-up days; (2) Duration of therapy (DOT), measured by number of days with treatment; (3) Drop-out ratio, measured by the number of patients who dropped out divided by the total number the total number of patients and multiplied by 100%. In the subsequent analyses, PDC was chosen as the primary method to represent medication adherence.

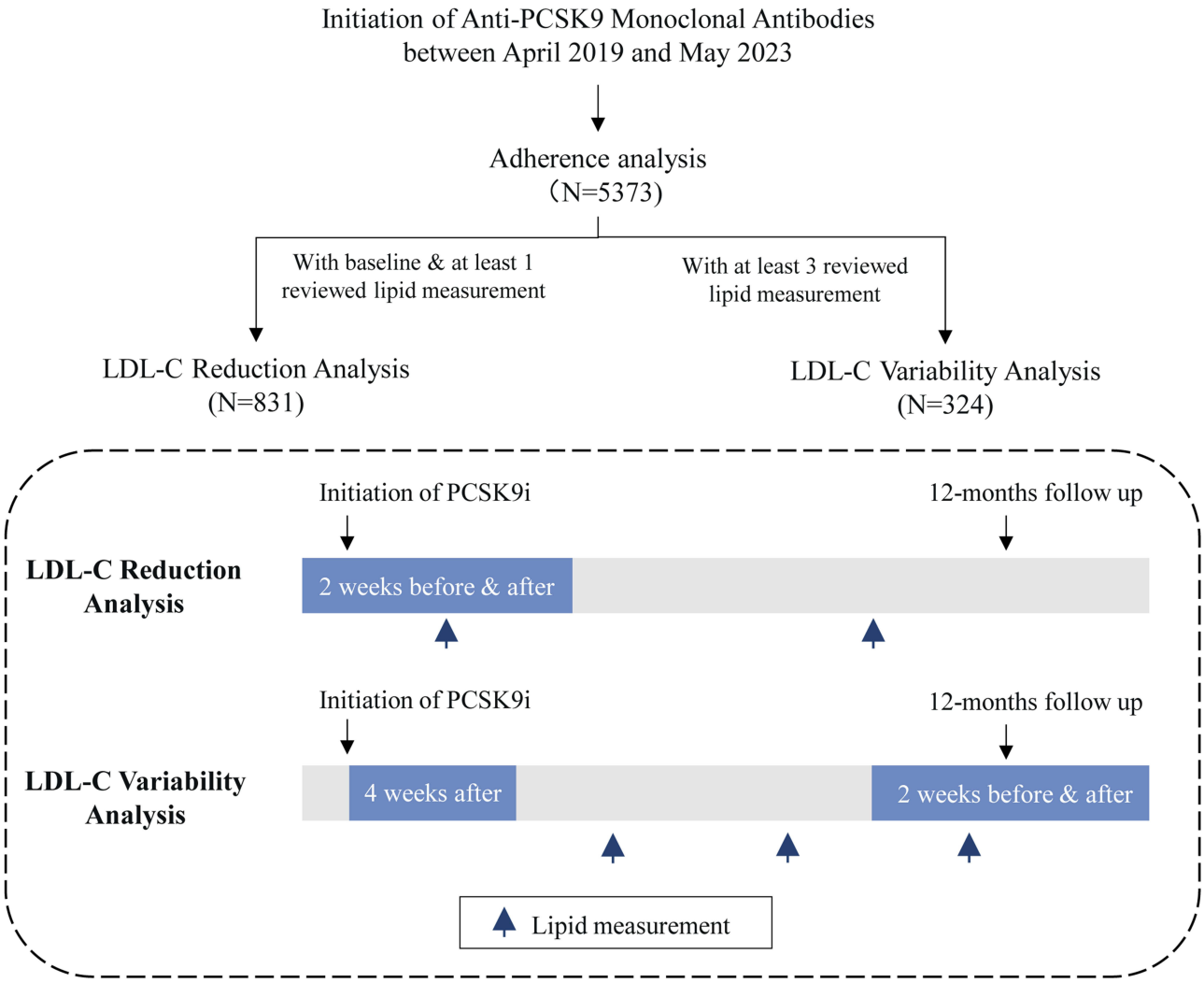

Figure 1 Flow chart.

LDL-C reduction was calculated as base value minus minimum reviewed value. LDL-C reduction ratio (percentage points, range 0–100) was calculated as LDL-C reduction value divided by base value. LDL-C visit-to-visit variability was assessed in two ways: (1) standard deviation (SD) of LDL-C levels, and (2) SD/mean. SD was selected as the primary means of representing variability in this analysis.

Statistics Analysis

Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile ranges based on normal or non-normal distribution. Categorical data were presented as numbers and percentages. PDC (range 0–1) was scaled by 10 in the model. Using linear curve fitting, we explored the association between PCSK9i PDC and LDL-C reduction and variability separately. Multivariable linear models were constructed in order to assess the association of PCSK9i PDC and LDL-C change and variability. Variables adjusted for in each model included baseline lipid, age, sex, medication for diabetes, medication for hypertension, and statins. Beta coefficients with 95% confidence intervals (CI) are reported. All analyses were conducted in IBM SPSS Statistics 26 and R version 4.3.2. A two-sided P value < 0.05 was considered statistically significant.

https://doi.org/10.2147/CLEP.S507761

Results

Distribution of PCSK9i PDC

A total of 5373 patients used PCSK9 inhibitors for the first time in our outpatient/inpatient departments. The specifics of PCSK9 inhibitor adherence were explored using every 3 months as a time cutoff. At 3, 6, and 9 months, the mean PDC was 0.25 ± 0.16, 0.15 ± 0.13, and 0.11 ± 0.11, respectively, whereas at 12 months, the mean PDC decreased to 0.09 ± 0.10. At 3 months, the overall drop-out ratio was 81.4%, and by 12 months, less than 10% continued to use PCSK9i, not excluding intermediate discontinuations. At 12 months, PCSK9i was used for an average of 33 days. A separate analysis of the 3126 patients enrolled after 2022 (when PCSK9 inhibitors included in China's health insurance) found adherence slightly improved (Table 1). Overall, the PDC for PCSK9i showed a skewed distribution, with the majority receiving only 1–2 injections, and this distribution was also present in the subsequent LDL-C analysis (Figure 2).

Baseline Characteristics

A total of 831 patients (Figure 1) were included in the analysis of LDL-C reduction, 67.9% were male, mean age was 61.9±12.1 years, 26.6% were on hypoglycemic agents, 78.7% were on antihypertensive agents, while 73.3% were on statins, and 62.9% were on cholesterol absorption inhibitors at baseline. The baseline value of LDL-C was 3.26 ±1.23 mmol/L. At 12 months, mean PDC was 0.13± 0.13, and the mean LDL-C reduction was 1.46±1.14 mmol/L (Table 2). In the variability analysis, we included a total of 324 people with different time cutoffs for follow-up (3, 6, 9, and 12 months), 63.9% were male, mean age was 58.8±13.7 years, 29.3% were on hypoglycemic agents, 76.5% were on antihypertensive agents, while 70.7% were on statins, and 60.4% were on cholesterol absorption inhibitors at baseline. Mean PDC was 0.25±0.20, mean LDL-C SD was 0.60±0.43, mean LDL-C SD/Mean was 0.29±0.16 (Table 2).

Association Between PDC of PCSK9i and LDL-C Level

An estimated linear association between PDC of PCSK9i with the reduction ratio and variability of LDL-C was observed (Figure 3). Meanwhile, we performed linear regression analyses for each of the two. There was a positive correlation between PCSK9i PDC at 12 months and the reduction ratio of LDL-C (β 1.90, 95% CI [0.41, 3.39]), p=0.012), and the correlation persisted after adjustment for age, sex, medication for diabetes, medication for hypertension, statins,

Table 1 Adherence of PCSK9i at Different Time Point

	All N=5373	**After 2022 N=3126**
Proportion of days covered		
3 months	0.25±0.16	0.28±0.17
6 months	0.15±0.13	0.17±0.14
9 months	0.11±0.11	0.13±0.12
12 months	0.09±0.10	0.10±0.11
Duration of treatment (days)		
3 months	22.88±14.76	25.08±15.29
6 months	27.57±23.24	31.11±24.80
9 months	30.71±29.88	35.00±32.43
12 months	33.18±35.76	37.68±38.82
Drop-out ratio (%)		
3 months	81.4	77.0
6 months	87.3	84.7
9 months	90.3	89.7
12 months	91.1	94.5

Note: Plus-minus values are mean±SD.
Abbreviations: PDC, Proportion of days covered; SD, standard deviation.

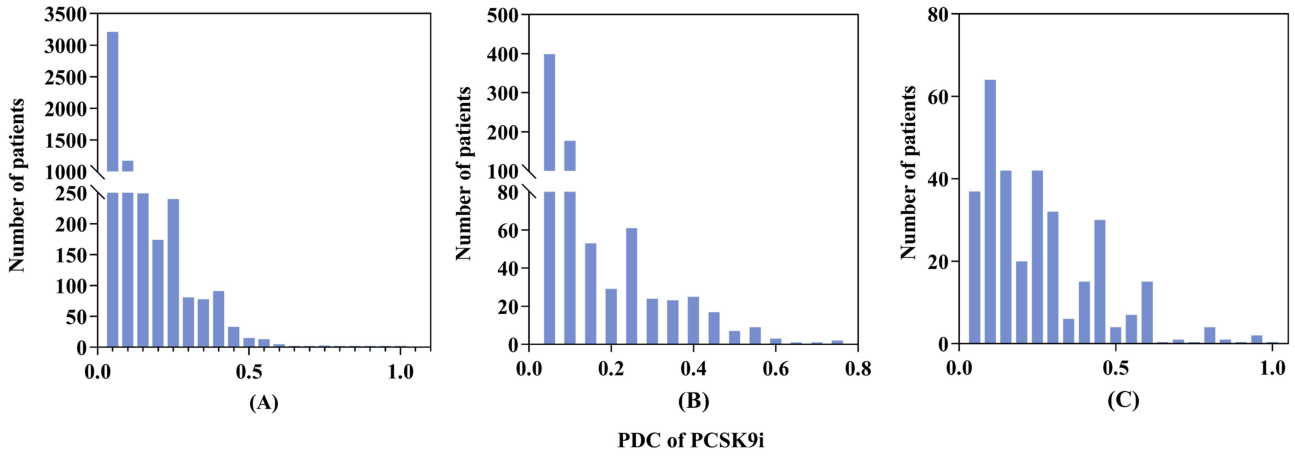

Figure 2 Distribution of PCSK9i PDC. (**A**) Patients in adherence analysis (N=5373). (**B**) In reduction analysis (N= 831). (**C**) In variability analysis (N=324).

cholesterol absorption inhibitors and baseline LDL-C level (β 4.05, 95% CI [2.61, 5.50]), p<0.001), which means for every 0.1-unit increase in PDC, the LDL-C reduction ratio increases by 4.05 percentage points.(Figure 4). For other follow-up time points, the results remained significant (Supplement Table 1). For LDL-C variability analysis, PCSK9i PDC was negatively correlated with LDL-C SD (β −0.042, 95% CI [−0.066, −0.018]), p=0.001), and SD/Mean (β −0.013, 95% CI [−0.022, −0.005]), p=0.011) at all time point after adjustment for age, sex, medication for diabetes, medication for hypertension, statins, and cholesterol absorption inhibitors the correlation persisted (Figure 5). For every 0.1-unit increase in PDC, the LDL-C standard deviation decreased by 0.042 units, indicating improved lipid stability with higher adherence. However, separate analysis at different time points showed noncorrelated results (Supplement Table 2). To explore the non-linear portion of PCKS9i PDC and LDL-C change, PCSK9i PDC was divided into four groups based on quartiles. Compared with Q1, the average lipid reduction ratio of group Q2, Q3 and Q4 increased. In the analysis of LDL-C variability, there was no difference between each group (Supplement Tables 3 and 4).

Discussion

This study shows a correlation between adherence to PCSK9 inhibitors and LDL-C levels; better adherence is associated with greater LDL-C reductions, along with lower LDL-C variability. Even though PCSK9 inhibitors can substantially

Table 2 Baseline Characteristics of Patients Included in LDL-C Reduction and Variability Analysis

	Reduction Analysis (N=831)	Variability Analysis (N=324)
Male (n, %)	564 (67.9)	207 (63.9)
Age (mean±SD)	61.9±12.1	58.8±13.7
Medication for diabetes (n, %)	221 (26.6)	95 (29.3)
Medication for hypertension (n, %)	654 (78.7)	248 (76.5)
Statins (n, %)	609 (73.3)	229 (70.7)
Cholesterol absorption inhibitors (n, %)	523 (62.9)	196 (60.4)
PDC (mean±SD)	0.13±0.13	0.25±0.20
PDC (median±IQR)	0.08±0.09	0.20±0.28
LDL-C reduction (mmol/L, mean±SD)	1.46±1.14	-
LDL-C at baseline (mmol/L, mean±SD)	3.26±1.23	-
LDL-C SD (mean±SD)	-	0.60±0.43
LDL-C SD/mean (mean±SD)	-	0.29±0.16

Abbreviations: PDC, Proportion of days covered; SD, standard deviation; IQR, inter-quartile range.

https://doi.org/10.2147/CLEP.S507761

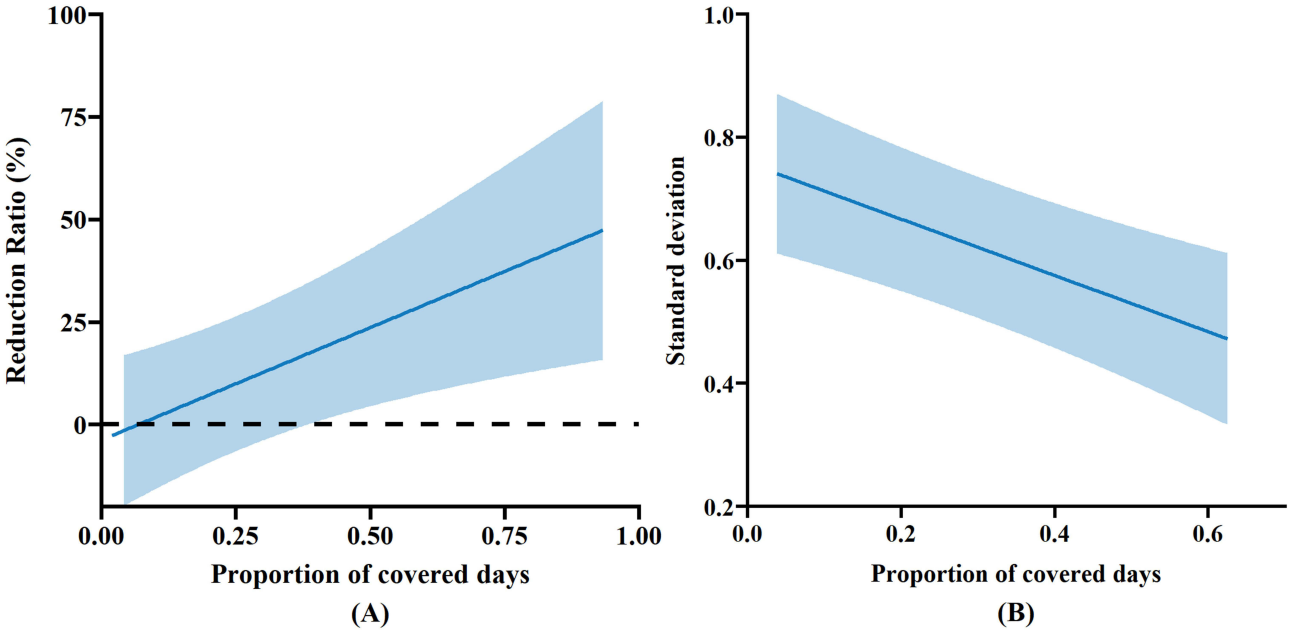

Figure 3 Curve fitting between PDC and LDL-C change. Linear curve fitting between PCSK9i PDC and estimated LDL-C reduction ratio (**A**) and variability (**B**).

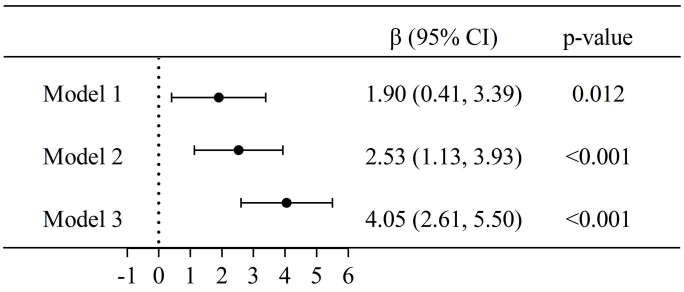

Figure 4 Association between PDC of PCSK9 inhibitor and reduction ratio of LDL-C. PDC was included in model as PDC multiplied by 10. Model 1: Unadjusted; Model 2: Adjusted for LDL-C level at baseline; Model 3: Adjusted for LDL-C level at baseline, sex, age, medication for diabetes, medication for hypertension, statins and cholesterol absorption inhibitors.
Abbreviation: PDC, Proportion of days covered.

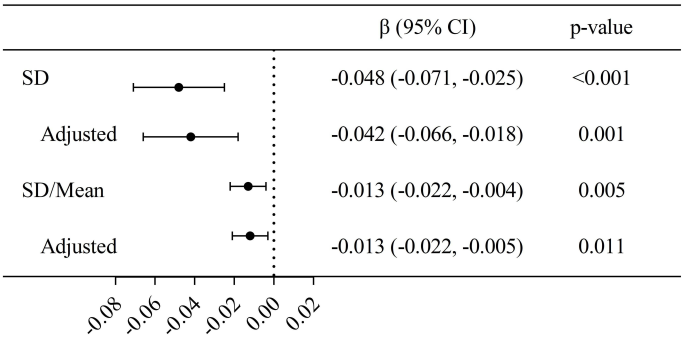

Figure 5 Association between PDC of PCSK9 inhibitor and LDL-C variability. PDC was included in model as PDC multiplied by 10. Adjusted for sex, age, medication for diabetes, medication for hypertension, statins and cholesterol absorption inhibitors.
Abbreviations: PDC, Proportion of days covered; SD, Standard deviation.

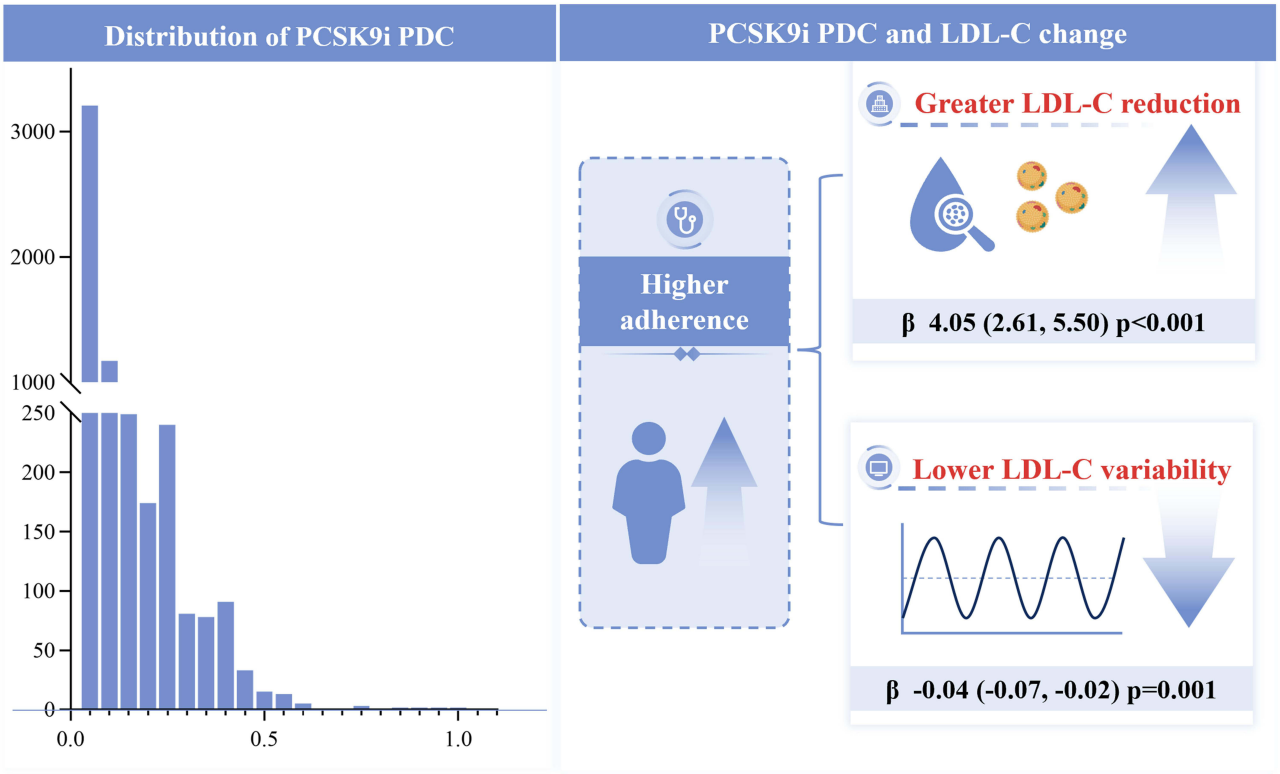

Figure 6 PCSK9i nonadherence compromises LDL-C control. PCSK9i PDC had a skewed distribution in Chinese clinical practice. PCSK9i PDC was positively correlated with LDL-C reduction ratio and negatively correlated with LDL-C standard deviation.

reduce LDL-C levels, unsatisfactory short- and long-term adherence may nevertheless compromise their lipid-lowering effects, both in terms of level of decline and stability (Figure 6).

Drug adherence is becoming a public concern,[19] so it seems important to recognize and investigate the adherence of PCSK9i in different countries. To the best of our knowledge, the distribution of adherence to PCSK9 inhibitors in developing countries, such as China, has not been previously reported. In this study, a skewed distribution of PCSK9 adherence in the Chinese population was demonstrated, with the vast majority of patients receiving only 1 injection and none achieving ideal drug adherence (PDC ≥ 80%). Several reasons could explain the low adherence to PCSK9i. The administration cycle of PCSK9 inhibitors is different from that of conventional oral medications, making long-term medication habits difficult to be developed. Adherence improved after PCSK9i was covered by China Health Insurance Corporation in 2022, suggesting that high medication costs may account for part of the problem.

A retrospective study using American public pharmacy data enrolled 13,151 patients and found a mean PDC of 0.63 after reviewing their use of PCSK9 inhibitors over a 180-day period. In comparing self-pay and Medicare patients, no significant difference in PDC was found for PCSK9i.[20] In a 1-year follow-up of 1600 Israeli patients, 28.1% discontinued PCSK9i after 6 months, along with only 30% patients achieved acceptable adherence rates within the first year.[18] Recently, SANTORINI registry reported a suboptimal rate of PCSK9 inhibitors in Europe population.[21] Above studies demonstrated deficiencies in adherence to PCSK9 inhibitors in clinical practice, and to some extent are consistent with the results of the current study. Adherence studies from other countries reported different findings. 99.7% of 798 patients enrolled in an Italian observational study on the use of PCSK9i remained on therapy after 6 months. Only 3.5% discontinued PCSK9i in 18-months follow-up.[22] HEYMANs study reported 98% persistence at 24 months,[23] whereas in GOULD study 92% patients receiving PCSK9i persisted at 24 months.[24] These few studies show that adherence to PCSK9i in clinical practice is already comparable to that in randomized trials,[17] while well exceeding adherence to conventional oral lipid-lowering medications.[25] There are various potential reasons for the differences from current study,

https://doi.org/10.2147/CLEP.S507761

including reimbursement policies of different health systems, promotion coverage in rural and urban areas, ease of access to medication.

Intraindividual LDL-C variability and optimal LDL-C level are regarded as vital in gaining cardiovascular benefits. In this study, we conclude that poor PCSK9i treatment adherence is associated with elevated LDL cholesterol variability and modest LDL cholesterol reduction. Besides, previous studies have concluded that adherence to statins requires >80% to achieve significant reductions in recurrent cardiovascular events and mortality in secondary prevention.[26,27] Because of low treatment adherence and reduced lipid-lowering, intended benefit of use of lipid-lowering agents may not be available to patients. Recent study demonstrated that PCSK9 inhibitors reduce atheroma volume and stabilize lipid-rich plaques, with the extent of these effects correlating with the LDL-C levels achieved after one year of treatment, which is impacted by PCSK9 inhibitors adherence.[28] Therefore, new long-lasting therapies and patterns of delivery which is simplified and simultaneously high-intensity is needed to enhance adherence to treatment.[29] For instance, inclisiran, a siRNA agent targeting PCSK9, reduce 57.2% of LDL-C on the basis of statins and only require two injections per year in ORION-18 in Asian population,[30] which may be considered as potential lipid-lowering drugs to promote adherence. The results from ORION-1 implied that administration of inclisiran is associated with lower intraindividual variability.[31] Correlation between adherence of inclisiran and LDL-C variability and reduction in Asian populations needs to be further explored.

Limitations

There are several potential limitations to this study. First, the collection of patient-related data (including testing of lipid levels, and the number of specific doses of medication used) was derived from the electronic medical records of a single study center and relatively small sample size which may have led to a misassessment of the distribution of medication adherence and an underestimation of the effect of medication. Second, as a historical prospective cohort study, we were unavailable to assess specific reasons for not continued use of PCSK9i, such as adverse reactions or economic or geographic factors. Third, the inclusion population was patients attending our hospital, which may not be a representative cohort of PCSK9i use in China, and does not have the ability to extend the results to the general population.

Conclusions

In conclusion, this study demonstrates the poor adherence to PCSK9i in a Chinese clinical practice. At the same time, PCSK9i adherence was correlated with the LDL-C reduction and variability, suggesting that low adherence to PCSK9i may affect the therapeutic efficacy of the medication.

Data Sharing Statement

The corresponding author would share the data underlying this article upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the National Natural Science Foundation of China (81870195, 82070384 to X.Liao), Guangdong Basic and Applied Basic Research Foundation (2021A1515011668 to X.Liao) and Chinese Cardiovascular Association-Access fund (Grant No. 2019-CCA-ACCESS-87 to X.Zhuang).

Disclosure

The authors report no potential conflicts of interest in this work.

References

1. 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 (32):2459–2472. doi:10.1093/eurheartj/ehx144
2. Navarese EP, Robinson JG, Kowalewski M, et al. Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: a systematic review and meta-analysis. *JAMA*. 2018;319(15):1566–1579. doi:10.1001/jama.2018.2525
3. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376 (18):1713–1722. doi:10.1056/NEJMoa1615664
4. Kaasenbrood L, Boekholdt SM, van der Graaf Y, et al. Distribution of estimated 10-year risk of recurrent vascular events and residual risk in a secondary prevention population. *Circulation*. 2016;134(19):1419–1429. doi:10.1161/CIRCULATIONAHA.116.021314
5. Bangalore S, Breazna A, DeMicco DA, Wun CC, Messerli FH. TNT steering committee and investigators. visit-to-visit low-density lipoprotein cholesterol variability and risk of cardiovascular outcomes: insights from the TNT trial. *J Am Coll Cardiol*. 2015;65(15):1539–1548. doi:10.1016/j.jacc.2015.02.017
6. Boey E, Gay GMW, Poh KK, Yeo TC, Tan HC, Lee CH. Visit-to-visit variability in LDL- and HDL-cholesterol is associated with adverse events after ST-segment elevation myocardial infarction: a 5-year follow-up study. *Atherosclerosis*. 2016;244:86–92. doi:10.1016/j.atherosclerosis.2015.10.110
7. Kim MK, Han K, Kim HS, et al. Cholesterol variability and the risk of mortality, myocardial infarction, and stroke: a nationwide population-based study. *Eur Heart J*. 2017;38(48):3560–3566. doi:10.1093/eurheartj/ehx585
8. Clark D, Nicholls SJ, St John J, et al. Visit-to-visit cholesterol variability correlates with coronary atheroma progression and clinical outcomes. *Eur Heart J*. 2018;39(27):2551–2558. doi:10.1093/eurheartj/ehy209
9. Abela GS, Vedre A, Janoudi A, Huang R, Durga S, Tamhane U. Effect of statins on cholesterol crystallization and atherosclerotic plaque stabilization. *Am J Cardiol*. 2011;107(12):1710–1717. doi:10.1016/j.amjcard.2011.02.336
10. Rohatgi A, Khera A, Berry JD, et al. HDL cholesterol efflux capacity and incident cardiovascular events. *N Engl J Med*. 2014;371(25):2383–2393. doi:10.1056/NEJMoa1409065
11. Chen H, Ren JY, Xing Y, et al. Short-term withdrawal of simvastatin induces endothelial dysfunction in patients with coronary artery disease: a dose-response effect dependent on endothelial nitric oxide synthase. *Int J Cardiol*. 2009;131(3):313–320. doi:10.1016/j.ijcard.2007.10.044
12. Descamps O, Tomassini JE, Lin J, et al. Variability of the LDL-C lowering response to ezetimibe and ezetimibe + statin therapy in hypercholesterolemic patients. *Atherosclerosis*. 2015;240(2):482–489. doi:10.1016/j.atherosclerosis.2015.03.004
13. Mann DM, Glazer NL, Winter M, et al. A pilot study identifying statin nonadherence with visit-to-visit variability of low-density lipoprotein cholesterol. *Am J Cardiol*. 2013;111(10):1437–1442. doi:10.1016/j.amjcard.2013.01.297
14. Karlson BW, Wiklund O, Palmer MK, Nicholls SJ, Lundman P, Barter PJ. Variability of low-density lipoprotein cholesterol response with different doses of atorvastatin, rosuvastatin, and simvastatin: results from VOYAGER. *Eur Heart J Cardiovasc Pharmacother*. 2016;2(4):212–217. doi:10.1093/ehjcvp/pvw006
15. Murphy SA, Pedersen TR, Gaciong ZA, et al. Effect of the PCSK9 inhibitor evolocumab on total cardiovascular events in patients with cardiovascular disease: a prespecified analysis from the Fourier trial. *JAMA Cardiol*. 2019;4(7):613–619. doi:10.1001/jamacardio.2019.0886
16. O'Donoghue ML, Giugliano RP, Wiviott SD, et al. Long-term evolocumab in patients with established atherosclerotic cardiovascular disease. *Circulation*. 2022;146(15):1109–1119. doi:10.1161/CIRCULATIONAHA.122.061620
17. Farnier M, Colhoun HM, Sasiela WJ, Edelberg JM, Asset G, Robinson JG. Long-term treatment adherence to the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab in 6 ODYSSEY Phase III clinical studies with treatment duration of 1 to 2 years. *J Clin Lipidol*. 2017;11 (4):986–997. doi:10.1016/j.jacl.2017.05.016
18. Zafrir B, Egbaria A, Stein N, Elis A, Saliba W. PCSK9 inhibition in clinical practice: treatment patterns and attainment of lipid goals in a large health maintenance organization. *J Clin Lipidol*. 2021;15(1):202–211.e2. doi:10.1016/j.jacl.2020.11.004
19. Brandts J, Ray KK. Novel and future lipid-modulating therapies for the prevention of cardiovascular disease. *Nat Rev Cardiol*. 2023;20 (9):600–616. doi:10.1038/s41569-023-00860-8
20. Hines DM, Rane P, Patel J, Harrison DJ, Wade RL. Treatment patterns and patient characteristics among early initiators of PCSK9 inhibitors. *Vasc Health Risk Manag*. 2018;14:409–418. doi:10.2147/VHRM.S180496
21. Ray KK, Aguiar C, Arca M, et al. Use of combination therapy is associated with improved LDL cholesterol management: 1-year follow-up results from the European observational SANTORINI study. *Eur J Prev Cardiol*. 2024;31(15):1792–1803. doi:10.1093/eurjpc/zwae199
22. Gargiulo P. Efficacy, safety, adherence and persistence of PCSK9 inhibitors in clinical practice: a single country, multicenter, observational study (AT-TARGET-IT). 2023.
23. Ray KK, Dhalwani N, Sibartie M, et al. Low-density lipoprotein cholesterol levels exceed the recommended European threshold for PCSK9i initiation: lessons from the HEYMANS study. *Eur Heart J Qual Care Clin Outcomes*. 2022;8(4):447–460. doi:10.1093/ehjqcco/qcac009
24. Cannon CP, de Lemos JA, Rosenson RS, et al. Use of lipid-lowering therapies over 2 years in GOULD, a registry of patients with atherosclerotic cardiovascular disease in the US. *JAMA Cardiol*. 2021;6(9):1–9. doi:10.1001/jamacardio.2021.1810
25. Guglielmi V, Bellia A, Pecchioli S, et al. Effectiveness of adherence to lipid lowering therapy on LDL-cholesterol in patients with very high cardiovascular risk: a real-world evidence study in primary care. *Atherosclerosis*. 2017;263:36–41. doi:10.1016/j.atherosclerosis.2017.05.018
26. Rodriguez F, Maron DJ, Knowles JW, Virani SS, Lin S, Heidenreich PA. Association of statin adherence with mortality in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2019;4(3):206–213. doi:10.1001/jamacardio.2018.4936
27. Wei L, Wang J, Thompson P, Wong S, Struthers AD, MacDonald TM. Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow up study. *Heart*. 2002;88(3):229–233. doi:10.1136/heart.88.3.229
28. Biccirè FG, Kakizaki R, Koskinas KC, et al. Lesion-level effects of LDL-C-lowering therapy in patients with acute myocardial infarction: a post hoc analysis of the PACMAN-AMI trial. *JAMA Cardiol*. 2024;9(12):1082–1092. doi:10.1001/jamacardio.2024.3200
29. Choudhry NK, Fischer MA, Avorn J, et al. The implications of therapeutic complexity on adherence to cardiovascular medications. *Arch Intern Med*. 2011;171(9):814–822. doi:10.1001/archinternmed.2010.495

30. Huo Y, Lesogor A, Lee CW, et al. Efficacy and safety of inclisiran in Asian patients: results from ORION-18. *JACC*. 2023. doi:10.1016/j.jacasi.2023.09.006
31. Ray KK, Stoekenbroek RM, Kallend D, et al. Effect of 1 or 2 doses of inclisiran on low-density lipoprotein cholesterol levels: one-year follow-up of the ORION-1 randomized clinical trial. *JAMA Cardiol*. 2019;4(11):1067–1075. doi:10.1001/jamacardio.2019.3502