Real world effectiveness of PCSK-9 inhibitors combined with statins versus statins-based therapy among patients with very high risk of atherosclerotic cardiovascular disease in China (RWE-PCSK study)

Yu-Qi LIU¹, Dan-Dan LI¹, Meng CHAI², Hong-Liang CONG³, Xiao-Qiang CONG⁴, Jun DAI⁵, Rong-Pin DU⁶, Ming GAO⁷, Jin-Cheng GUO⁸, Yan-Qing GUO⁹, Xiao-Jian HONG¹⁰, Rong-Chong HUANG¹¹, Feng-Shun JIA¹², Jia-Yu LI¹³, Qing LI¹⁴, Jia-Mei LIU¹⁵, Xin-Ping LIU¹⁶, Yu-Guo LIU¹⁷, Hong-Gang NIE¹⁸, Bing SHAO¹⁹, Xiao-Yu SHEN²⁰, Hai-Qing SONG²¹, Yi-Jun SONG²², Li-Jun WANG²³, Shuo WANG²⁴, Dong-Mei WU²⁵, Jing XIA²⁶, Zhi-Yong YANG²⁷, Hong-Ying YU²⁸, Hui ZHANG²⁹, Tie-Mei ZHANG³⁰, Ji-Yi ZHAO³¹, Ming-Qi ZHENG³², Yun-Dai CHEN¹,✉

¹. Department of Cardiology, Chinese PLA General Hospital, Beijing, China; 2. Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart Lung and Blood Vessel Disease, Beijing Key Laboratory of Precision Medicine of Coronary Atherosclerotic Disease, Clinical Center for Coronary Heart Disease, Capital Medical University, Beijing, China; 3. Department of Cardiology, Tianjin Chest Hospital, Tianjin, China; 4. Department of Cardiology, the First Hospital of Jilin University, Changchun, China; 5. Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; 6. Department of Cardiology, Hebei People’s Hospital, Shijiazhuang, China; 7. Department of Cardiology, Kailuan General Hospital, Hebei Union University, Tangshan, China; 8. Department of Cardiology, Beijing Luhe Hospital, Capital Medical University, Beijing, China; 9. Department of Cardiology, Shanxi Cardiovascular Hospital, Taiyuan, China; 10. Department of Cardiology, the Fourth Affiliated Hospital of Harbin Medical University, Harbin, China; 11. Department of Cardiology, Beijing Friendship Hospital, Capital Medical University, Beijing, China; 12. Department of Cardiology, Tangshan Worker’s Hospital, Tangshan, China; 13. Department of Cardiology, China-Japan Friendship Hospital Affiliated Jilin University, Changchun, China; 14. Department of Cardiology, Handan Central Hospital, Hebei, China; 15. Heart Center, Beijing Key Laboratory of Hypertension, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China; 16. Department of Cardiology, the First Affiliated Hospital of Dalian Medical University, Liaoning, China; 17. Department of Cardiology, the Second Affiliated Hospital of Harbin Medical University, Harbin, China; 18. Department of Cardiology, the Second Affiliated Hospital of Shenyang Medical College, Shenyang, China; 19. Department of Cardiology, the Second Hospital of Shanxi Medical University, Taiyuan, China; 20. Department of Neurology, Xuanwu Hospital Capital Medical University, Beijing, China; 21. Department of Neurology, Tianjin Medical University General Hospital, Tianjin, China; 22. Department of Cardiology, the Third Hospital of Shijiazhuang City, Shijiazhuang, China; 23. Department of Cardiology, the First Hospital of Shijiazhuang City, Shijiazhuang, China; 24. Department of Cardiology, Taigang General Hospital, Shanxi Medical University, Taiyuan, China; 25. Department of Cardiology, the Sixth Medical Center of Chinese PLA General Hospital, Beijing, China; 26. Department of Cardiology, Shengjing Hospital of China Medical University, Shenyang, China; 27. Department of Cardiology, Daqing Oilfield General Hospital, Heilongjiang, China; 28. Department of Cardiology, the Second Hospital of Baoding, Hebei, China; 29. Department of Cardiology and Macrovascular Disease, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; 30. Department of Cardiology, the First Affiliated Hospital of Harbin Medical University, Harbin, China; 31. Department of Cardiology, Jilin Central Hospital, Changchun, China; 32. Heart Center, the First Hospital of Hebei Medical University, Shijiazhuang, China

✉ Correspondence to: cyundai@vip.163.com
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ABSTRACT

BACKGROUND The efficacy and safety of proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors were confirmed by several clinical trials, but its effectiveness in routine clinical practice in China has not been evaluated. This study aims to describe the real world effectiveness of PCSK-9 inhibitors combined with statins compared with statins-based therapy among patients with very high risk of atherosclerotic cardiovascular disease (ASCVD).

METHODS This is a multi-center observational study, enrolled patients from 32 hospitals who underwent percutaneous coronary intervention (PCI) from January to June in 2019. There are 453 patients treated with PCSK-9 inhibitors combined with statins in PCSK-9 inhibitor group and 2,610 patients treated with statins-based lipid lowering therapies in statins-based group. The lipid control rate and incidence of major adverse cardiovascular events (MACE) over six months were compared between two groups. A propensity score-matched (PSM) analysis was used to balance two groups on confounding factors. Survival analysis using Kaplan-Meier methods was applied for MACE.

RESULTS In a total of 3,063 patients, 89.91% of patients had received moderate or high-intensity statins-based therapy before PCI, but only 9.47% of patients had low-density lipoprotein cholesterol (LDL-C) levels below 1.4 mmol/L at baseline. In the PSM selected patients, LDL-C level was reduced by 42.57% in PCSK-9 inhibitor group and 30.81% (P < 0.001) in statins-based group after six months. The proportion of LDL-C ≤ 1.0 mmol/L increased from 5.29% to 29.26% in PCSK-9 inhibitor group and 0.23% to 6.11% in statins-based group, and the proportion of LDL-C ≤ 1.4 mmol/L increased from 10.36% to 47.69% in PCSK-9 inhibitor group and 2.99% to 18.43% in statins-based group [P < 0.001 for both]. There was no significant difference between PCSK-9 inhibitor and statins-based treatment in reducing the risk of MACE (hazard ratio = 2.52, 95% CI: 0.49–12.97, P = 0.250).

CONCLUSIONS In the real world, PCSK-9 inhibitors combined with statins could significantly reduce LDL-C levels among patients with very high risk of ASCVD in China. The long-term clinical benefits for patients received PCSK-9 inhibitor to reduce the risk of MACE is still unclear and requires further study.

Atherosclerotic cardiovascular disease (ASCVD) has been demonstrated to be the leading cause of death and disease burden in China and worldwide, and lipid lowering drugs are proven to be the cornerstone of treatment and beneficial to the cardiovascular disease (CVD) outcomes. Numerical studies over the past decades have demonstrated a causal relationship between low-density lipoprotein cholesterol (LDL-C) and progression/manifestation of CVD. Elevation of LDL-C is an important risk factor associated with development of CVD events in acute coronary syndrome patients.

To date, all guidelines recommended LDL-C control as the main intervention target for lipid management. The Chinese guidelines for the prevention and treatment of dyslipidemia in adults (revised in 2016) recommended the management of dyslipidemia of ASCVD patients should be targeted at LDL-C < 1.8 mmol/L, and/or LDL-C is reduced by at least 50%. The AHA/ACC guidelines and China’s expert consensus in 2018 recommended that LDL-C should be controlled below 1.4 mmol/L or even lower for patients with very high risk of ASCVD (more than two severe ASCVD events or one severe ASCVD event combined with more than two high risk factors). The 2019 ESC/EAS dyslipidemia guidelines have recommended a LDL-C target of 1.4 mmol/L as goal for patients with very high risk of ASCVD. However, the proportion of patients with very high risk of ASCVD achieved the target value of LDL-C is low in China. Based on the community study in China, the LDL-C achieved rate among ASCVD patients was only 6.8%, and only 14.5% of them were treated by anti-hyperlipidemia drugs.

Although guidelines recommended high-intensity statins as first-line therapy for patients with established CVD, Chinese patients have limited benefit from high intensive statin treatment. The DYSIS-China study showed that high-intensity statins only resulted in an additional 6% reduction in LDL-C. Ezetimibe is recommended as second-line therapy for patients who are either intolerant to statins or do not achieve their LDL-C goals despite receiving maximally tolerated statin therapy. Proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors, as a new class of cholesterol lowering drugs, have been approved for treating hyperlipidemia in China in 2019. The phase II clinical trial showed that PCSK-9 inhibitor monotherapy could further reduce LDL-C by 37.3% to 52.5%, and reduce by 45% to 60% com-
bined with statins.\textsuperscript{[11]} ODYSSEY outcomes and FOURIER studies have also shown that PCSK-9 inhibitors can further reduce LDL-C levels, major adverse cardiovascular events (MACE), and improve clinical outcomes.\textsuperscript{[12,13]} Although these large randomized controlled trials (RCTs) have confirmed the clinical efficacy and safety of PCSK-9 inhibitors combined with statins, using PCSK-9 inhibitors in routine clinical practice of Chinese setting in very high risk of ASCVD patients has not been evaluated. In this study, we aim to compare the real world effectiveness of PCSK-9 inhibitors combined with statins or statins-based therapies among patients with very high risk of ASCVD.

METHODS

Study Design and Population

This study was based on a real world, multi-center patient cohort. Patients with very high risk of ASCVD who underwent percutaneous coronary intervention (PCI) in 32 hospitals were recruited from January to June in 2019 in China and were followed up for six months. A total of 453 patients treated with PCSK-9 inhibitors combined with statins and 2,610 patients treated with statins-based lipid lowering therapy were included in current study.

Patients who met the following criteria are eligible for the study: (1) age ≥ 18 years with very high risk of ASCVD;\textsuperscript{[14]} (2) underwent PCI during the study recruitment period; and (3) treated with statins-based lipid lowering drugs or PCSK-9 inhibitor. Patients who met any of the following criteria will not be eligible for this study: (1) malignant tumor or disease of the blood system; (2) severe hepatic and renal insufficiency; (3) severe allergic reactions history; (4) aspartate aminotransferase or alanine amino transferase more than three times the upper limit of normal (ULN); and (5) creatinine greater than three times the ULN.

In this study, patients’ LDL-C, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) at baseline and over six months after discharged from hospitals was compared. LDL-C control rate was analyzed and compared between patients with PCSK-9 inhibitors combined with statins and patients with statins-based agents. The impact of PCSK-9 inhibitors combined with statins or statins-based therapies on incidence of MACE was also compared. An independent Ethics Committee had approved the protocol (No.S2018-083). Written informed consents for both participation and publication were obtained from all participants.

Measures of Treatment Outcomes

The targeted lipid control rates were considered as LDL-C levels goals under 1.0 mmol/L or 1.4 mmol/L. The MACE included cardiac death, myocardial infarction (MI), target vessel revascularization (TVR), target lesion revascularization and stroke. The re-angina and re-hospitalization were also considered separately. Cardiac death was defined as any death due to cardiac cause, unwitnessed death and death of unknown cause. Spontaneous MI was defined as the presence of clinical or electrocardiographic changes consistent with myocardial ischemia and circulating cardiac biomarker concentrations above the ULN, in accordance with the universal definition.\textsuperscript{[15]} TVR was defined as the requirement for a repeated PCI or surgical bypass of any segment of a target vessel.

Propensity Score

Propensity score-matched (PSM) method was applied to balance the confounding factors between PCSK-9 inhibitor group and statins-based group. The selected variables to be potential confounders associated with clinical outcomes were age, gender, body mass index (BMI), hypertension, diabetes mellitus, stroke, smoker, chronic kidney disease, LDL-C, HDL-C, TC and TG. The PCSK-9 inhibitor group and statins-based therapies groups were paired at 1:1 using nearest matching with a caliper size of 0.05. We adjusted for imbalanced variables including medical history, inpatient diagnosis following mixed-effect Cox model.

Statistical Analysis

Continuous variables were presented as mean ± SD or median (interquartile range). Categorical variables were presented as frequency and percentage. The difference of continuous variables between the subgroups was tested by Student’s \textit{t}-test. The
difference of categorical variables between the subgroups was tested by Pearson’s chi-squared test and Fisher’s exact probability test. Survival analysis using Kaplan-Meier methods associated with log-rank tests was applied for MACE. To explore prognostic factors associated with incidence of MACE, Cox proportional hazards regression model was used. All statistical tests were two-sided and statistical significance was set at $P$-value < 0.05, which were performed using Stata software version 14.0 (Stata Corp, College Station, TX, USA).

RESULTS

Baseline Demographic and Clinical Characteristics of Patients with Very High Risk of ASCVD

A total of 453 patients treated with PCSK-9 inhibitors combined with statins and 2,610 patients treated with statins were recruited in the cohort. Among all patients, 89.91% of patients had received moderate or high-intensity statin therapy before PCI (Figure 1A), but only 9.47% of them had LDL-C levels below 1.4 mmol/L at baseline (Figure 1B). In the PSCK-9 inhibitor group, compared before and after treatment, the proportion of LDL-C < 1.0 mmol/L increased from 5.29% to 29.26%, the proportion of LDL-C < 1.4 mmol/L increased from 10.36% to 47.69% (Figure 1C).

PSM selected a subgroup of 868 patients (434 patients treated with PCSK-9 and 434 patients treated with statins-based therapy) were used for comparative effectiveness analysis in current study. The follow-up rate of 868 patients was 100% at six months. The patient flow chart was showed in Figure 2.

The baseline characteristics of matched patients were summarized in Table 1. There was no statistically significant difference in age, gender, BMI, co-morbidities, smoker and medical treatment after matched, but incidence of past history of MI, PCI, coronary artery bypass grafting, ST-elevation myocardial infarction and ischemic cardiomyopathy in PSCK-9 inhibitor group was higher (all with $P < 0.001$). The unselected patients for PSM analysis treated with statins-based therapy were demonstrated in Table 2.

During the follow-up period, 46 patients used Evolocumab 420 mg per month treatment plan, and 388 patients used 140 mg per two weeks. The time on treatment was 4.4 ± 1.2 weeks, and number of injections of Evolocumab was $3.3 ± 1.2$ for patients received 140 mg per two weeks plan.

Comparison of Lipid Profile between Two Treatment Groups

The LDL-C level was significantly reduced by 42.57% in PCSK-9 inhibitor group and 30.81% ($P < 0.001$) in statins-based group after six months follow-up. The TC level decreased by 25.15% and 21.02% ($P < 0.001$) in PCSK-9 inhibitor group and statins-based group, respectively (Figure 3). The proportion of LDL-C ≤ 1.0 mmol/L increased from 5.29% at baseline to 29.26% in the PCSK-9 inhibitor group and 0.23% to 6.11% in statins-based group over six months follow-up ($P < 0.001$, Figure 1C), and the proportion of LDL-C ≤ 1.4 mmol/L increased from 10.36% to 47.69% and 2.99% to 18.43% ($P < 0.001$).

Figure 1  The overall patient treated with statins and goal LDL-C level in the real world. (A): Different intensities of statin treatment; (B): LDL-C control before PCI; and (C): LDL-C control of the PCSK-9 inhibitor group and statins-based group over six months after PCI. LDL-C: low-density lipoprotein cholesterol; PCI: percutaneous coronary intervention.
Figure 2  The flow chart of patients. LDL-C: low-density lipoprotein cholesterol; PCI: percutaneous coronary intervention; PCSK-9: proprotein convertase subtilisin/kexin type 9.

Table 1  Demographic and diseases characteristics of patients in PCSK-9 inhibitor and statins-based treatment groups after matched.

| Variables                      | Statins-based group (n = 434) | PCSK-9 inhibitor group (n = 434) | P-value |
|--------------------------------|-------------------------------|----------------------------------|---------|
| Age, yrs                       | 60 (54–66)                    | 60 (52–68)                      | 0.350   |
| Male gender                    | 287 (66.1%)                   | 294 (67.7%)                     | 0.614   |
| Body mass index                | 24.68 (23.28–27.09)           | 24.77 (23.36–26.50)             | 0.059   |
| Hypertension                   | 288 (66.4%)                   | 293 (67.5%)                     | 0.718   |
| Diabetes mellitus              | 98 (22.6%)                    | 117 (27.0%)                     | 0.135   |
| Stroke                         | 60 (13.8%)                    | 58 (13.4%)                      | 0.843   |
| Chronic kidney disease         | 3 (0.7%)                      | 7 (1.6%)                        | 0.341   |
| Smoker                         | 206 (47.5%)                   | 207 (47.7%)                     | 0.945   |
| Medical history                |                               |                                  |         |
| Myocardial infarction          | 24 (5.5%)                     | 121 (27.9%)                     | < 0.001 |
| Percutaneous coronary intervention | 28 (6.5%)                  | 88 (20.3%)                      | < 0.001 |
| Coronary artery bypass graft   | 3 (0.7%)                      | 43 (9.9%)                       | < 0.001 |
| Inpatient diagnose             |                               |                                  |         |
| Stable angina                  | 44 (10.1%)                    | 23 (5.3%)                       | 0.008   |
| Unstable angina                | 273 (62.9%)                   | 263 (60.6%)                     | 0.485   |
| Non-ST-elevation myocardial infarction | 73 (16.8%)    | 61 (14.1%)                      | 0.260   |
| ST-elevation myocardal infarction | 44 (10.1%)                  | 79 (18.2%)                      | < 0.001 |
| Ischemic cardiomyopathy        | 0                             | 8 (1.8%)                        | –       |
| Medication                     |                               |                                  |         |
| Other lipid lowering therapy   | 10 (2.3%)                     | –                                | –       |
| Aspirin                        | 390 (89.9%)                   | 392 (90.3%)                     | 0.820   |
| β-blocker                      | 170 (39.2%)                   | 186 (42.9%)                     | 0.270   |
| Calcium channel blockers       | 149 (34.3%)                   | 155 (35.7%)                     | 0.669   |
| Renin angiotensin-aldosterone  | 71 (16.4%)                    | 63 (14.5%)                      | 0.452   |

Data are presented as n (%). *Presented as median (interquartile range). PCSK-9: proprotein convertase subtilisin/kexin type 9.
Comparison of Cardiovascular Events between Two Treatment Groups

There was no significant difference between PCSK-9 inhibitors combined with statins and statins-based treatment in reducing the risk of MACE [hazard ratio (HR) = 2.52, 95% CI: 0.49–12.97, P = 0.250] (Figure 4). The results showed lower risk of re-hospitalization (adjusted HR = 0.09, 95% CI: 0.03–0.31, P < 0.001; Figure 5), but there were no differences in MACE, TVR, MI and re-angina between two groups.

DISCUSSION

The management of LDL-C plays a significant role in the prevention of ASCVD. However, our study showed that less than 10% of patients reached the recommended LDL-C ≤ 1.4 mmol/L goal when patients were with very high risk at baseline in China. After being discharged from hospitals over six months, patients who received PCSK-9 inhibitor therapy had a significant LDL-C reduction, about 50% of patients reached ≤ 1.4 mmol/L goal compared to those with statins-based therapy. There was no significant difference in reducing the risk of MACE between PCSK-9 inhibitor group and statins-based group.

The guidelines of dyslipidemia management recommended that patients with acute coronary syn-
drome should start with medium-intensity statins, and adjust the appropriated dosage according to the efficacy and tolerance of individuals. If the cholesterol level fails to meet the goal, other lipid-regulating drugs, including Ezetimibe and PCSK-9 inhibitors, should be considered.\textsuperscript{[6–8]} Compared to Zhang, et al.\textsuperscript{[9]} study that only 14.5\% of patients with dyslipidemia in China receive lipid lowering treatment, our study showed that more than 80\% of patients received moderate or high-intensity statins-based therapy before PCI, which may be partially explained by higher awareness of hyperlipidemia management in ASCVD patients. Our study demonstrated a highly efficient lowering of LDL-C with PCSK-9 inhibitors treatment among the patients with very high risk of ASCVD, which was consistent with previous RCTs studies. The meta-analysis study showed that PCSK-9 inhibitors significantly reduced LDL-C by 54\% to 74\% versus placebo and 26\% to 46\% versus Ezetimibe.\textsuperscript{[16]}

The most common anti-hyperlipidemia medicine was statins monotherapy before and discharged from hospitals. Ezetimibe can offer additional LDL-C reduction and be recommended to add to maximally tolerated statin therapy when the LDL-C level remains ≥ 1.8 mmol/L in patients with very high risk of ASCVD. However, only 15 patients at baseline and 63 patients during the follow-up in our study received combination therapy (statins + Ezetimibe) in China. Combination therapy (statins + Ezetimibe) was more effective for achieving LDL-C goals as safety as the equivalent statin monotherapy, which has been supported by many clinical trials.\textsuperscript{[14,15]} Few patients treated by statins combined with Ezetimibe in our observational study could be one of the reasons of low achievement rate of LDL-C level at baseline. A total of 453 patients were pre-
scribed PCSK-9 inhibitors after PCI with about one-month continuous time on treatment. The low usage of PCSK-9 inhibitors in China was consistent with other studies published in the USA, UK, and other countries.[17–19] Many factors may contribute to the low rates of prescribing for PCSK-9 inhibitors. The high cost of treatment in China could be the main reason limited the use of PCSK-9 inhibitors. With acceptable PCSK-9 inhibitor price or be reimbursed, it could benefit more patients especially those with very high risk of ASCVD in Chinese real world clinical practice.

This study is a real world, multi-center study based on the national-level patients’ cohort covered more than 30 hospitals in China. Therefore, our results could be generalized to the whole Chinese patients with very high risk of ASCVD. The study results derived from analysis by a propensity score matching, applied to minimize confounding and indication bias. However, it is capable to correct only known confounders and some predictive factors were unbalanced after matching, which could be considered as limitations of real world study design. We demonstrated a superior real world ef-
fectiveness of PCSK-9 inhibitor despite short-term usage and six months follow-up. Whether the short-term effectiveness could accurately reflect long-term outcomes for patients who received PCSK-9 inhibitor is unknown and requires further study.

LIMITATIONS

This study is an observational study on patients underwent PCI from the real world, which has several limitations. Firstly, as this is an observational study, despite the establishment of full adjusted Cox model and propensity score weighting to remove the potential confounding factors, some potential factors may exist, which we have not considered. Secondly, in the real world, due to the economic limitation, PSCK-9 inhibitor was used only for one month. Therefore, the effect of long-term treatment with PSCK-9 inhibitor on patients underwent PCI on lipid lowering efficacy and clinical outcomes could not be obtained. Last but not least, the follow-up time of this study was six months, and the effect of PSCK-9 inhibitor on long-term prognosis required further data analysis in the next follow-up later.

CONCLUSIONS

In conclusion, treatment with PCSK-9 inhibitors combined with statins could significantly reduce LDL-C levels among patients with very high risk of ASCVD in China real world clinical practice.

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