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

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Abstract

Background The efficacy and safety of PCSK-9 inhibitors were confirmed by several clinical trials, but its effectiveness in routine clinical practice in China is unknown. Objective To describe the real world effectiveness of initiated with PCSK-9 inhibitors combined with statins compared with statins among patients with very high risk of ASCVD and underwent percutaneous coronary intervention (PCI). Methods This is a prospective study, enrolled patients from 32 hospitals between January to June 2019. The lipid control rate and incidence of cardiovascular events over 6 months were compared between two groups. A propensity score-matched analysis was used to balance two groups on confounding factors. Survival analysis using Kaplan-Meier methods was applied for cardiovascular events. Results In a total of 3063 patients, 89.91% had received moderate or high-intensity statin therapy before PCI, but only 9.47% had LDL levels below 1.4mmol/L at baseline. In the PSM selected patients, LDL level was reduced by 42.57% in PCSK-9 inhibitor group and 30.81% (P<0.001) in statins group after 6 months. The proportion of LDL[?]1.0mmol/L increased from 5.29% to 29.26% in PCSK-9 inhibitor group and 0.23% to 6.11% in statins group, and the proportion of LDL[?]1.4mmol/L increased from 10.36% to 47.69% and 2.99% to 18.43% (P<0.001 for both). PCSK-9 inhibitor significantly reduced the incidence of cardiovascular events versus statins treatment (2.07% vs 8.29%, HR, 0.24, 95% CI, 0.12-0.51). Conclusion In the real world, PCSK-9 inhibitors combined with statins could significantly reduce LDL levels and risk of cardiovascular events among patients with very high risk of ASCVD.

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Running title: RWE-PCSK 9 study in China

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Objective

To describe the real world effectiveness of initiated with PCSK-9 inhibitors combined with statins compared with statins among patients with very high risk of ASCVD and underwent percutaneous coronary intervention (PCI).

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This is a prospective study, enrolled patients from 32 hospitals between January to June 2019. The lipid control rate and incidence of cardiovascular events over 6 months were compared between two groups. A propensity score-matched analysis was used to balance two groups on confounding factors. Survival analysis using Kaplan-Meier methods was applied for cardiovascular events.

Results In a total of 3063 patients, 89.91% had received moderate or high-intensity statin therapy before PCI, but only 9.47% had LDL levels below 1.4mmol/L at baseline. In the PSM selected patients, LDL level was reduced by 42.57% in PCSK-9 inhibitor group and 30.81% (P <0.001) in statins group after 6 months. The proportion of LDL[?]1.0mmol/L increased from 5.29% to 29.26% in PCSK-9 inhibitor group and 0.23% to 6.11% in statins group, and the proportion of LDL[?]1.4mmol/L increased from 10.36% to 47.69% and 2.99% to 18.43% (P <0.001 for both). PCSK-9 inhibitor significantly reduced the incidence of cardiovascular events versus statins treatment (2.07% vs 8.29%, HR, 0.24, 95% CI, 0.12-0.51).

Conclusion

In the real world, PCSK-9 inhibitors combined with statins could significantly reduce LDL levels and risk of cardiovascular events among patients with very high risk of ASCVD.

Key words: PCSK-9 inhibitor; Real world; LDL-c; Cardiovascular events

What is already known about this topic?

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, as a new class of cholesterol lowering drugs, have been approved for treating hyperlipidemia in China 2019. The efficacy and safety of PCSK-9 inhibitors were confirmed by several clinical trials, but its effectiveness in routine clinical practice in China is unknown.

What does this article add?

To our knowledge, it is the first real-world multi-center study in China to demonstrate the real world effectiveness of initiated with PCSK-9 inhibitors combined with statins therapy among patients on very-high risk ASVD and underwent PCI.

We found that patients received PCSK-9 inhibitor therapy had a significant LDL-c reduction by about 50% patients reached [?]1.4mmol/L goal and reduced 76% risk of cardiovascular events, compared to those with statins during the 6 months follow-up period.

Introduction

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 outcomes [1-3]. Numerous studies over the past decades have demonstrated a causal relationship between 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 (ACS) patients. To date, all guidelines recommended LDL-c control as the main intervention target for lipid management [5, 6]. However, adherence and using to lipid-lowering medications reach desirable LDL cholesterol levels remains a serious concern in China. The China Chronic Disease and Risk factor Monitoring Database (CCDRFS) study showed that the LDL compliance rate was still unsatisfactory [4]. Among individuals with high risk of ASCVD patients, 74.5% had uncontrolled LDL-C levels (<2.6mmol/L). For very-high-risk individuals, 93.2% didn't achieve their LDL-lowering goals (<1.8mmol/L) and only 14.5% of them were treated. The AHA/ACC Guidelines and China's expert consensus in 2018 recommended that LDL should be controlled below 1.4mmol/L or even lower for patients with very high-risk ASCVD (more than two severe ASCVD events or one severe ASCVD event combined with more than two high-risk risk factors).

Although guidelines recommended the early initiation or continuation of high intensive statin therapy in all ACS patients [5], Chinese patients have limited benefit from high intensive statin treatment due to poor tolerance. The DYSIS-China study showed that high-intensity statins only resulted in an additional 6% reduction in LDL-C [7]. 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 (PCSK9) inhibitors, as a new class of cholesterol lowering drugs, have been approved for treating hyperlipidemia in China 2019. The Phase II clinical trial showed that PCSK-9 inhibitor monotherapy could further reduce LDL-c by 37.3% to 52.5% [8], and reduce by 45-60% combined with statin. ODYSSEY Outcomes and FOURIER studies have also shown that PCSK-9 inhibitors can further reduce LDL levels, major cardiovascular events (MACE), and improve clinical outcomes [9, 10]. Although these large RCTS have confirmed the clinical efficacy and safety of PCSK-9 inhibitors combined with statin, using PCSK-9 inhibitors in routine clinical practice of Chinese setting in very-high risk ASCVD patients is still unknown. In this study, we aim to compare the real-world effectiveness of PCSK-9 inhibitors combined with statins therapy or statins therapies among patients with very high risk and underwent percutaneous coronary intervention (PCI).

Methods

Study design and patients

This study was based on a real world, multicenter patient cohort. All the patients underwent PCI with very high risk of ASCVD in 32 hospitals were recruited between January to June 2019 in China, with 6 months follow up. A total of 453 patients treated with PCSK-9 inhibitors combined with statin and 2,610 patients treated with statins were included in current study.

Patients who met the following criteria are eligible for the study: age [?] 18 years with very high risk of ASCVD which defined as had more than two severe ASCVD events or one severe ASCVD event combined with more than two high-risk factors [11]; underwent PCI during the study recruitment period; treated with statin w/wo other lipid-lowering drugs or initiated treated with PCSK-9 inhibitor evolocumab 140mg per 2 weeks or 420 mg per month after PCI. All patients received PCSK-9 inhibitor treatment for 1 month then changed to statin w/wo other lipid-lowering drugs. Patients who met any of the following criteria will not be eligible for this study: malignant tumor or disease of the blood system; severe hepatic and renal insufficiency; severe allergic reactions history; aspartate aminotransferase or alanine amino transferase more than three times the upper limit of normal (ULN); creatinine greater than three times ULN.

In this study, patients' treatment of statin before and over 6 months after PCI was described. LDL-c control rate over 6 months after PCI in the real world was analyzed and compared between patients initiated with PCSK-9 inhibitors combined with statin and patients with statins agents. The impact of PCSK-9 inhibitors combined with statins or statins on incidence of cardiovascular events was also compared. An independent ethics committee had approved the protocol. Written informed consent for both participation and publication

was obtained from all the participants.

Measures of treatment outcomes

The targeted lipid control rates were considered as LDL-C levels goals under 1.0mmol/L or 1.4mmol/L. Cardiovascular events were defined as a total of death, MI, TVR, re-angina and re-hospitalization for cardiac events. Death was considered to be of cardiac origin unless an alternate cause was unequivocally established, even in participants with serious non-cardiac comorbidities. Spontaneous MI was defined as the presence of clinical or electrocardiographic changes consistent with myocardial ischemia and circulating cardiac biomarker concentrations above the upper limit of normal, in accordance with the universal definition [12]. TVR was defined as the requirement for a repeated percutaneous intervention or surgical bypass of any segment of a target vessel. A target vessel was defined as the entire major coronary vessel proximal and distal to the target lesion, which included the upstream and downstream branches and the target lesion itself.

Propensity score

Propensity score-matched method was applied to balance the confounding factors between two groups. The selected variables to be potential confounders associated with clinical outcomes were age, gender, BMI, hypertension (HT), diabetes mellitus (DM), stroke, smoker, CKD, LDL, HDL, TC and TG. The PCSK-9 inhibitor group and statins therapies groups were paired at 1:1 using nearest matching with a caliper size of 0.05. We adjusted for imbalanced variables past history (MI, PCI, and CABG), diagnose (stable angina, unstable angina, NSTEMI, STEMI and ischemic cardiomyopathy) following mixed-effect Cox model.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median (interquartile range). Categorical variables were presented as frequency and percentage. The difference of continuous variables between the subgroups was tested by t-test, or Wilcoxon rank sum test. The difference of categorical variables between the subgroups was tested by Pearson chi-square test, Fisher's exact probability test. Survival analysis using Kaplan-Meier methods associated with log-rank tests was applied for cardiovascular events. To explore prognostic factors associated with incidence of cardiovascular events, Cox proportional hazards regression model was used. All statistical tests are two-tailed and statistical significance is set at $p<0.05$, which were performed using Stata version 14.0 (College Station, TX).

Results

Baseline characteristics of patients with very high risk of ASCVD

A total of 453 patients treated with PCSK-9 inhibitors combined with statin and 2,610 patients treated with statins were recruited in the cohort. Among all patients, 89.91% had received moderate or high-intensity statin therapy before PCI (eFigure 1A), but only 9.47% of them had LDL levels below 1.4mmol/L (eFigure 1B). The proportion of patients with Lp(a) level >430mmol/L was 44.85%.

PSM selected a subgroup of 868 patients (434 initiated treated with PCSK-9 and 434 treated with statins) were used for comparative effectiveness analysis in current study. The follow-up rate of 868 patients was 100% at 6 months. The patient flow chart was showed in eFigure 2.

The baseline characteristics of matched patients were summarized in Table 1. There was no statistical significant difference in age, gender, BMI, comorbidities, smoker and medical treatment after matched, but incidence of past history of MI, PCI, CABG, STEMI and ischemic cardiomyopathy in PSCK-9 inhibitor group is higher (all with$P$ <0.001).

Comparison of lipid profile in two treatment groups

Compared to statins group, lipid profile improved significantly in the patients imitated with PCSK-9 inhibitor therapy (Figure 1). The LDL level was reduced by 42.57% in PCSK-9 inhibitor group and 30.81% (P <0.001)

in statins group after 6 month follow-up. The HDL level increased by 10.00% and 9.01% , and TC level decreased by 25.15% and 21.02% (P <0.001) in PCSK-9 inhibitor group and statins group.

More patients initiated with PCSK-9 inhibitor achieved the targeted LDL-C [?]1.0mmol/L and 1.4 mmol/L. The proportion of LDL[?]1.0mmol/L increased from 5.29% to 29.26% in the PCSK-9 inhibitor group and 0.23% to 6.11% in statins group over 6 months follow-up (P <0.001, efigure 1C), and the proportion of LDL[?]1.4mmol/L increased from 10.36% to 47.69% and 2.99% to 18.43% (P <0.001).

Comparison of cardiovascular events in two treatment groups

Initiated with PCSK-9 inhibitor combined with statins significantly reduce the incidence of cardiovascular events versus statins treatment (incidence 2.07% vs 8.29%, hazard ratio, 0.24, 95% CI, 0.12-0.51, P<0.0001) (Figure 2). The results showed lower risk of re-hospitalization (adjusted HR, 0.09; 95%CI, 0.03-0.31;P <0.001, figure 3), but there're no difference in TVR, MI and re-angina between two groups. All prognostic subgroups received benefit from the PCSK-9 inhibitor combined statin treatment, while male patients treated by PCSK-9 inhibitor had a lower risk of cardiovascular events than those treated by statin w/wo other lipid lowering therapies (Figure 4).

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[?]1.4mmol/L goal when patients with very high risk and underwent PCI at baseline in China, due to irregular lipid lowering treatment and poor tolerance to high-intensity therapies [13]. After being discharged from hospitals over 6 months, patients received PCSK-9 inhibitor therapy had a significant LDL-c reduction by about 50% patients reached [?]1.4mmol/L goal and reduced 76% risk of cardiovascular events, compared to those with statin w/ow other lipid-lowering therapies. Reduction in cardiovascular events was observed in the overall population, especially in men.

The guidelines of dyslipidemia managements in China recommended that patients with acute coronary syndrome should initial 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 PCSK9 inhibitors, should be considered [14-16]. Ezetimibe is an intestinal cholesterol absorption inhibitor by acting on NPC1L1 which is recommended as second line therapy. It can offer additional LDL-C reduction, but the percentage of patients achieving the target level of LDL-C is relatively low [17, 18].

PCSK9 is a negative regulator of the hepatic LDL receptor [19-21]. Our study demonstrated a highly efficient lowering of LDL-c with PCSK-9 inhibitors treatment among the patients with very high risk of ASCVD underwent PCI, which were consistent with previous study. A meta-analysis published in 2010 by Cholesterol Treatment Trialists' (CTT) Collaboration from 26 clinical trials showed a 22% decrease in MACE for 1 mmol/L (38.7 mg/dl) reduction in LDL-c in patients receiving statins [22]. IMPROVE-IT showed that combination of ezetimibe with simvastatin therapy in high-risk ASCVD patients can reduce LDL level to 1.4 mmol/L (53.2 mg/ dL), compared with reduction to 1.8 mmol/L (69.9 mg/ dL) in patients with simvastatin monotherapy. When added to statin therapy, ezetimibe results in improved cardiovascular outcome, which was 32.7% compared to 34.7% (P=0.016) [14]. The other clinical trial study showed that evolocumab on the background of statin therapy lowered LDL-c levels to a 0.78 mmol/L after 48 weeks treatment and significantly reduced the risk of composite of cardiovascular outcomes [10].

PCSK-9 inhibitor is an innovative therapeutic approach to improve control of elevated LDL-C levels, and recommended as an appropriate clinical use in patients at high risk of cardiovascular risk but still with substantially elevated LDL-C levels by Consensus of ESC and EAS Task. However, time on treatment of PCSK-9 inhibitor in our study was only 1 month, and then all the patients switched to statin therapy. The main reason of short-term time on treatment was poor affordability of evolocumab in China. 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 top hospitals in China. Therefore, our results could be generalized to the whole Chinese patients with high risk of ASCVD underwent PCI. 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 retrospective study design. We demonstrated a superior real world effectiveness of PCSK-9 inhibitor despite with short-term usage and 6 months follow-up. Whether the short-term effectiveness could accurately reflect long-term outcomes for patients received PCSK-9 is unknown and need further study with long-term follow-up.

In conclusion, initiated treatment with PCSK-9 inhibitors combined with statins after PCI could significantly reduce LDL levels and risk of cardiovascular events among patients with very high risk of ASCVD.

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Authors' contributions: Liu YQ, Chen YD was involved in the conceptualization and design of the study, data interpretation, and drafting and provided critical revisions of the manuscript. Li DD was involved in data interpretation and provided critical revisions of the manuscript. Cai M, Cong HL, Cong X, Dai J, Du R, Gao M, Guo J, Guo Y, Hong X, Huang R, Jia F, Li J, Li Q, Liu J, Liu X, Liu Y, Nie H, Shao B, Shen X, Song H, Song Y, Wang L, Wang S, Wu D, Xia J, Yang Z, Yu H, Zhang H, Zhang T, Zhao J, Zhao L and Zheng M were involved in data acquisition and data analysis and provided critical revisions of the manuscript. All authors approved the final draft to the manuscript and take accountability for accuracy and integrity.

Declaration of interest:

All authors declare that there are no conflicts of interest.

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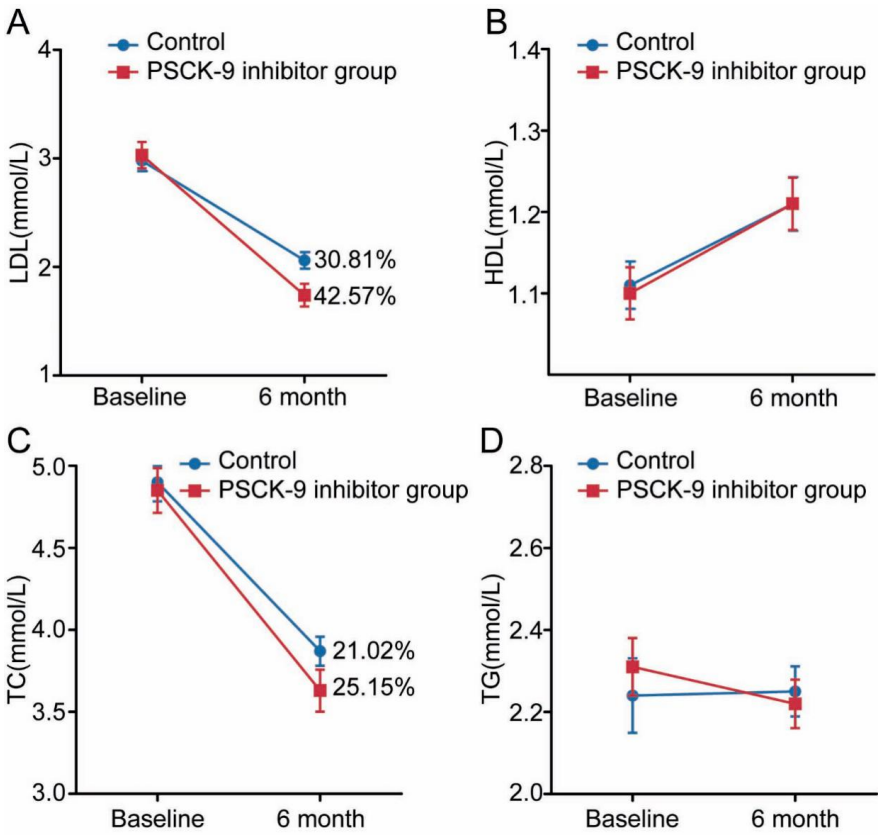

LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; TC: total cholesterol; TG: Triglyceride

Figure 1 Comparison of lipid profile before and after imitation of PCSK-9 inhibitor and statins treatment group

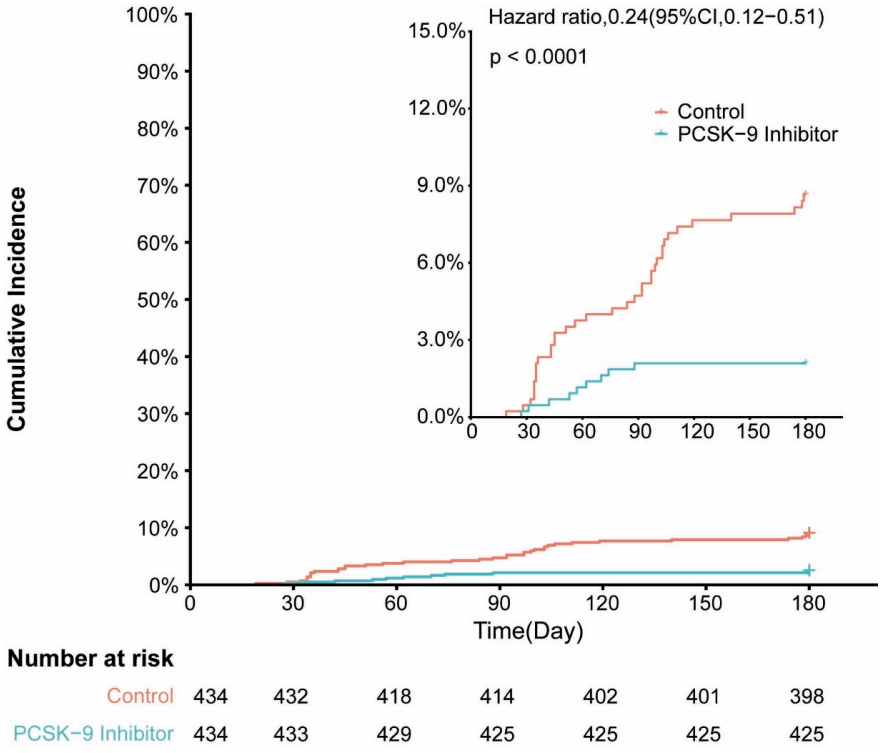

Figure 2 Kaplan-Meier curves of cardiovascular events

	PCSK-9		No PCSK-9		
	No. of Events	No. of Paticipants	No. of Events	No. of Paticipants	HR(95%CI)
AE	9	434	36	434	0.24(0.12,0.51)
TVR	1	434	1	434	1(0.06,16.01)
MI	4	434	1	434	4.02(0.45,35.95)
Reangina	7	434	1	434	7.06(0.87,57.36)
Rehospital	3	434	33	434	0.09(0.03,0.31)

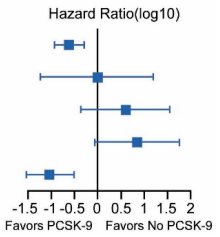

Figure 3 Hazard Ratios of using PCSK-9 inhibitor for cardiovascular events.

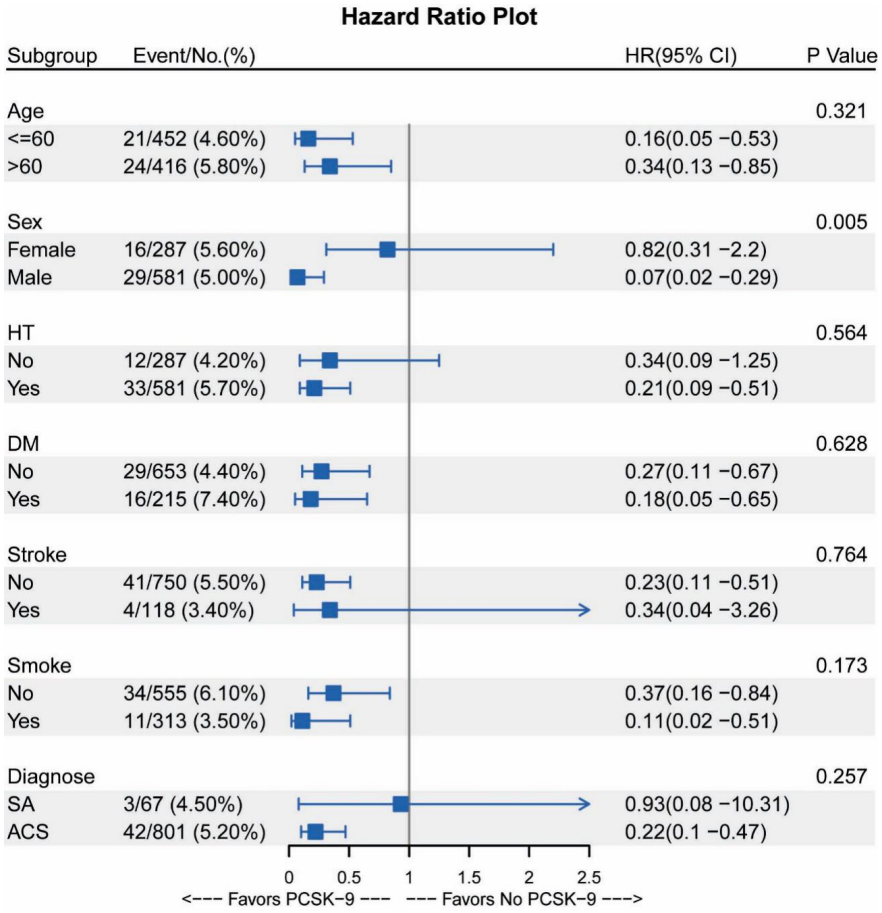

Figure 4 Subgroup analysis forest plot for cardiovascular events

*Medical history (MI, PCI, and CABG), Inpatient diagnose (stable angina, unstable angina, NSTEMI, STEMI and ischemic cardiomyopathy) were also adjusted in Cox proportional hazards regression. HT: Hypertension; DM: Diabetes; SA: stable angina; ACS: acute coronary syndrome

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

	Statins N=434	PCSK-9 inhibitor N=434	P value
Age, (IQR)	60 (54,66)	60.00(52,68)	0.350
Male (%)	287(66.1%)	294(67.7%)	0.614
Body Mass Index (IQR)	24.68 (23.28, 27.09)	24.77(23.36,26.50)	0.059
Hypertension (%)	288(66.4%)	293(67.5%)	0.718
Diabetes (%)	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			
MI	24(5.5%)	121(27.9%)	<0.001

	Statins N=434	PCSK-9 inhibitor N=434	P value
PCI	28(6.5%)	88(20.3%)	<0.001
CABG	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
NSTEMI	73(16.8)	61(14.1%)	0.260
STEMI	44(10.1%)	79(18.2%)	0.001
Ischemic cardiomyopathy	0(0.0%)	8(1.8%)	0.008
Medication			
Other LLT	10(2.3%)	None	
Aspirin	390(89.9%)	392(90.3%)	0.820
ß-blocker	170(39.2%)	186(42.9%)	0.270
CCB	149(34.3%)	155(35.7%)	0.669
RAAS	71(16.4%)	63(14.5%)	0.452

MI:myocardial infarction; PCI: percutaneous coronary intervention; CABG:coronary artery bypass graft; NSTEMI:non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; LLT: lipid-lowering treatment; CCB:calcium channel blockers; RAAS: Renin angiotensin–aldosterone system

eTable 1 Demographic and diseases characteristics of patients in PCSK-9 inhibitor and statins group before matched

	Statins N=2610	**PCSK-9 inhibitor (n=453)**	***P* value**
Age, median (IQR)	59(52, 65)	60(51, 68)	0.510
Male gender, n (%)	620(23.8%)	311(68.7%)	<0.001
Body Mass Index, median(IQR)	25.71(23.72, 27.78)	24.78(23.29, 26.53)	<0.001
Hypertension, n(%)	1521(58.3%)	302(66.7%)	0.001
Diabetes, n(%)	730(28.0%)	125(27.6%)	0.869
Stroke (%)	172(6.6%)	61(13.5%)	<0.001
Chronic Kidney Disease, n(%)	19(0.7%)	7(1.5%)	0.80
Smoke, n(%)	1315(50.4%)	216(47.7%)	0.289
Medical history			
MI	225(8.6%)	123(27.2%)	<0.001
PCI	316(12.1%)	90(19.9%)	<0.001
CABG	26(1.0%)	44(9.7%)	<0.001
Inpatient diagnose			<0.001
Stable angina	231(8.9%)	25(5.5%)	0.018
Unstable angina	1589(60.9%)	274(60.5%)	0.844
NSTEMI	494(18.9%)	66(14.6%)	0.026
STEMI	292(11.2%)	80(17.7%)	<0.001
Ischemic cardiomyopathy	4(0.2%)	8(1.8%)	<0.001
Lab test			
LDL (mmol/L), median(IQR)	2.31(1.78, 2.97)	3.04(2.16, 4.00)	<0.001
HDL(mmol/L), median(IQR)	0.97(0.82, 1.14)	1.08(0.92, 1.28)	<0.001
TC (mmol/L), median(IQR)	3.90(3.30, 4.70)	4.97(3.95, 6.04)	<0.001
TG (mmol/L), median(IQR)	1.45(1.04, 2.01)	1.97(1.24, 3.09)	<0.001

MI:myocardial infarction; PCI: percutaneous coronary intervention; CABG:coronary artery bypass graft; NSTEMI:non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; TC: total cholesterol; TG: Triglyceride;