Cardiovascular Outcomes in Patients with Initial Diagnosis of Obstructive Coronary Artery Disease and LDL-C below 1.8 mmol/L

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Research

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Abstract

Background To investigate individuals at high risk for atherosclerotic cardiovascular disease (ASCVD), but, without previous events and with low-density lipoprotein cholesterol(LDL-C)<1.8 mmol/L should be treated with statin.

Methods: We studied 1330 patients with LDL-C <1.8 mmol/L at the initial diagnosis of obstructive coronary atherosclerotic disease (OCAD) by angiography. Of 1330, 782 had not received prior statin therapy and 548 were treated with statin. Incidence of subsequent major adverse cardiac and cerebral event (MACCE) during a median of 25-month follow-up were identified and compared between patients with LDL-C <1.8 mmol/L without any prior statin [prior statin(-)] and those with LDL-C <1.8mmol/L achieved by prior statin therapy [prior statin(+)].

Results ACS occurred in 93.4% of individuals with LDL-C <1.8 mmol/L as an initial diagnosis of OCAD. Prior statin(+), comparing to prior statin(-) who displayed similar ASCVD risk burden including 71.6% with hypertension, 39.1% with diabetes and 76.1% with ≥3 risk factors, had significantly lower incidence of acute myocardial infarction(AMI) (10.4% vs. 28.8%, P<0.001), higher left ventricular ejection fraction(LVEF)(0.67±0.07 vs. 0.64±0.09, P <0.001), lower incidences of subsequent MACCE (4.7% vs. 10.4%, P =0.001), total mortality (2.4% vs. 6.8%, P =0.001) and cardiovascular(CV) death (1.5% vs. 4.3%, P =0.006) during follow-up. After multivariable adjustment, no prior statin therapy was significantly and independently associated with subsequent CV death, particularly in the subgroups of age≥65 years and hypertension.

Conclusions Prior statin therapy to achieve LDL-C <1.8 mmol/L comparing to LDL-C <1.8 mmol/L without statin independently predicted lower risk of subsequent CV death and better prognosis.

Background

Obstructive coronary atherosclerotic disease (OCAD) is the leading cause of death worldwide[1,2]. It is well established that elevated levels of low-density lipoprotein cholesterol (LDL-C) is associated with an increased risk of OCAD and its related major adverse cardiac and cerebral event (MACCE)[3,4]. Randomized clinical trials have demonstrated that LDL-C lowering therapies can reduce risk of OCAD and MACCE[5–9].

Currently, LDL-C lowering with statin therapy has been recommended as a corner stone of primary and secondary preventions by multiple practice guidelines[10–13].

For secondary prevention, it is clear that statin therapy should be initiated regardless of baseline LDL-C levels. The target level of LDL-C < 1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) should be achieved with LDL-C lowering therapies. In primary prevention setting, guidelines recommended initiation of LDL-C lowering therapy in LDL-C > 1.8 mmol/L, and recently added risk assessment algorithm and imaging and biomarker assessment with objective of improving identification of high-risk population. 2019 European Society of Cardiology(ESC)guidelines showed that in patients with type 2 diabetes mellitus(T2DM) at very-high risk, an LDL-C reduction of ≥ 50% from baseline and an LDL-C goal of < 1.4 mmol/L (< 55 mg/dL) is recommended[14]. In the real-world practice, acute coronary syndrome (ACS) can develop in individuals with LDL-C < 1.8 mmol/L and it is not clear whether individuals with LDL-C < 1.8 mmol/L and at high risk for atherosclerotic cardiovascular disease (ASCVD), but, without previous clinically established ASCVD related events, should also be treated with statin. To address this critical unanswered clinical question, we performed a retrospective analysis with objective to identify incidence of subsequent MACCE in patients with LDL-C < 1.8 mmol/L without any prior statin use and to compare these outcomes to a cohort of patients with LDL-C < 1.8 mmol/L achieved by prior statin therapy.

Methods

Study population

Study subjects were identified in the database at the Cardiovascular Center of Beijing Friendship Hospital. As shown in **Figure 1**, a total of 11137 patients underwent coronary angiography from January 2013 to September 2019. Of these 11137, 9339 were diagnosed with OCAD. Of the 9339 patients, 8009 were excluded according to the exclusion criteria including prior diagnosis of OCAD; LDL-C ≥1.8 mmol/L; triglycerides (TG) > 4.5mmol/L; acute infections; malignant tumor; missing clinical or follow-up data. Finally, a total of 1330 patients were included in this analysis, and 782 were identified not treated with statin prior to the initial diagnosis of OCAD and 548 were confirmed to receive statin for at least 1 month prior to the diagnosis. The median duration of statin use was 24.0 (IQR: 3.0, 60.0) months. All patients were followed up to December 31, 2019 with a median follow up of 25.0 (IQR: 11.8, 48.6) months.

The study data collections were approved by the Institutional Review Board of Beijing Friendship Hospital affiliated to Capital Medical University and were in accordance with the Declaration of Helsinki.

Data collections and definitions

Patient demographic information, medical and medication history, laboratory measurements, echocardiographic and angiographic evaluations, and clinical outcomes during the hospitalization of initial diagnosis of OCAD were collected and confirmed through electronic medical records. The subsequent outcomes on MACCE were collected and recorded through clinical follow-up visits.

OCAD was defined as atherosclerotic lesion(s) in coronary arteries causing >50% of the lumen obstruction by coronary angiography, which causing myocardial ischemia or necrosis.

MACCE included all-cause death, non-fatal myocardial infarction (MI) and non-fatal stroke. Non-fatal MI was defined as chest pain with new ST-segment changes and elevation of myocardial necrosis markers to at least twice of the upper limit of the normal range. Non-fatal stroke included ischemic and hemorrhagic stroke, was defined as cerebral dysfunction caused by cerebral vascular obstruction or sudden rupture, and was diagnosed based on signs of neurological dysfunction or evidence of brain imaging.

Statistical analysis

Continuous variables were expressed as mean value± SD or median and interquartile range (IQR), depending on the distribution of the data. Comparisons between the study groups were performed by Student t-test or Mann-Whitney U-test. Categorical variables were expressed as number and percentage, and compared using the Pearson chi-square test or Fisher's exact test. The cumulative incidence of MACCE was estimated by Kaplan-Meier survival Curves, and the groups were compared using the log-rank test. A multivariable Cox regression analysis was performed in order to determine whether no prior statin therapy was an independent predictor for all-cause mortality, cardiovascular (CV) death and composite MACCE. Baseline variables that were significantly correlated with outcomes by univariate analysis and clinically relevant were entered into the multivariate model. In model 1, we adjusted for age, gender and body mass index. In model 2, we further adjusted for history of current/ex-smoker, hypertension, antiplatelet agent use prior admission and angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers/beta-blocker (ACEI/ARB/β-blocker) use prior admission. In model 3, we further included left ventricular ejection fraction(LVEF). All analyses were two-tailed and P value <0.05 was considered statistically significant. Data were analyzed using SPSS statistical package version 24.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

As shown in **Figure 1**, of 9339 subjects undergoing coronary angiography(CAG), 1330(14.2%) patients were diagnosed to have OCAD for the first time. Patient demographic, medical and clinical, laboratory, echocardiographic and angiographic characteristics are presented and compared between prior statin(-) and (+) groups as shown in **Table 1**.

Comparing to prior statin(+), subjects in the prior statin(-) group showed significantly lower body mass index(BMI), higher percent of male gender and smokers, lower percent of hypertension, significantly less likely to receive antiplatelet therapy, ACEI/ARBs, or β-blocker prior to the current admission. The prevalence of ACS as a clinical presentation of the initial diagnosis of OCAD was 93.4% and similar between prior statin(-) and (+) groups (93.9% vs 92.7%, P =0.402). Among ACS, 22.7% (282/1242) was confirmed as acute myocardial infarction(AMI). However, incidence of AMI was significantly higher in the prior statin(-) group than prior statin(+) (28.8% vs. 10.4%, P <0.001). Furthermore, among patients who suffered AMI, peak troponin I level was significantly higher in the prior statin(-) group than prior statin(+) [3.86 (0.70,13.35) ng/ml vs. 2.43 (0.22,5.64) ng/ml, P =0.011]. Echo evaluation showed that prior statin(-) had significantly lower LVEF(0.64±0.09 vs. 0.67±0.07, P <0.001) and higher percentage of LVEF<0.50(7.4% vs. 3.3%, P =0.001) than prior statin(+). Laboratory values, angiography findings, in-hospital medical and interventional treatments were similar between the 2 groups. Subjects in the prior statin(-) group had a significant longer average hospital stay (6.0 vs. 5.0 days, P <0.001).

During the median of 25 months of follow-up, 91.5% of patients in prior statin(-) group and 94.8% of those in prior statin(+) group continued statin therapy since the OCAD hospital discharge. The LDL-C levels were similar between the 2 groups in follow-up (1.47±0.26mmol/L vs. 1.47±0.25mmol/L, P =0.805).

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Subsequent MACCE and mortality

As presented in **Figure 2** and **Table 2**, during a median of 25-month (IQR 11.8, 48.6) follow-up, subsequent MACCE occurred in 10.4% of prior statin(-) and 4.7% of prior statin(+) (HR=2.09, 95%CI: 1.34,3.24, P =0.001). All-cause mortality was observed in 6.8% of prior statin(-) and 2.4% of prior statin(+) (HR=2.74, 95%CI: 1.49,5.03, P =0.001). CV death was identified in 4.3% of prior statin(-) and 1.5% of prior statin(+) (HR=2.92, 95%CI: 1.35,6.31, P =0.006). Subsequent non-fatal MI and non-fatal stroke were not statistically significant between the 2 patient groups. Kaplan-Meier curves of significantly increased MACCE, all-cause mortality and CV death in prior statin(-) than prior statin(+) are illustrated in **Figure 3**.

Independent association of subsequent MACCE and mortality

Multivariate analysis included variables that were identified to be significantly associated with MACCE, total mortality and CV death in the univariate model. Also, intercorrelations among variables were taken into consideration in the multivariate analysis, for example, LVEF<0.50 and diagnosis of AMI at admission were found significantly associated with MACCE by univariate analysis. However, LVEF<0.50 was significantly correlated with AMI (r=0.38, P <0.001), therefore, LVEF<0.50 was the variable entered in the multivariate analysis. As shown in **Table 2**, no prior statin therapy was significantly and independently associated with CV death (HR=2.47, 95%CI 1.13-5.36, P =0.023). In addition, no prior statin therapy showed a trend in association with an increased risk of all-cause death (HR=1.76, 95%CI 0.92-3.37, P =0.090) and composite MACCE (HR=1.47, 95%CI 0.91-2.38, P =0.112).

Effects of no prior statin therapy on CV death by prespecified subgroups

There were 34 participants with CV death in the prior statin(-) group and 8 in the prior statin(+) group (4.3% vs 1.5%, HR=2.47, 95%CI 1.13-5.36, *P* =0.023). No prior statin therapy was also significantly and independently associated with CV death in the subgroups of age≥65 years(HR=3.70, 95%CI 1.28-10.68, *P* =0.016) and hypertension (HR=3.67, 95%CI 1.40-9.6, *P* =0.008) (**Figure 4**).

Discussion

The present study involved 1330 patients with LDL-C levels < 1.8 mmol/L who were first diagnosed with OCAD and 58.8% of these patients did not receive prior statin therapy. There are 2 important observations: (1) The risk of AMI occurrence remained high in individuals with LDL-C < 1.8 mmol/L, especially in those without prior statin therapy. (2) We found that prior statin therapy for lowering LDL-C to < 1.8 mmol/L comparing to LDL-C < 1.8 mmol/L without statin was significantly associated with lower incidences of subsequent MACCE (4.7% vs. 10.4%, *P* = 0.001), total mortality (2.4% vs. 6.8%, *P* = 0.001) and CV death (1.5% vs. 4.5%, *P* = 0.006) during a median of 25-month follow-up. The multivariate analysis revealed that no prior statin therapy remained an independent and strong predictor of CV death, particularly in the subgroups of age ≥ 65 years and hypertension.

Populations studies and randomized clinical trials have established that increased levels of LDL-C are associated with increased risk of ASCVD and subsequent MACCE[3,4] and every 1 mmol/L LDL-C lowering with interventions is associated with 20% MACCE risk reduction[5,15], even in people who were considered to be at low risk. Genetic studies in the recent years have demonstrated that genetic mutation associated lower levels of LDL-C are correlated with further reduced risk for coronary heart disease[3,16–18]. Data from the intensively treated patients in the PROVE IT-TIMI 22 (The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) trial showed that LDL-C ≤ 40 mg/dL and 40–60 mg/dL groups had fewer major cardiac events (death, MI, stroke, recurrent ischemia or revascularization) than LDL-C > 60–80 mg/dL groups[19]. The recent trials with Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition confirmed that further LDL-C reduction to 30–50 mg/dl with combination of PCSK9 inhibitor and statin can lead to further reduction of ASCVD events comparing statin alone[7,8,20]. The cumulated evidence in the past 50 years has impacted the development of practice guidelines recommending LDL-C as the primary treatment target for people at different ASCVD risk levels[10–13, 21].

Initiation of LDL-C therapy is recommended in people with established vascular diseases (secondary prevention) at any levels of LDL-C. If ASCVD risk management is entirely based on LDL-C levels, LDL-C lowering therapy is commonly recommended when LDL-C > 1.8 mmol/L (70 mg/dL) in individuals without previous vascular events (primary prevention). Indeed, physicians have initiated statin therapy in a group of high-risk subjects with LDL-C > 1.8 mmol/L to achieve LDL-C < 1.8 mmol/L. Not surprised, in our study, this group with prior statin comparing to subjects with LDL-C < 1.8 mmol/L without statin displayed a lower incidence of AMI, lower levels of peak troponin I for less myocardium ischemic damage when MI was not prevented, and decreased risk of subsequent MACCE and mortality, which are consistent with results seen in the previous primary prevention trails[22–24] and also can be explained by improved plaque stability with statin therapy demonstrated in the previous imaging studies[25–28].

The lower incidence of AMI and less myocardium ischemic damage with statin-induced LDL-C < 1.8 mmol/L comparing to "naturally" LDL-C < 1.8 mmol/L suggest that non-lipid effects of statin[29–31] and a greater LDL-C toxicity[5,32]. Importantly, the higher incidence of AMI and the increased risk of subsequent MACCE and mortality in subjects with LDL-C < 1.8 mmol/L without prior statin raise a question whether statin therapy should be given to high-risk individuals without previous vascular events regardless of LDL-C levels because LDL-C < 1.8 mmol/L did not offer cardiovascular protection in this population.

The most recent guidelines began to suggest that ASCVD risk assessment and initiation of statin therapy should not limited to LDL-C levels. In our study, patients treated with and without prior statin showed high and similar ASCVD risk burden (76.3% vs. 76.1%) with ≥ 3 risk factors. Statin therapy was obviously given to patients with LDL-C > 1.8 mmol/L. However, among subjects not treated with prior statin, 39.1% of them had type-2 diabetes, despite LDL-C level < 1.8 mmol/L, should receive statin therapy according to guideline recommendations, and 7.0% with chronic kidney disease also should be treated with statin. Furthermore,

76.1% of subjects displayed ≥ 3 ASCVD risk factors in our study could have benefited from statin therapy as HOPE-3 demonstrated that rosuvastatin 10 mg daily significantly lowered risk of ASCVD events than placebo in an intermediate-risk and ethnically diverse population with 1–2 risk factors without established cardiovascular disease[25]. Furthermore, the benefits of rosuvastatin were consistent across all subgroups defined based on LDL-C level, blood pressure, C-reactive protein level, cardiovascular risk at baseline, age, sex, and race or ethnic group. However, the baseline LDL-C in HOPE-3 was > 1.8 mmol/L. The role of lowering LDL-C with statins in the primary prevention among people without clinically established cardiovascular disease, regardless of lipid levels, inflammatory markers, hypertension status, or diabetes status, has not been established. Our subgroup analyses emphasized the importance of early statin therapy for the population with age ≥ 65 years or hypertension. Further investigations, in light of our study findings, are needed to determine whether statin or other LDL-C lowering therapy would reduce ASCVD events in patients with multiple risk factors, but, LDL-C < 1.8 mmol/L.

The present study found that 1231 (92.6%) patients with initial diagnosis of OCAD and LDL-C < 1.8 mmol/L presented as ACS at admission. The underutilization of statin was also led by under diagnosis of OCAD prior to the first presentation of ACS in our study. At the time of initial diagnosis of OCAD, about 80% of patients already had multivessel or left main coronary disease and near 10% had chronic total occlusion by angiography. If the OCAD was fully recognized prior to the first presentation of ACS, at least 80% of patients should have given statin therapy and benefited from the treatment. These findings, on one hand, support the potential role of using coronary CT angiography and coronary artery calcium scoring to detect the underlying coronary atherosclerosis in patients with low LDL-C. On the other hand, these data also present challenges in the real-world practice given the high burden of ASCVD worldwide, cost of imaging test for OCAD diagnosis and complexity of proper use of imaging test. In this situation, the risk score calculation recommended by guidelines[10–12] can help to identify individuals at increased risk for ASCVD despite of LDL-C < 1.8 mmol/L.

Limitations

There are limitations with this study. First, this is a single-center study, although with a large sample size, but, limited number of MACCE, which limits the generalization of the findings and statistical power to account for all possible confounders. Second, it is a retrospective analysis with potential unmeasured bias. Prospective cohort studies are needed to confirm our findings. Future randomized clinical trials will be able to investigate the effects of statin or other lipid therapies on reduction of MACCE in high-risk patients with LDL-C < 1.8 mmol/L.

Conclusion

Prior statin therapy for lowering LDL-C to < 1.8 mmol/L comparing to LDL-C < 1.8 mmol/L without statin was significantly and independently predictive of subsequent CV death. Statin therapy was largely underutilized in this high-risk population with multiple ASCVD risk factors despite of LDL-C < 1.8 mmol/L. These findings suggest that statin therapy for primary prevention of OCAD should be considered based ASCVD risk assessment, not driven by LDL-C level only.

Abbreviations

OCAD
Obstructive coronary atherosclerotic disease; LDL-C:Low-density lipoprotein cholesterol; MACCE:Major adverse cardiac and cerebral event; ESC:European Society of Cardiology; T2DM:Type 2 diabetes mellitus; ACS:Acute coronary syndrome; ASCVD:Atherosclerotic cardiovascular disease; TG:Triglycerides; MI:Myocardial infarction; CV:Cardiovascular; ACEI/ARB /β-blocker:Angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers/beta-blocker; LVEF:Left ventricular ejection fraction; CAG:Coronary angiography; BMI:Body mass index; AMI:Acute myocardial infarction; PCSK9:Proprotein convertase subtilisin/kexin type 9.

Declarations

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Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The study data collections were approved by the Institutional Review Board of Beijing

Friendship Hospital affiliated to Capital Medical University, and written informed consent

was obtained from all patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from

the corresponding author on reasonable request

Authors' contributions

WPL, XQZ and HWL contributed to the conception or design of the work. WPL, XQZ, YZ, XSD, DDL and HC contributed to the acquisition, analysis, or interpretation of data for the work. WPL, XQZ and YZ drafted the manuscript. All authors critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

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Tables

Table 1. Clinical characteristics of patients without or with prior statin therapy

	Prior statin(-) (n=782)	Prior statin(+) (n=548)	P value
Age, years	65.7±10.2	65.5±9.4	0.711
Male gender	571 (73.0)	367 (67.0)	0.017
BMI, kg/m^2	25.3±3.4	25.9±3.2	0.002
Systolic blood pressure, mmHg	129.5±19.1	130.2±15.4	0.566
Diastolic blood pressure, mmHg	74.8±11.9	75.3±10.7	0.445
Medical history			
Current/ex-Smoker	470 (60.1)	266 (48.5)	<0.001
Diabetes mellitus	306 (39.1)	217 (39.6)	0.863
Hypertension	560 (71.6)	432 (78.8)	0.003
Chronic kidney disease	55 (7.0)	28 (5.1)	0.153
≥3 risk factors*	595(76.1)	418(76.3)	0.936
Medication use prior admission			
Antiplatelet agent	175 (22.4)	384 (70.1)	<0.001
ACEI/ARB	267 (34.1)	252 (46.0)	<0.001
Beta-blocker	150 (19.2)	192 (35.0)	<0.001
Laboratory values			
Hemoglobin, g/L	132.9±16.4	134.3±15.4	0.198
Fasting glucose, mmol/L	5.3(4.7,6.3)	5.4(4.8,6.4)	0.252
Glucose at admission, mmol/L	7.3(5.9,9.8)	7.3(5.8,9.4)	0.576
eGFR, ml/min/1.73m^2	84.7(70.5,99.5)	87.4(73.8,98.8)	0.057
TC, mmol/L	3.10±0.39	3.07±0.42	0.347
TG, mmol/L	1.09(0.80,1.40)	1.05(0.77,1.33)	0.435
LDL-C, mmol/L	1.51±0.23	1.49±0.23	0.133
HDL-C, mmol/L	1.05±0.27	1.08±0.27	0.073
Non-HDL, mmol/L	2.01±0.30	1.99±0.31	0.197
TRL-C, mmol/L	0.48(0.40,0.59)	0.48(0.41,0.57)	0.963
Echocardiography			
LVEF	0.64±0.09	0.67±0.07	<0.001
LVEF<0.5	58(7.4)	18(3.3)	0.001
Angiography findings			
Multi-vessel/LM	640 (81.8)	437 (79.7)	0.338
CTO	73 (9.3)	55 (10.0)	0.669
Proximal LAD	234 (29.9)	156 (28.5)	0.566
Diagnosis of AMI at admission	225(28.8)	57(10.4)	<0.001
In-hospital treatment			
PCI/CABG	512 (65.5)	339 (61.9)	0.177
Antiplatelet agent	748 (95.7)	532 (97.1)	0.178
ACEI/ARB	434 (55.5)	294 (53.6)	0.505
Beta-blocker	522 (66.8)	346 (63.1)	0.173
Statin	711 (90.9)	509 (92.9)	0.201
Hospital stay, days	6.0 (4.0,8.0)	5.0 (4.0,7.0)	<0.001

Values are presented as mean±SD, median (IQR) or number (%).

BMI, body mass index; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Non-HDL, non-high-density lipoprotein cholesterol (Non-HDL=TC minus HDL-C); TRL-C, triglyceride-rich lipoprotein cholesterol (TRL-C=TC minus HDL-C minus LDL-C); LVEF, left

ventricular ejection fraction; LM, left main coronary artery; CTO, chronic total occlusions; LAD, left anterior descending; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

*: risk factors include: male ≥45 years of age or female ≥55 years of age, smoking, hypertension, diabetes mellitus, BMI ≥28kg/m^2 and HDL-C <1.0mmol/L.

Table 2. Cox proportional hazard regression analysis of MACCE

	Univariable		Multivariable					
			Model 1		Model 2		Model 3	
	HR(95%CI)	P value	HR(95%CI)	P value	HR(95%CI)	P value	HR(95%CI)	P value
Composite MACCE								
Prior statin(+)	1.00(Ref)	-/-	1.00(Ref)	-/-	1.00(Ref)	-/-	1.00(Ref)	-/-
Prior statin(-)	2.09(1.34,3.24)	0.001	2.07(1.33,3.23)	0.001	1.60(0.99,2.57)	0.053	1.47(0.91,2.38)	0.112
All cause death								
Prior statin(+)	1.00(Ref)	-/-	1.00(Ref)	-/-	1.00(Ref)	-/-	1.00(Ref)	-/-
Prior statin(-)	2.74(1.49,5.03)	0.001	2.71(1.48,4.98)	0.001	1.93(1.01,3.68)	0.046	1.76(0.92,3.37)	0.090
CV death								
Prior statin(+)	1.00(Ref)	-/-	1.00(Ref)	-/-	1.00(Ref)	-/-	1.00(Ref)	-/-
Prior statin(-)	2.92(1.35,6.31)	0.006	2.89(1.34,6.25)	0.007	2.74(1.21,6.01)	0.010	2.47(1.13,5.36)	0.023

MACCE, major adverse cardiac and cerebral event; CV, cardiovascular; HR, harzard Ratio; CI, confidence interval.

Model 1 included age, gender and body mass index.

Model 2 included age, gender, body mass index, current/ex-smoker, hypertension, antiplatelet agent use prior admission and ACEI/ARB/β-blocker use prior admission.

Model 3 included age, gender, body mass index, current/ex-smoker, hypertension, antiplatelet agent use prior admission, ACEI/ARB/β-blocker use prior admission and LVEF<0.5.

Figures

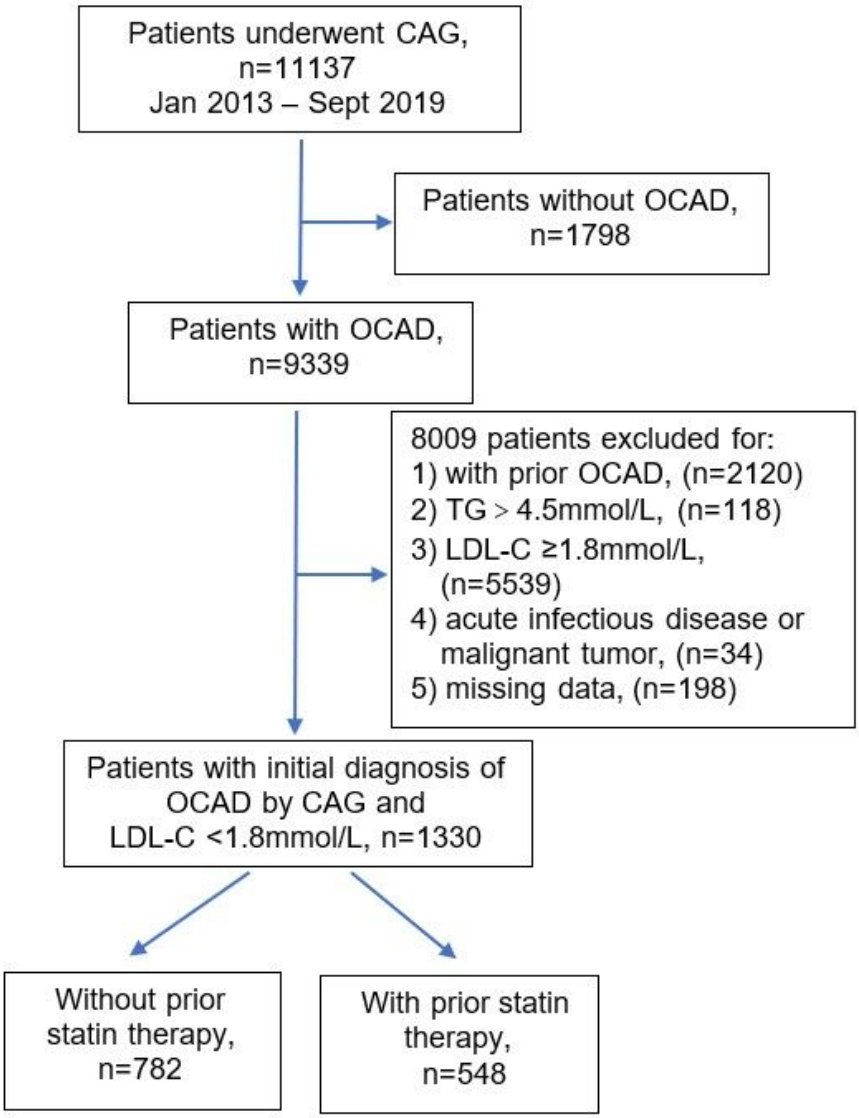

Figure 1

The study subject selection flow chart. CAG: Coronary angiography; OCAD: Obstructive coronary atherosclerotic disease; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol.

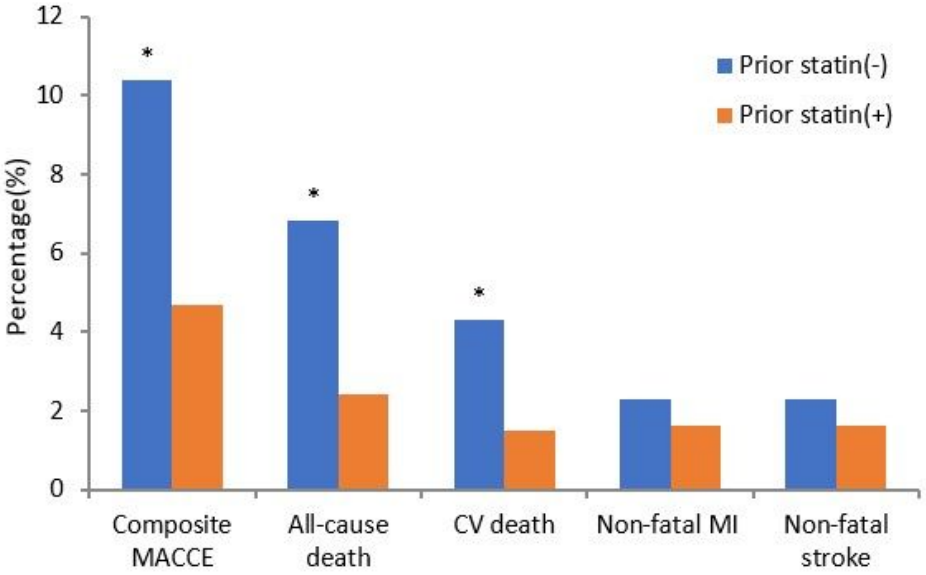

Figure 2

Subsequent MACCE during a median of 25-month follow-up in patients without and with prior statin therapy.* P<0.05 versus prior statin(+) group. MACCE: Major adverse cardiac and cerebral event; CV: Cardiovascular; MI: Myocardial infarction.

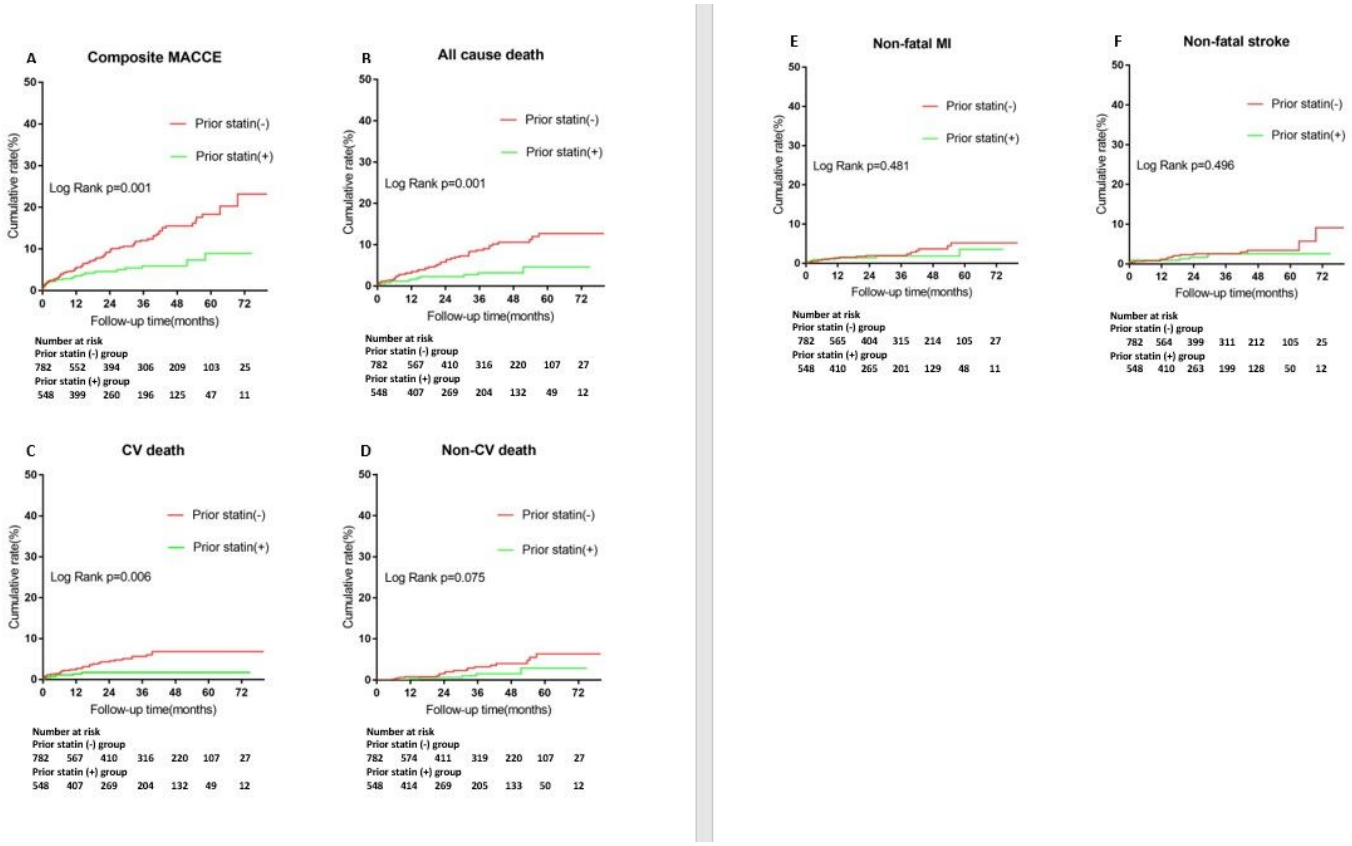

Figure 3

Kaplan-Meier curve for composite MACCE (A), all-cause death (B), CV death (C), non-CV death (D), non-fatal MI (E) and non-fatal stroke (F) of the prior statin (-) group (red line) versus prior statin (+) group (green line) during a median of 25 months of follow-up. MACCE, major adverse cardiac and cerebral event; CV, cardiovascular; MI, myocardial infarction.

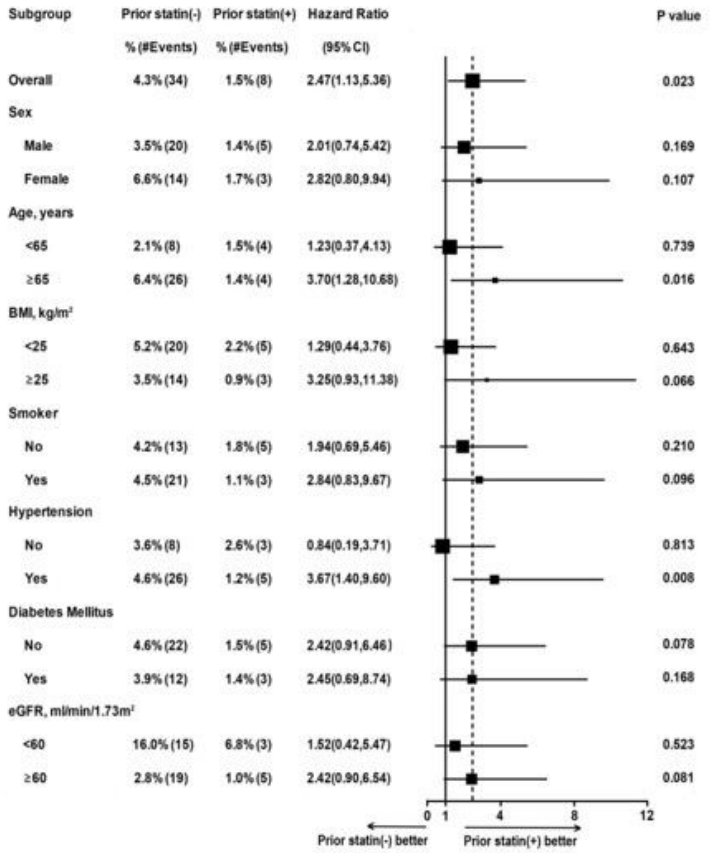

Figure 4

Forest plot of CV death according to subgroups. The dashed vertical line represents the hazard ratio for the overall study population. The box sizes are proportional to the precision of the estimates (with larger boxes indicating a greater degree of precision). Adjusted model included age, gender, BMI, current/ex-smoker, hypertension, antiplatelet agent use prior admission, ACEI/ARB/β-blocker use prior admission and LVEF<0.5. BMI, body mass index; HT, hypertension; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; CV, cardiovascular.