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Higher serum triglyceride can predict recurrent coronary revascularization events in patients undergoing percutaneous coronary intervention with baseline LDL-C <55 mg/dL

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ABSTRACT

Patients with low baseline low-density lipoprotein cholesterol (LDL-C) but experiencing recurrent coronary revascularization events have been rarely investigated. In this retrospective cohort study, we enrolled patients undergoing percutaneous coronary intervention (PCI) with baseline LDL-C <55 mg/dL at the First Affiliated Hospital of Xi'an Jiaotong University between January and December 2017. Subsequent ischemia-driven coronary revascularization events and all-cause death were documented during a 4-year follow-up. Cox analysis was used to evaluate the association between baseline clinical characteristics and long-term events. As a result, among 388 patients (mean age 63 years; 79.1% male) enrolled, 32 patients underwent recurrent revascularization events, and 38 patients occurred all-cause death. After adjustment for age, diabetes mellitus, multi-vessel disease, and lipoprotein(a), multivariate Cox analysis showed that baseline serum triglyceride (TG) (HR 1.691, 95% CI 1.178 to 2.428, p=0.004) was an independent predictor of recurrent coronary revascularization events. Kaplan-Meier analysis revealed that a higher TG level (≥1.17 mmol/L, determined by receiver operating characteristic curve) was associated with increased risk of recurrent revascularization events than lower TG level (<1.17 mmol/L) (p=0.021). Female (HR 2.647, 95% CI 1.350 to 5.190, p=0.005) and previous atrial fibrillation (HR 3.163, 95% CI 1.403 to 7.132, p=0.006) were associated with increased risk of all-cause death. In conclusion, for patients undergoing PCI with baseline LDL-C <55 mg/dL, higher baseline TG can predict recurrent coronary revascularization events.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients undergoing percutaneous coronary intervention (PCI) still have the risk of recurrent coronary events even with low level of baseline low-density lipoprotein cholesterol (LDL-C).

WHAT THIS STUDY ADDS

⇒ Baseline triglyceride is associated with recurrent revascularization events in patients undergoing PCI with baseline LDL-C <55 mg/dL.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study suggests that those patients may gain additional benefits from triglyceride-lowering therapy.

INTRODUCTION

Low-density lipoprotein cholesterol (LDL-C) is one of the most critical risk factors for atherosclerotic cardiovascular disease (ASCVD). Consistent evidence proves that LDL-C lowering provides incremental cardiovascular benefits. Since PCSK9 inhibitor is verified to strongly reduce LDL-C to an extremely low level and bring further cardiovascular benefits, the current guideline has updated and set a new LDL-C goal of <55 mg/dL in patients at very high risk of ASCVD for secondary prevention.[1]

However, regardless of which lipid-lowering agent is used, the clinical benefits depend on the baseline LDL-C level and the absolute magnitude of LDL-C reduction.[2] The higher the baseline LDL-C is, the more benefits derived from lipid-lowering therapy. Cardiovascular benefit from intensified LDL-C lowering was expected less in patients with baseline LDL-C <100 mg/dL.[3 4] Serial intravascular ultrasound analysis also indicated that statin therapy in inducing coronary plaque regression was less effective in patients with low LDL-C.[5] However, in clinical practice, a challenging problem is that a group of patients develop ASCVD despite low LDL-C level and continue experiencing recurrent ischemic events even under statin therapy.[6–8] In addition to LDL-C, what other risk factors are involved in this specific patient group have been scarcely studied. Therefore, our study aimed to explore which baseline risk factor could be associated with recurrent

revascularization events in patients undergoing percutaneous coronary intervention (PCI) with baseline LDL-C <55 mg/dL.

MATERIALS AND METHODS

Population

This is a retrospective cohort study. Consecutive patients with coronary artery disease (CAD) undergoing PCI from January to December 2017 at the First Affiliated Hospital of Xi'an Jiaotong University were screened. Patients with successful PCI and baseline LDL-C <55 mg/dL were included in our study. The exclusion criteria were as follows: (1) no statin therapy at discharge; (2) occurring in-hospital death; (3) the occurrence of recurrent revascularization due to withdrawal of anti-platelet or statin treatment; (4) loss of follow-up.

Baseline clinical information was collected from standard medical records, including demographic data, diagnosis at presentation, and detailed previous histories. Fasting blood tests including alanine aminotransferase (ALT), serum albumin (ALB), serum creatinine (CRE), HbA1c, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), total cholesterol (TC), and lipoprotein(a) were collected. Platelet (PLT) and hemoglobin tested at admission were recorded. Left ventricular ejection fraction (LVEF) measured by Simpson's method was collected.

The manifestations of coronary angiography (CAG) were characterized by the affected number of three major epicardial arteries (stenosis of the lumen diameter >50%), defined as one-vessel, two-vessel, and multi-vessel diseases.

Clinical outcomes

During a 4-year follow-up, all-cause death, acute myocardial infarction (AMI), angina, any recurrent coronary revascularization (unplanned PCI or coronary artery bypass graft (CABG)), and stroke were documented. The endpoint was any unplanned coronary revascularization due to recurrent ischemic events and all-cause death. All follow-up information was obtained in April 2021 by telephone interview or by checking patient visits to the outpatient clinic or readmission medical records.

Statistical analysis

Patients were stratified into two groups according to the occurrence of recurrent revascularization events. Continuous normally distributed data were presented as mean with SD, and non-normally distributed data were shown as median with 25th and 75th percentiles; unpaired t-test and Mann-Whitney U test were used as appropriate. For discrete variables, differences were expressed as counts and percentages and were analyzed with χ^2 or Fisher exact test.

Cox regression analysis was used to estimate the adjusted HRs and 95% CIs for revascularization events and all-cause death predictors. When analyzing the independent predictors of recurrent revascularization, we put the variables with p value ≤0.2 obtained in the univariate Cox regression (including age, TG, lipoprotein(a)) and established risk factors (diabetes mellitus and multi-vessel disease) into stepwise forward selection multivariate Cox analysis. Kaplan-Meier analysis was used to compare the cumulative hazard of recurrent revascularization events by log-rank test.

When analyzing the independent predictors of all-cause death, we put the variables with p value ≤0.1 obtained in the univariate Cox regression (including age, sex, hemoglobin, and history of atrial fibrillation and multi-vessel disease) into the multivariate analysis.

A two-tailed p value ≤0.05 was considered statistically significant. Statistical analysis involved the use of SPSS V.25.0.

RESULTS

Study population

From January to December 2017, a total of 2955 patients undergoing successful PCI and receiving stating therapy at discharge were screened; 2530 patients with LDL-C ≥55 mg/dL were excluded, and the remaining 425 patients (14.3%) with LDL-C <55 mg/dL and statin therapy at discharge were enrolled. One patient experiencing recurrent PCI due to withdrawal of statin was excluded; 36 patients were lost to follow-up. At last, 388 patients were included in this study (figure 1). At presentation, 287 patients (74.0%) were diagnosed with unstable angina (UA), 63 patients (16.2%) with ST-elevation myocardial infarction (STEMI), 29 patients (7.5%) with non-ST elevation

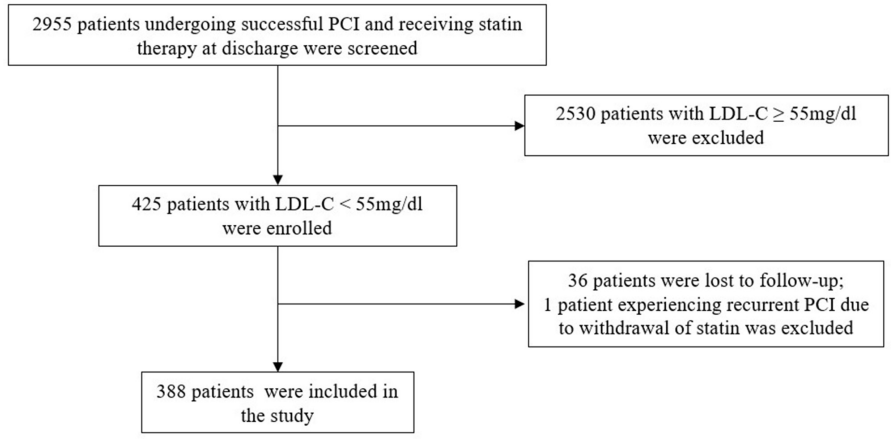

Figure 1 Study flowchart. LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention.

Table 1 Comparison of clinical, laboratory, and angiographic characteristics and clinical outcomes between two groups

	The whole (n=388)	Non-revascularization group (n=356)	Revascularization group (n=32)	P value
Male, n (%)	307 (79.1)	280 (78.7)	27 (84.4)	0.431
Age, years	63±10	63±10	64±10	0.895
Presentation, n (%)				0.405
UA	287 (74.0)	261 (73.3)	26 (81.3)	
STEMI	63 (16.2)	58 (16.3)	5 (15.6)	
NSTEMI	29 (7.5)	28 (7.9)	1 (3.1)	
Ischemic cardiomyopathy	9 (2.3)	9 (2.5)	0 (0)	
History of disease, n (%)				
AF	24 (6.2)	23 (6.5)	1 (3.1)	0.708
OMI	51 (13.1)	47 (13.2)	4 (12.5)	1
Previous PCI	26 (6.7)	24 (6.7)	2 (6.3)	0.998
HP	242 (62.4)	221 (62.1)	21 (65.6)	0.547
DM	145 (37.4)	132 (37.1)	13 (40.6)	0.693
Previous stroke	19 (4.9)	19 (5.3)	0 (0)	0.387
Laboratory test				
ALT, U/L	25 (16–38)	25 (16–38)	29 (19–47)	0.223
ALB, g/L	39.2 (36.6–41.8)	39.2 (36.7–41.7)	39.1 (34.9–42.3)	0.739
CRE, mmol/L	70 (60–83)	69 (59–82)	77 (67–86)	0.030
HbA1c, mmol/L	5.9 (5.4–6.8)	5.8 (5.4–6.8)	6.2 (5.4–7.3)	0.261
HB, g/L	132 (122–140)	132 (122–140)	131 (120–143)	0.948
PLT, 10^9/L	170 (137–210)	170 (136–210)	175 (146–219)	0.409
TC, mmol/L	2.57 (2.37–2.76)	2.56 (2.37–2.76)	2.63 (2.46–2.73)	0.402
TG, mmol/L	0.99 (0.77–1.33)	0.97 (0.76–1.29)	1.24 (0.83–1.43)	0.078
HDL-C, mmol/L	0.83 (0.72–0.95)	0.83 (0.72–0.95)	0.82 (0.68–0.96)	0.845
LDL-C, mmol/L	1.21 (1.07–1.32)	1.21 (1.07–1.32)	1.21 (1.02–1.35)	0.780
Lipoprotein(a), mg/L	115 (59–220)	113 (58–219)	145 (75–229)	0.354
LVEF, %	63 (53–69)	63 (53–69)	63 (50–71)	0.943
Angiographic characteristics, n (%)				0.030
1-vessel	58 (14.9)	57 (16.0)	1 (3.1)	
2-vessel	109 (28.1)	102 (28.7)	7 (21.9)	
Multi-vessel	221 (575)	197 (55.3)	24 (75.0)	
Follow-up, n (%)				
All-cause death	38 (9.8)	38 (10.7)	0 (0)	0.058
AMI	11 (2.8)	0 (0)	11 (34.4)	<0.001
Angina	70 (18)	49 (13.8)	21 (65.6)	<0.001
Stroke	5 (1.3)	5 (1.4)	0 (0)	1

AF, atrial fibrillation; ALB, serum albumin; ALT, alanine aminotransferase; AMI, acute myocardial infarction; CRE, creatinine; DM, diabetes mellitus; HB, hemoglobin; HDL-C, high-density lipoprotein cholesterol; HP, hypertension; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; OMI, old myocardial infarction; PCI, percutaneous coronary intervention; PLT, platelet; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol; TG, triglyceride; UA, unstable angina.

myocardial infarction (NSTEMI), and 9 patients (2.3%) with ischemic cardiomyopathy.

Follow-up clinical events

During a 4-year follow-up, 32 patients (8.2%) underwent recurrent ischemia-driven revascularization procedures (29 PCI and 3 CABG), and 38 patients (9.8%) occurred all-cause death. The comparison of clinical, laboratory, and angiographic characteristics and follow-up information between the revascularization group and the non-revascularization group are listed in table 1. Patients in the revascularization group presented higher serum CRE (p=0.03), more multi-vessel disease (p=0.03), and more events of AMI and angina in follow-up (both p<0.001).

Predictors of recurrent revascularization and all-cause death

Table 2 lists the results of univariate Cox analysis for recurrent revascularization events and all-cause death.

Univariate Cox regression showed that only TG was statistically associated with recurrent revascularization events (HR 1.691, 95% CI 1.178 to 2.428, p=0.004). When analyzing the independent predictors of recurrent revascularization events, we put the variables with p value ≤0.2 obtained in the univariate analysis (including age, lipoprotein(a), TG) and established risk factors (diabetes mellitus and multi-vessel disease) into multivariate Cox analysis. As a result, baseline TG (HR 1.691, 95% CI 1.178 to 2.428, p=0.004) was still the only independent predictor

Table 2 Univariate Cox regression for predictors of recurrent revascularization and all-cause death

	Recurrent revascularization			All-cause death		
Variables	HR	95% CI	P value	HR	95% CI	P value
Age	0.972	0.944 to 1.001	0.055	1.035	0.996 to 1.076	0.083
Female	0.598	0.229 to 1.561	0.293	2.374	1.226 to 4.598	0.010
History of AF	0.320	0.043 to 2.355	0.263	2.700	1.215 to 5.999	0.015
History of OMI	0.917	0.315 to 2.699	0.873	0.845	0.297 to 2.400	0.751
History of HP	1.069	0.512 to 2.229	0.859	0.875	0.448 to 1.709	0.697
History of DM	1.081	0.516 to 2.226	0.837	1.211	0.616 to 2.382	0.579
Previous PCI	1.938	0.956 to 3.927	0.366	0.670	0.324 to 1.386	0.281
ALT	0.999	0.995 to 1.002	0.466	1.000	0.999 to 1.002	0.434
CRE	1.001	0.990 to 1.012	0.897	1.006	0.998 to 1.015	0.136
HbA1c	0.990	0.781 to 1.255	0.936	1.109	0.912 to 1.350	0.300
HB	1.014	0.994 to 1.034	0.268	0.980	0.964 to 0.996	0.016
PLT	1.001	0.995 to 1.007	0.771	1.003	0.997 to 1.008	0.365
TC	1.647	0.497 to 5.473	0.415	1.626	0.566 to 4.665	0.366
TG	1.691	1.178 to 2.428	0.004	0.745	0.371 to 1.495	0.407
HDL-C	0.682	0.133 to 3.500	0.647	2.521	0.607 to 10.467	0.203
Lipoprotein(a)	1.002	0.999 to 1.004	0.181	1.001	0.998 to 1.003	0.566
LVEF	0.999	0.969 to 1.031	0.964	0.994	0.966 to 1.022	0.668
Multi-vessel disease	1.411	0.628 to 3.170	0.404	0.467	0.241 to 0.901	0.023

AF, atrial fibrillation; ALT, alanine aminotransferase; CRE, creatinine; DM, diabetes mellitus; HB, hemoglobin; HDL-C, high-density lipoprotein cholesterol; HP, hypertension; LVEF, left ventricular ejection fraction; OMI, old myocardial infarction; PCI, percutaneous coronary intervention; PLT, platelet; TC, total cholesterol; TG, triglyceride.

for recurrent revascularization in patients undergoing PCI with baseline LDL-C<55 mg/dL.

Since there is no established cut-point for TG, we used receiver operating characteristic curve (ROC) analysis to acquire the optimal cut-off value. Patients were further divided into two groups: higher TG group (≥1.17 mmol/L) and lower TG group (<1.17 mmol/L). Kaplan-Meier analysis demonstrated that a higher TG level was associated with a higher risk of recurrent revascularization events than a lower TG level (p=0.021 by log-rank test) (figure 2).

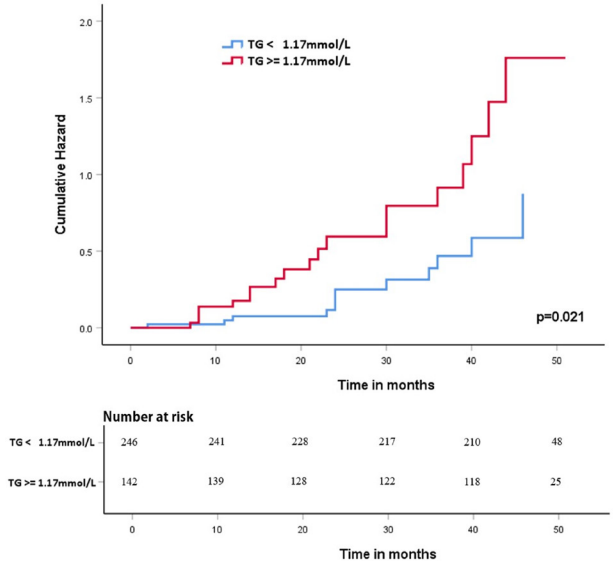

Figure 2 Kaplan-Meier analysis demonstrated that a higher triglyceride (TG) level (≥1.17 mmol/L) resulted in a higher risk of recurrent revascularization events than a lower TG level (<1.17 mmol/L) (p=0.021 by log-rank test).

When analyzing the potential predictors of all-cause death, we put the variables with p value ≤0.1 obtained in the univariate Cox regression (including age, sex, hemoglobin, history of atrial fibrillation, and multi-vessel disease) into the multivariate analysis. The results showed that female (HR 2.647, 95% CI 1.350 to 5.190, p=0.005) and previous atrial fibrillation (HR 3.163, 95% CI 1.403 to 7.132, p=0.006) were associated with higher risk of all-cause death in patients undergoing PCI with baseline LDL<55 mg/dL.

DISCUSSION

The main findings of the current study are as follows: (1) despite baseline LDL-C <55 mg/dL and statin therapy, the risk of recurrent ischemia-driven revascularization events in patients undergoing PCI remained high (8.2%); (2) baseline TG was an independent predictor of recurrent revascularization events in those patients; (3) female and previous atrial fibrillation were associated with a higher risk of all-cause death in those patients.

An LDL-C <70 mg/dL was the previous target goal in secondary prevention for patients with ASCVD before the PCSK-9 inhibitor came out. However, ASCVD can occur in individuals even with low LDL-C levels. Patients with AMI with baseline LDL-C <70 mg/dL occupied 7.1% in the KAMIR study.[9] In the TERCET study, the proportion rose to 20.7% among patients with acute coronary syndrome (ACS).[10] In a PCI registry study, the ratio reached 41.9%.[11] Even with low baseline LDL-C, statin therapy improves clinical prognosis.[6–9] However, the benefit is less prominent as compared with high LDL-C, and recurrent vascular

events continue to occur,[3 4] which suggests that other risk factors, rather than LDL-C, are involved in atherosclerosis progression for those patients.

Numerous studies have shown an association between baseline serum TG and ASCVD. Elevated TG is related not only to subclinical atherosclerosis and vascular inflammation despite normal LDL-C[12] but also equally to residual cardiovascular risk among patients receiving statin therapy,[13] especially those with diabetes mellitus.[14] Among patients with ACS with all baseline levels of LDL-C and treated effectively with statins, studies have found that TG was associated with recurrent ischemic events after ACS.[15 16] Our study focused on patients with baseline LDL-C <55 mg/dL and got consistent results.

The American Heart Association suggests that optimal fasting TG level should be defined as <1.2 mmol/L.[17] It points out that TG-rich lipoproteins and the remnants accumulate in the plasma when TG >1.2 mmol/L, while efficient lipolysis results in limited accumulation of remnant particles when TG <1.2 mmol/L.[18] Our study used ROC analysis to acquire a similar cut-off value of 1.17 mmol/L and found that patients with TG ≥1.17 mmol/L had a statistically higher risk of recurrent revascularization than TG <1.17 mmoL/L. The 2019 European Society of Cardiology/European Atherosclerosis Society guideline suggests that TG-lowering drugs could be prescribed in high-risk patients only when TG is >2.3 mmol/L[1]. The recent REDUCE-IT trial demonstrated that icosapent ethyl, one TG-lowering agent, could reduce the need for first and subsequent coronary revascularizations in statin-treated patients with LDL-C <100 mg/dL and fasting TG >1.52 mmol/L.[19 20] The optimal cut-point for initiating TG-lowering therapy in patients with different LDL-C level may need further exploration.

Although higher TG was related to a higher risk of revascularization, it was not associated with all-cause death in our study. This conclusion was not consistent with the previous research,[21] which could be explained by the different baseline characteristics of the enrolled patients. Patients with low baseline LDL-C usually present worse clinical profiles, such as more comorbidities and older age.[10 22] Our study showed females and patients with AF faced a higher risk of all-cause death. By comparing baseline characteristics, we found that patients with atrial fibrillation were older, more often with lower LDL-C and hemoglobin levels, presenting higher creatinine (all $p<0.05$) than those without. Older age and worse baseline conditions would be a reasonable explanation for AF contributing to all-cause death.

In conclusion, we explored why ischemia-driven revascularization events recurrently occurred in patients with low LDL-C levels (<55 mg/dL) and found that baseline TG was an independent risk factor. Whether TG-lowering agent can yield additional cardiovascular benefits in addition to statin therapy in those patients is under investigation.

LIMITATIONS

The present study had some limitations. First, patients with baseline LDL-C <55 mg/dL had two situations: receiving statin therapy or being born this way, which could potentially affect the results concluded in our study. However, if patients can easily reach the target goal under statin therapy but continue to suffer recurrent events, they should be paid equal attention. Second, in addition to TG, other risk factors are also involved in the residual cardiovascular risk, such as C reactive protein. We could not study it because of data deficiency. Third, the study was a retrospective cohort design with inherent prejudice.

Contributors Conceptualization: XF, YW. Data collection and analysis: XF, XN, YL, XW, WX, TZ. Writing—original draft preparation: XF. Writing—review and editing: XW, YW. Supervision: JS, YW. All authors have read and agreed to the published version of the manuscript. YW is responsible for the overall content as guarantor.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the ethics committee of our institution. Written informed consent was waived due to a retrospective design. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available on reasonable request. Data are available from the corresponding author on reasonable request.

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