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Original Article

Fasting Triglycerides is a Risk Factor for Cardiovascular Event in T-SPARCLE Registry in Taiwan

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SUMMARY

Background: The association between fasting triglyceride (TG) and the occurrence of major adverse cardiovascular event (MACE) remains elusive. The objectives of the present study were to analyze the magnitude of the association between TG and MACE in the Taiwanese Secondary Prevention for Patients with AtheRosCLErotic Disease (T- SPARCLE) registry.

Methods: Two-year follow-up data from a nationwide cohort study of 6050 patients with atherosclerotic cardiovascular disease (aged 68 years, 71% men) were used to identify risk factors for the occurrence of MACE, defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke. 196 cases of MACE occurred during the follow up. The Cox proportional hazard model was applied to detect the independent risk factors for MACE. Adjustment was made for variables including age, sex, history of stroke, heart failure, MI/coronary artery disease, hypertension, diabetes, lipid-lowering agents except statin, statin, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol.

Results: Compared with TG (91–150) mg/dL, multivariate-adjusted HRs for MACE ranged from 1.47 (95% confidence interval (CI): 1.02–2.13) for TG of ≤ 90 mg/dL, 1.13 (95% CI: 0.73–1.76) for TG of 151–200 mg/dL, 1.27 (95% CI: 0.71–2.29) for TG 201–250 mg/dL to 1.65 (95% CI: 0.99–2.77) for TG ≥ 251 mg/dL.

Conclusions: The common belief that low TG are beneficial for health is not universally observed. By using the long-term follow-up data of T-SPARCLE registry, we provided evidence that increased CV events at both ends of the TG distributions.

1. Introduction

One meta-analysis and most published studies suggest a moderate association between fasting triglyceride (TG) levels and coronary heart disease (CHD).[1–4] In a meta-analysis of 14 randomized trials of statins involving patients with CHD, statins were shown to decrease the relative risk of cardiovascular (CV) deaths, nonfatal myocardial infarction, and stroke.[5] However, CV events remained high despite optimal low density lipoprotein-cholesterol (LDL-C) reduction on intensive statin therapy and the residual risk may attribute to TG and lipoprotein abnormalities.[6,7] Hypertriglyceridemia was also associated with the severity of CHD.[8] The study of secondary prevention of CHD, comparing standard and high-intensity statin therapy after acute coronary syndrome (ACS), found that each 10 mg/dL decrease in on-treatment TG reduced the incidence of death, myocardial infarction (MI), and recurrent ACS by 1.6% and 1.4% after adjustment for LDL-C or non-high-density lipoprotein cholesterol

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(HDL-C) and other covariates.[9] In a 22-year follow-up of the Bezafibrate Infarction Prevention (BIP) trial, a higher TG was associated with increased all-cause mortality.[10] The results of the dal-OUTCOMES (A Study of RO4607381 in Stable Coronary Heart Disease Patients with Recent Acute Coronary Syndrome) and MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) trials also showed an increased TG risk of a CV event after ACS.[11] In contrast, the Emerging Risk Factors Collaboration, collecting data from 68 prospective studies, indicated that the relationship between plasma TG and CV disease lost significance after further adjustment for high-density lipoprotein (HDL)-cholesterol and non-HDL-cholesterol.[12] Moreover, most studies were mainly conducted in western populations and data from Asians were fragmented. Current US and European guidelines focus mainly on LDL cholesterol levels. Therefore, TG has continued to be a controversial risk factor and might be an additional target for residual CV risk reduction.

In most previous epidemiological studies, most participants with atherosclerosis were excluded.[3,12–15] Although, there were a few studies that focused on the associations between TG levels and secondary prevention of atherosclerotic CV disease (ASCVD). To help quantify a more reliable association of plasma TG concentrations with long-term CV events among atherosclerotic patients, we investigated stepwise increasing levels of TG related with major adverse CV events (MACE) from the Taiwanese Secondary Prevention for Patients with AtheRosCLErotic Disease (T-SPARCLE) registry.

2. Materials and methods

2.1. Study population

The T-SPARCLE Registry was initiated by the Taiwan Society of Lipids and Atherosclerosis in 2011 to investigate the control of dyslipidemia and the association between dyslipidemia and future cardiovascular events. Fourteen hospitals (8 medical centers and 6 regional hospitals) were invited to participate in this registry.[16] The enrollment criteria were as follows: (1) patients with atherosclerotic vascular diseases, including coronary atherosclerosis as diagnosed by cardiac catheterization examination, history of myocardial infarction as evidenced by electrocardiography (ECG) or hospitalization, angina diagnosed by ischemic ECG changes, or positive response to stress test; (2) patients with cerebral vascular disease, cerebral infarction, and intracerebral hemorrhage, excluding those with intracerebral hemorrhage caused by other diseases (such as cancer); and patients with transient ischemic attack (TIA) whose carotid artery duplex showed atheromatous change with more than 70% stenosis. Peripheral atherosclerosis with symptoms of ischemia that were confirmed by Doppler ultrasound or angiography. All participants enrolled in our study had documented ASCVD and were considered as very high CV risk according to 2019 ESC/EAS Guidelines for the management of dyslipidemias.[17]

There were 7866 participants that met the enrollment criteria. Finally, a total of 6050 patients with complete lipid measure values [total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C)] were included in this analysis. The study flowchart was shown in Figure 1. Data of demographic characteristics, medical history, and drug history were collected. Hypertension (HTN) was defined as: (1) known history of hypertension; (2) taking antihypertensive drugs at referral; and (3) systolic blood pressure (BP) $\geq$ 140 mmHg or diastolic BP $\geq$ 90 mmHg based on the medical chart review. Those patients with an established diagnosis of diabetes mellitus (DM) or those on glucose-lowering drugs or fasting glucose $\geq$ 126 mg/dL were diagnosed with DM. The estimated glomerular filtration rate (GFR) was calculated using the simplified Modification of Diet in Renal Disease (MDRD) Study equation [GFR (mL/min/1.73 m^2) = 186.3 $\times$ (serum creatinine in mg/dL)$^{-1.154}$ $\times$ (age)$^{-0.203}$ $\times$ (0.742 if female)].[18] CKD was defined as a GFR less than 60 mL/min/1.73 m^2. This range is related to stage 3 or higher CKD by the National Kidney Foundation's classification and helps identify subjects with clinically significant CKD.[19] Lipid-lowering agents were prescribed following the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines.[20] Atorvastatin 40 or 80 mg and rosuvastatin 20 mg were defined as high-intensity statins. MACE was defined as CV death, stroke (fatal or nonfatal), MI (fatal or nonfatal), and cardiac arrest. During the study period, each hospital had a dedicated person responsible for following patients. If an event occurs, the attending physician in charge of the patient will make a diagnosis to determine whether it is MACE. This study was approved by the Joint Institutional Review Board of Taiwan for each participating hospital. The JIRB number was 09-S-015. Written informed consent was obtained from each patient.

2.2. Statistical methods

Data are expressed as mean $\pm$ SD or percentage. The student's t-test was used for continuous data, and Chi-square tests of categorical data were used to compare the differences between groups. Baseline fasting TG levels were stratified into 5 categories ($\leq$ 90 mg/dL, 91–150 mg/dL, 151–200 mg/dL, 201–250 mg/dL and $\geq$ 251 mg/dL). The Cox proportional hazard model was used to estimate the hazard ratio and 95% confidence intervals in crude and multivariate models. Missing values for biological data represented less than 5% for history of cigarette smoking, HTN, and heart failure and more than 5% for body mass index (BMI), LDL-C, HDL-C, TG, eGFR, diastolic BP, systolic BP and history of diabetes. Multiple imputation, built on missing-at-random (MAR) assumption, was a practical approach to missing data problems and may provide unbiased and valid estimates.[21] We used multiple imputation (PROC MI procedure in SAS) to handle missing values, and the predictor variables in the imputa-

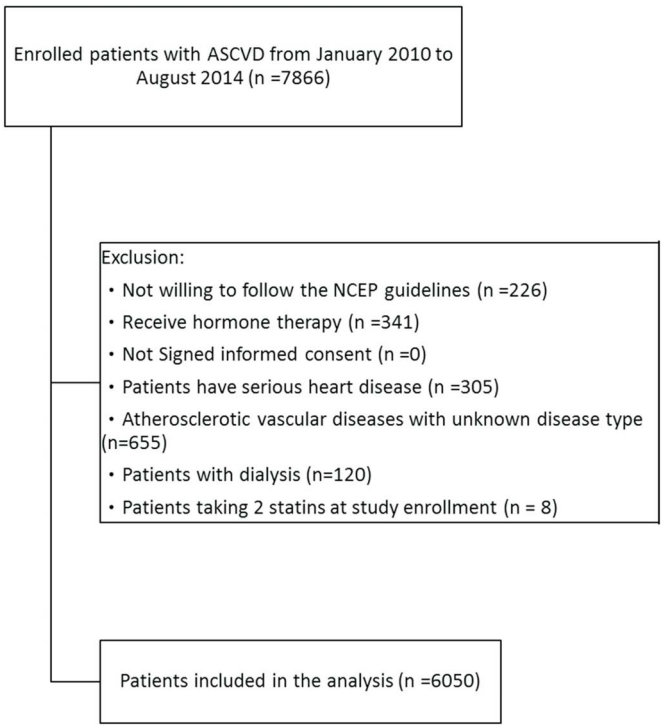

Figure 1. Study flowchart.

tion model included BMI, LDL-C, HDL-C, TG, eGFR, diastolic BP, systolic BP, history of cigarette smoking, HTN, heart failure, and diabetes, as well as non-missing variables such as age, gender, and MACE. The imputation step resulted in 20 complete data sets, each with one unique estimate of the missing values. After imputation, we used SAS/PROC PHREG to fit the Cox proportional hazards model for each dataset, and subsequently, used SAS/PROC MIANALYZE to combine results from the 20 Cox proportional hazards models. All analyses were performed using SAS statistical software version 9.2 (SAS Institute, Carey, NC, USA).

3. Results

Baseline characteristics of individuals from the atherosclerotic patients based on TG levels are shown in Table 1. The patients with TG ≤ 90 mg/dL were significantly older and had lower waist measurements, body mass index (BMI), prevalence rate of DM and CKD, percentage of current smoking, TC, LDL-C and higher HDL-C than the other four groups. In addition, individuals with TG ≥ 251 mg/dL were significantly more likely to take fibrate and unicontin. Subjects with a TG 91–150 mg/dL had a higher percentage of statin use. Regarding crude cumulative incidence rates of MACE during the median follow-up of 2.3 years according to fasting serum TG concentrations, the corresponding incidence rates of MACE (per 1000 patients) were 13.9 in subjects with ≤ 90 mg/d, 9.6 in subjects with 91–150 mg/dL, 12.1 in subjects with 151–200 mg/dL, 13.2 in subjects with 201–250 mg/dL and 17.2 in subjects with ≥ 251 mg/dL (p = 0.19).

To further clarify the relationship between TG and MACE, the Cox proportional hazards model was performed (Table 2). The relation between TG and MACE was assessed by successive adjustment for age, gender, and other potential confounding factors and covariates. Overall, a clear gradient of risk of MACE was found with increasing TG levels. The multivariable hazard ratio [95% confidence interval (CI)] of MACE ranged from 1.47 (95% CI: 1.02–2.13) for TG of ≤ 91 mg/dL, 1.13 (95% CI: 0.73–1.76) for TG of 151–200 mg/dL, 1.27 (95% CI: 0.71–2.29) for TG of 201–250 mg/dL to 1.65 (95% CI: 0.99–2.77) for TG ≥ 251 mg/dL, compared with TG of 91–150 mg/dL. The results of TG < 150 vs. ≥ 150 mg/dL on MACE employed by Cox proportional hazards model was summarized in Supplementary data. The relations between TG and risk for MACE, adjusted for age, sex,

Table 1
Baseline characteristics of individuals by triglyceride levels.

TG / Variables	≤ 90 mg/dL (N = 1682)	91–150 mg/dL (N = 2214)	151–200 mg/dL (N = 926)	201–250 mg/dL (N = 437)	≥ 251 mg/dL (N = 482)	p value
Age (yrs)	68.5 ± 11.5	66.3 ± 11.1	65.9 ± 11.0	63.0 ± 11.9	61.1 ± 12.0	< 0.001
Gender (men, %)	1283 (76.3)	1631 (73.7)	692 (74.7)	308 (70.5)	356 (73.9)	0.12
WC (cm)	90.6 ± 9.9	93.1 ± 9.5	94.4 ± 10.0	95.3 ± 10.9	94.7 ± 9.8	< 0.001
BMI (kg/m^2)	25.2 ± 3.6	26.4 ± 3.6	26.8 ± 3.9	27.4 ± 4.0	27.3 ± 3.7	< 0.001
HTN (yes, %)	1202 (71.5)	1590 (71.8)	701 (75.7)	330 (75.7)	357 (74.1)	0.07
HF (yes, %)	190 (11.3)	233 (10.5)	109 (11.8)	52 (11.9)	62 (12.9)	0.59
DM (yes, %)	645 (41.6)	994 (49.1)	483 (56.2)	252 (61.8)	278 (60.2)	< 0.001
CKD (yes, %)	400 (25.6)	512 (25.6)	262 (31.5)	116 (29.4)	146 (33.5)	< 0.001
MI or CAD (yes, %)	1531 (91.0)	1978 (89.3)	832 (89.8)	386 (88.3)	435 (90.2)	0.36
Ischemic stroke (yes, %)	183 (10.9)	278 (12.6)	124 (13.4)	56 (12.8)	51 (10.6)	0.24
Current smoker (yes, %)	219 (13.0)	323 (14.6)	161 (17.4)	89 (20.4)	135 (28.0)	< 0.001
TC (mg/dL)	159.4 ± 35.1	167.9 ± 36.0	175.3 ± 38.6	184.3 ± 37.2	194.6 ± 42.7	< 0.001
TG (mg/dL)	68.9 ± 14.6	117.8 ± 16.8	171.9 ± 14.4	223.9 ± 14.6	361.1 ± 156.6	< 0.001
LDL-C (mg/dL)	93.8 ± 31.1	98.8 ± 31.9	99.3 ± 34.6	100.3 ± 34.8	97.6 ± 47.1	< 0.001
HDL-C(mg/dL)	50.6 ± 13.3	45.0 ± 12.4	41.1 ± 11.0	39.2 ± 11.9	36.1 ± 9.3	< 0.001
Statin (yes, %)	1108 (65.9)	1579 (71.3)	647 (69.9)	295 (67.5)	304 (63.1)	< 0.001
High-intensity statin (yes, %)	63 (3.8)	72 (3.3)	28 (3.0)	12 (2.8)	17 (3.5)	0.79
Fibrate (yes, %)	30 (1.8)	85 (3.8)	58 (6.3)	53 (12.1)	110 (22.8)	< 0.001
Ezetimibe & Questran (yes, %)	69 (4.1)	101 (4.6)	50 (5.4)	22 (5.0)	41 (8.5)	< 0.01
Nicotinic acid & Olbetam (yes, %)	5 (0.3)	6 (0.3)	1 (0.1)	1 (0.2)	4 (0.8)	0.21
MACE (per 1000 patients)	13.9	9.6	12.1	13.2	17.2	0.19

WC: waist circumference; BMI: body mass index; HTN: hypertension; HF: heart failure; DM: diabetes mellitus; MI: myocardial infarction; CAD: coronary artery disease; TC: total cholesterol; TG: triglyceride; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; high intensity statin: atorvastatin 40 or 80 mg and rosuvastatin 20 mg; MACE: major adverse cardiovascular event.

Table 2
Hazard ratios for major adverse cardiovascular events by increasing levels of triglyceride.

	Model 1		Model 2		Model 3		Model 4		Model 5	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
≤ 90 mg/dL	1.35 (0.94–1.94)	0.10	1.36 (0.95–1.94)	0.09	1.41 (0.98–2.02)	0.06	1.40 (0.97–2.00)	0.07	1.47 (1.02–2.13)	0.04
91–150 mg/dL	reference		reference		reference		reference		reference	
151–200 mg/dL	1.25 (0.81–1.94)	0.31	1.23 (0.80–1.91)	0.34	1.17 (0.75–1.81)	0.48	1.17 (0.75–1.81)	0.49	1.13 (0.73–1.76)	0.58
201–250 mg/dL	1.43 (0.80–2.54)	0.23	1.43 (0.80–2.55)	0.22	1.34 (0.75–2.39)	0.32	1.34 (0.75–2.39)	0.32	1.27 (0.71–2.29)	0.42
> 251 mg/dL	1.99 (1.22–3.27)	< 0.01	1.95 (1.19–3.20)	< 0.01	1.76 (1.07–2.89)	< 0.05	1.78 (1.07–2.95)	< 0.05	1.65 (0.99–2.77)	0.06

HR: Hazard ratio; CI: confidence interval.
Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, history of stroke, HF and MI/CAD.
Model 3: adjusted for age, sex, history of stroke, HF, MI/CAD, HTN, DM and CKD.
Model 4: adjusted for age, sex, history of stroke, HF, MI/CAD, HTN, DM, CKD, statin and other lipid-lowering agents (except statin).
Model 5: adjusted for age, sex, history of stroke, HF, MI/CAD, HTN, DM, CKD, statin, other lipid-lowering agents (except statin), HDL-C and LDL-C.

history of stroke, HF, MI/CAD, HTN, DM, CKD, statin, other lipid-lowering agents (except statin), HDL-C and LDL-C, are shown in Figure 2.

4. Discussion

This study showed that TG levels were a quasi-significant independent predictor of MACE in patients with ASCVD. Overall, TG had a U-shaped association with MACE in ASCVD Taiwanese. The incidence of MACE was almost significantly higher in the patients with TG ≥ 251 mg/dL but significantly higher in the patients with TG ≤ 90 mg/dL compared those with TG from 91 to 150 mg/dL. This study suggests that TG ≥ 251mg/dL, as well as TG ≤ 90 mg/dL, is a risk factor for MACE in patients with ASCVD. TG lost attention as a causal risk of CV disease (CVD) because attenuating the association between TG levels and CV events while adjusting for HDL-C and other confounders was found in previous studies conducted in western countries.[12] However, there was growing evidence indicating a causal relationship between TG and CV risk and that treating hypertriglyceridemia may be beneficial. In the dal-OUTCOMES and MIRACL study, subjects with hypertriglyceridemia increased the likelihood of CV events. However, the results did not reach statistical significance because of the low statistical power.[11] Elevated TG levels were associated with an increase in stroke risk in a meta-analysis and Korean study.[22,23] Patients with a TG > 200 mg/dL had a higher incidence of all-cause and CV death, compared to those with TG (90–150 mg/dL) in the meta-analysis of 61 prospective studies.[24] Our study had similar results with an increased MACE rate for a fasting TG level > 251 mg/dL, compared with a TG level of 91–150 mg/dL. Therefore, focus on elevated TG levels deserved renewed attention because one-third of Taiwanese adults had a TG > 150 mg/dL, even when they were treated with lipid-lowering agents according to previous studies.[25] Regarding the mechanisms involved in the positive association between TG and MACE, triglyceride-rich lipoproteins (TRLs) were shown to penetrate the arterial wall, contributed the cholesterol to atherosclerotic lesions and caused ischemic heart disease.[26–28] In addition, high TG levels were associated with increased small dense LDL particles, which was considered as a predictor of CVD.[29,30] High TG levels are also associated with increased coagulation factor VII activity,[31] as well as with increased cell adhesion molecules (CAM), which may tend to promote atherosclerosis and thrombosis.[32]

In our study, patients with TG ≤ 90 mg/dL had higher HDL level and lower percentage of DM and CKD than other subgroups. After adjusting these confounders, TG ≤ 90 mg/dL still had a higher MACE, compared with 91 ≤ TG ≤ 150 mg/dL. In previous studies, lower TG was associated with increased adverse cardiac events in patient with MI.[33,34] To explain the association between lower TG and MACE was following: 1) TG is too low to maintain cell membrane homeostasis.[35] 2) Lower TG was a surrogate marker of poor nutritional status.[36] Future studies are needed to better characterize this phenotype.

The strengths of this study lie in its long-term prospective design of a nation-representative and large-scale systematically available medical records and the multicenter survey about the baseline characteristics, especially regarding the TG levels and MACE in atherosclerotic patients from the T-SPARCLE registry, which represented multiple areas of Taiwan. The main limitation of this study was inherent to its observational nature. First, we had no information about nutritional status, diet control and lifestyle interventions. Second, the frequencies of risk factors in the study population might also be underestimated, as we identified patients with HF, HTN, and DM from medical records. Third, the baseline TG levels were included in our analysis of CV events. Not every subject had series of lipid levels measured during follow-up period. The impact of possibly fluctuated TG levels on CV events was not known in our studies. Consequently, the possibility of selection bias cannot be excluded. Fourth, the interpretation of our results should be cautious because the impact of unbalance data may exist in our observation cohort. Further study such as propensity score matching study may be needed to eliminate the effect of unbalance data. However, despite these limitations, this study provided a real-world view of the relationship between triglyceride levels and the incidence of important clinical events.

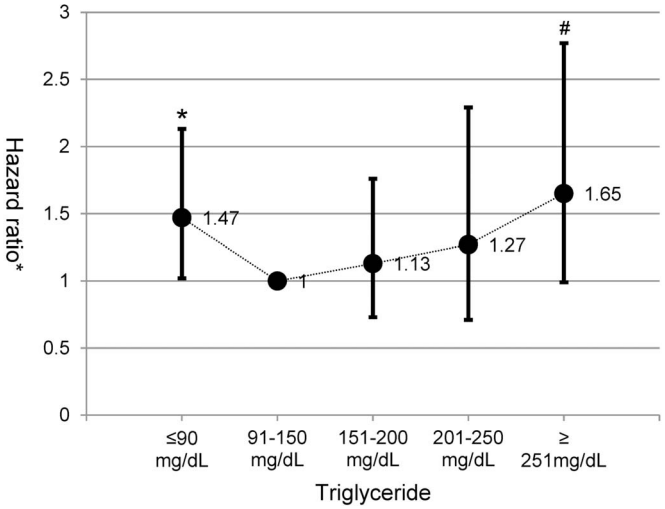

Figure 2. Multivariable-adjusted hazard ratio for adverse cardiac events by triglyceride levels obtained from Cox proportional hazard model (model 5). *: p = 0.04; #: p = 0.06.

In conclusion, the results of our prospective observational study suggest that early identification of ASCVD patients with TG ≥ 251 mg/dL is important as well as those with TG ≤ 90 mg/dL and had a nonlinear U shaped association with MACE in patients with ASCVD. The future study should focus on maintaining the TG level within normal range by using fibrate, omega-3-fatty acid or statin in patients with hypertriglyceridemia and providing nutritional support and treating the underlying condition that's causing low TG for patients with lower TG levels could improve outcome in patients with ASCVD.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Results

The relation between TG and MACE was assessed by successive adjustment for age, gender, and other potential confounding factors and covariates. From model 1 to model 5, the multivariable hazard ratio [95% confidence interval (CI)] of TG ≥ 150 mg/dL for MACE was 1.28 (95% CI: 0.94–1.73),1.26 (95% CI: 0.93–1.71), 1.16 (95% CI: 0.85–1.58), 1.16 (95% CI: 0.85–1.59) and 1.10 (95% CI: 0.79–1.52), respectively, compared with TG < 150 mg/dL.

Supplementary Table 1

Hazard ratios for major adverse cardiovascular events by increasing levels of triglyceride.

	Model 1		Model 2		Model 3		Model 4		Model 5	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
< 150 mg/dL	reference		reference		reference		reference		reference	
≥ 150 mg/dL	1.28 (0.94–1.73)	0.11	1.26 (0.93–1.71)	0.14	1.16 (0.85–1.58)	0.34	1.16 (0.85–1.59)	0.34	1.10 (0.79–1.52)	0.57

HR: hazard ratio; CI: confidence interval.

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, history of stroke, HF and MI/CAD.

Model 3: adjusted for age, sex, history of stroke, HF, MI/CAD, HTN, DM and CKD.

Model 4: adjusted for age, sex, history of stroke, HF, MI/CAD, HTN, DM, CKD, statin and other lipid-lowering agents (except statin).

Model 5: adjusted for age, sex, history of stroke, HF, MI/CAD, HTN, DM, CKD, statin, other lipid-lowering agents (except statin), HDL-C and LDL-C.