European Review for Medical and Pharmacological Sciences 2017; 21: 1060-1064

The predictive value of baseline LDL-TG level on major adverse cardiovascular events in a followed up cohort population

X.-H. DING[1,2], P. YE[1], X.-N. WANG[1], R.-H. CAO[1], X. YANG[1], W.-K. XIAO[1], Y. ZHANG[1], Y.-Y. BAI[1], H.-M. WU[1]

[1]Department of Geriatric Cardiology, Chinese PLA General Hospital, Beijing, China
[2]Department of Health Care and Geriatrics, Lanzhou General Hospital of Lanzhou Military Command, Lanzhou, Gansu province, China

Xiao-Han Ding and *Xiaona Wang* contributed equally to this study

Abstract. – OBJECTIVE: We aimed at identifying the predictive roles of Low-Density Lipoprotein Triglycerides (LDL-TG) for major adverse cardiovascular events (MACEs).

PATIENTS AND METHODS: A longitudinal study in a routine health check-up population was performed with an average follow-up of 4.8 years. The participants involved in this study were 1680, from 2007 to 2009, and all had followed-up for all-cause mortality, cardiovascular disease mortality, and the development of MACEs. The demographic information and anthropometric parameters at baseline were recorded. The baseline and follow-up conventional lipid parameters were measured. We also examined the level LDL-TG, as well as the relationship between its level and MACEs.

RESULTS: MACEs individuals were characterized by statistically higher baseline LDL-TG (17.22 ± 8.05 *vs.* 16.39 ±7.35 nmol/l, $p = 0.017$). The univariate regression for MACEs group indicated that the LDL-TG ($\beta = 0.813$, HR = 2.254, 95% CI: 1.454-3.494, $p < 0.001$), older age, sex and other factors were a significant risk for MACEs. Furthermore, in the adjusted Cox model showed that only higher baseline LDL-TG ($\beta = 0.512$, HR = 1.669, 95% CI: 1.013-2.748, $p = 0.044$) and older age ($\beta = 0.062$, HR = 1.064, 95% CI: 1.034-1.094, $p < 0.001$, Table IV) were still predictors for MACEs.

CONCLUSIONS: Higher baseline LDL-TG closely associated with MACEs and it is a moderate and independent predictive factor for MACEs.

Key Words:
Predictive value, Baseline LDL-TG, MACEs, Followed-up.

Introduction

It has been demonstrated that the dyslipidemia is an independent risk factor for cardiovascular diseases (CVD)[1,2]. The regulation of cholesterol and triglyceride strategies have been used in clinical to prevent the CVD. Previous studies[3] have indicated that dyslipidemia plays critical roles in CVD. Similar to cholesterol in the human beings, the triglyceride is consisting of Low-Density Lipoprotein Triglycerides (LDL-TG) and High-Density Lipoprotein Triglycerides (HDL-TG)[4]. LDL-TG as a sub-fraction of triglycerides has been demonstrated to be associated with the vascular adhesion molecules and CVD[1,5,6]. LDL-TG predicts stable CVD independently of LDL-C. TG participates in a large number of pathophysiological processes including the arteriosclerosis. Therefore, the equilibrium of TG would be with significantly roles in MACEs. LDL-TG has also been indicated to be predictive of cardiovascular (CV) outcomes.

Major adverse cardiovascular events (MACEs) are consisting of cardio cerebrovascular death (including both CV death and cerebrovascular death), non-fatal myocardial infarction, and stroke (including both ischemic and hemorrhagic stroke)[6,7]. MACEs covered the main and most of the CVD and are frequently used as endpoints in various researches. It represents the outcome of the CVD patients. Relationships between plasma lipoproteins and progression of cardiovascular disease evaluated by angiography and clinical events have also been indicated[5,9,10].

To the best of our knowledge, though a large number of studies has focused on the associations between LDL-TG and a signal CVD, there were few studies on the roles of LDL-TG for follow-up MACEs in healthy populations. Thus, we performed this follow-up observational study

Corresponding Author: Ping Ye, MD; e-mail: yeping301@sina.com

with the aim of identifying the predictive roles of LDL-TG for MACEs.

Patients and Methods

Participants and Procedures

Participants (n = 1680) who underwent a routine health examination were recruited between September 2007 and January 2009 from the Pingguoyuan area in the Shijingshan district in Beijing (Beijing, China). Subjects with any of the follow conditions were excluded: endocrine and metabolic disease (except DM), infection, and neoplastic or severe liver or renal diseases.

Follow-up and Outcome Assessment

All subjects were followed-up for all-cause mortality, cardiovascular disease mortality, and the development of MACEs from the initial screening to September 30, 2013. During the median 4.8-year follow-up of 1680 subjects, 181 participants were lost to follow-up and excluded from the analysis. Thus, 1499 subjects (follow-up rate 89.2%) completed the follow-up and were valid for the final analysis.

Our study was reviewed and approved by the Ethics Committee at the People's Liberation Army General Hospital (Beijing, China). The study was explained in detail to all of the subjects who agreed to participate, and all of the subjects signed informed consent forms before their examinations.

Clinical Data Collection

The participants were followed-up by our trained physicians, and a standardized self-report questionnaire was used to record demographic information, lifestyle factors, prevalent diseases, family history, and medication use. Self-reported smoking status and alcohol use were recorded. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were also measured. Body mass index (BMI) was also calculated. Arterial stiffness was assessed by automatic carotid-femoral pulse wave velocity (cf-PWV) measurements using a Complior SP device (Createch Industry Co., Ltd., Shenzhen, Guangdong, China).

Biomarker Variable Determination

Venous blood samples were obtained between 8 a.m. and 10 a.m. after an overnight fast. Plasma aliquots were obtained and stored at -80°C for further assays. Plasma UA, fasting blood glucose (FBG), triglyceride (TG), LDL-TG, LDL-C, high-density lipoprotein cholesterol (HDL-C) and uric acid (UA) concentrations were measured from venous blood samples using commercially available ELISA kits by Roche enzymatic assays (Roche Diagnostics GmbH, Mannheim, Germany). Estimated glomerular filtration rate (eGFR) was also calculated using Chronic Kidney Disease Epidemiology Collaboration equation.

Definition of Variables

MACEs is defined to be one of the following conditions: cardio-cerebrovascular death (including both CV death and cerebrovascular death), non-fatal myocardial infarction, and stroke (including both ischemic and hemorrhagic stroke).

Statistical Analysis

Normally distributed baseline continuous variables are expressed as the mean ± standard deviation (SD) and were analyzed with Student's *t*-tests, while the baseline dichotomous variables are presented as numbers (%) and compared using the X^2 test.

Further analyses by Cox proportional-hazard regression model were performed to identify the association between LDL-TG (baseline) and the follow-up MACEs and non-MACEs groups.

All analyses were performed using SPSS 19.0 for Windows (SPSS Inc.,, Chicago, IL, USA). $p < 0.05$ were considered statistically significant.

Results

The Distributions of the Followed-up Parameters Divided by the Baseline of LDL-TG

The baseline LDL-TG was divided into four quarters. The distributions of the followed-up parameters were showed to be different among the quarters (Table I). The SBP, TC, TG, LDL-C and UA were significantly higher in Quarter 4 than that in Quarter 1 ($p < 0.05$). Furthermore, the occurrences of MACEs were still significantly higher in Quarters 2, 3 and 4 than that in Quarter 1 (24, 48 and 61 *vs.* 21, $p < 0.05$).

Baseline Parameters Between Follow-up MACE and Non-MACE Groups

The differences in the baseline parameters between MACEs and non-MACEs groups were also compared. As shown in Table II, the MACEs individuals were characterized by statistically

Table I. The distributions of the followed-up parameters divided by the baseline of LDL-TG.

Followed-up parameters	Baseline LDL-TG						
	Q1	Q2	Q3	Q4	P4-1	P3-1	P2-1
Age (years)	65.35 ± 10.29	64.46 ± 10.84	63.65 ± 11.69	64.14 ± 1.14	0.237	0.097	0.386
SBP (mmhg)	128.33 ± 17.43	131.87 ± 17.09	130.64 ± 17.36	134.63 ± 18.05	< 0.001	0.157	0.031
DBP (mmhg)	76.09 ± 14.43	74. 96 ± 10.65	74.32 ± 9.95	75.68 ± 11.26	0.842	0.393	0.587
TC (mmol/l)	4.84 ± 0.95	5.16 ± 1.04	5.28 ± 0.97	5.55 ± 1.24	< 0.001	< 0.001	0.001
TG (mmol/l)	1.15 ± 0.62	1.26 ± 0.72	1.57 ± 0.74	2.07 ± 1.07	< 0.001	< 0.001	0.206
HDL-C (mmol/l)	1.59 ± 0.82	1.50 ± 0.39	1.34 ± 0.32	1.27 ± 0.32	< 0.001	< 0.001	0.069
LDL-C (mmol/l)	2.90 ± 1.27	3.13 ± 0.87	3.29 ± 0.79	3.48 ± 0.73	< 0.001	< 0.001	0.016
FBG (mmol/l)	5.36 ± 1.38	5.58 ± 1.47	5.71 ± 1.47	7.30 ± 1.91	0.030	0.700	0.807
eGFr (ml/min/1.73 m^2)	77.83 ± 14.89	79.54 ± 15.51	81.25 ± 14.00	80.78 ± 18.73	0.172	0.113	0.429
cf-PWV (m/s)	11.92 ± 2.87	11.63 ± 2.85	11.70 ± 2.89	12.48 ± 4.20	0.173	0.587	0.474
MACEs, n	21	24	48	61	< 0.001	< 0.001	< 0.001
UA	299.85 ± 78.15	298.69 ± 72.66	319.84 ± 75.23	319.84 ± 80.83	0.005	0.005	0.871

higher baseline LDL-TG (17.22 ± 8.05 *vs.* 16.39 ± 7.35 nmol/l, $p = 0.017$), age, LDL-C, cf-PWV and UA (all $p < 0.05$).

Cox Models Analyses by Using Baseline Parameters for MACEs

The univariate regression for MACEs group indicated that the LDL-TG (β = 0.813, HR = 2.254, 95% CI: 1.454-3.494, $p < 0.001$), older age, eGFr, sex and faster cf-PWV were significantly risked for MACEs (all $p < 0.05$, Table III).

Furthermore, in the adjusted Cox model showed that only higher baseline LDL-TG (β = 0.512, HR = 1.669, 95% CI: 1.013-2.748, $p = 0.044$) and older age (β = 0.062, HR = 1.064, 95% CI: 1.034-1.094, $p < 0.001$, Table IV) were still predictors for MACEs.

Discussion

In the current study, we found the association between baseline LDL-TG level and the occurrence of MACEs. The predictive value of baseline LDL-TG level for followed-up MACEs in an average of 4.8 years has also been identified.

LDL-TG as a critical components of TG, participates in a various number of processes in the

Table II. Baseline parameters between follow-up MACEs and Non-MACEs groups.

	MACE (n = 153)	Non-MACE (n = 1346)	*p*-value
Age (years)	67.36 ± 31	58.34 ± 11.33	< 0.001
Women, n (%)	87 (56.86)	782 (58.09)	0.991
BMI (kg/m^2)	25.33 ± 3.39	35.43 ± 3.35	0.770
SBP (mmhg)	130.60 ± 20.44	128.64 ± 17.54	0.268
DBP (mmhg)	74.53 ± 10.87	77.22 ± 10.17	0.012
LDL-TG (nmol/l)	17.22 ± 8.05	16.39 ± 7.35	0.017
TC (mmol/l)	5.10 ± 0.94	5.02 ± 0.92	0.409
TG (mmol/l)	1.76 ± 1.34	1.81 ± 1.23	0.750
HDL-C (mmol/l)	1.24 ± 0.51	1.35 ± 0.42	0.017
LDL-C (mmol/l)	3.09 ± 0.73	2.90 ± 0.72	0.012
FBG (mmol/l)	5.65 ± 2.12	5.37 ± 1.59	0.119
eGFr (ml/min/1.73 m^2)	85.10 ± 16.46	94.79 ± 13.99	< 0.001
cf-PWV (m/s)	12.41 ± 3.01	11.08 ± 2.80	< 0.001
Metabolic syndrome (%)	66 (43.14)	424 (31.50)	< 0.001
UA	297.09 ± 83.88	290.65 ± 78.34	0.448
Smoking	42 (27.45%)	352 (26.15%)	0.759

Table III. The univariate regression for MACEs.

Baseline data	β	HR	95% CI (HR)	*p*-value
Age (years)	0.070	1.073	1.053-1.093	< 0.001
Sex	0.504	1.655	1.106-2.475	0.014
BMI (kg/m^2)	0.031	0.969	0.940-1.000	0.048
SBP (mmhg)	0.006	1.006	0.995-1.017	0.254
DBP (mmhg)	-0.024	0.976	0.957-0.996	0.017
LDL-TG	0.813	2.254	1.454-3.494	< 0.001
TC (mmol/l)	0.093	1.098	0.883-1.364	0.400
TG (mmol/l)	-0.040	0.961	0.805-1.147	0.961
HDL-C (mmol/l)	-0.495	0.609	0.392-0.948	0.028
LDL-C (mmol/l)	0.119	0.632	0.748-1.193	0.632
FBG (mmol/l)	0.069	1.072	0.973-1.181	0.161
eGFr (ml/min/1.73 m$^{2)}$	-2.842	0.058	0.025-0.135	< 0.001
cf-PWV (m/s)	0.125	1.133	1.076-1.192	< 0.001
Metabolic syndrome	0.633	1.883	1.060-3.348	0.031
UA	0.001	1.001	0.999-1.004	0.371
Smoking	0.641	1.899	1.267-2.845	0.002

HR: hazard ratios, CI: confidence intervals.

human body[11]. The associations between LDL-TG and other serous parameters have also been observed. The higher baseline LDL-TG was accompanied by a higher UA, TG, LDL-C and other risk factors which indicating the roles of them in the CVD and other lipid metabolism-related diseases[12,13].

MACEs group was characterized with a higher baseline LDL-TG revealing that the MACEs individuals have a poor lipid metabolism or dyslipidemia which has been partly demonstrated by others' previous studies[13-16]. We next performed the univariate Cox regression to identify the roles of each single parameter for MACEs. The baseline LDL-TG was found to be a risk for MACEs. Furthermore, other related parameters such as age were also showed closely associated with the occurrence of MACEs. In the adjusted Cox model, LDL-TG remained independent predictive factor after adjustment for age, sex, other risk factors, TG, HDL-C and LDL-C.

Our present study indicated the independent predictive value of baseline LDL-TG on followed-up MACEs[6,17,18]. However, the precise underlying mechanisms have not been yet indicated. Firstly, the previously reported results indicated that elevated LDL-TG may be involved in the development of atherosclerosis and arterial complications in particular. Secondly, the association between LDL-TG and systemic low-grade inflammation reflected by CRP and vascular adhesion molecules, have also been found[5]. In humans, LDL-TGs are hydrolyzed primarily by hepatic lipase. Like lipoprotein lipase, hepatic lipase is subject to modulation by inflammatory cytokines. Thirdly, LDL metabolism characterized by high LDL-TG was correlated with coronary heart disease and systemic low-grade inflammation[15,19]. Our prospective work identified the predictive role of LDL-TG in the occurrence of MACEs. It seems that LDL-TG apparently being a better indicator for atherogenic alterations of LDL metabolism. The results may provide novel focuses and CVD managements strategies.

Conclusions

Our community-based prospective paper clearly demonstrated that baseline LDL-TG closely associated with MACEs, and it is a moderate and independent predictive factor for MACEs.

Table IV. The adjusted regression for MACEs

Baseline	β	HR	95% CI	*p*-value
Age (years)	0.062	1.064	1.034-1.094	< 0.001
LDLTG	0.512	1.669	1.013-2.748	0.044

Acknowledgements
The research is supported by the grant from the National Nature Science Foundation of China (81270941), the Key National Basic Research Program of China (2012CB517503, 2013CB530804) to Dr. Ye Ping. We are also grateful to all study participants for their participation in the study. We thank colleagues at the Department of Laboratory Medicine, the PLA General Hospital for help with biochemical measurements.

Conflict of Interest
The Authors declare that they have no conflict of interests.

References

1) Patel A, Barzi F, Jamrozik K, Lam TH, Ueshima H, Whitlock G, Woodward M. Serum triglycerides as a risk factor for cardiovascular diseases in the Asia-Pacific region. Circulation 2004; 110: 2678-2686.
2) Frisinghelli A, Mafrici A. Regression or reduction in progression of atherosclerosis, and avoidance of coronary events, with lovastatin in patients with or at high risk of cardiovascular disease: a review. Clin Drug Investig 2007; 27: 591-604.
3) Goff DC Jr, Bertoni AG, Kramer H, Bonds D, Blumenthal RS, Tsai MY, Psaty BM. Dyslipidemia prevalence, treatment, and control in the Multi-Ethnic Study of Atherosclerosis (MESA): gender, ethnicity, and coronary artery calcium. Circulation 2006; 113: 647-656.
4) Zhang PY, Xu X, Li XC. Cardiovascular diseases: oxidative damage and antioxidant protection. Eur Rev Med Pharmacol Sci 2014; 18: 3091-3096.
5) März W, Scharnagl H, Winkler K, Tiran A, Nauck M, Boehm BO, Winkelmann BR. Low-density lipoprotein triglycerides associated with low-grade systemic inflammation, adhesion molecules, and angiographic coronary artery disease: the Ludwigshafen risk and cardiovascular health study. Circulation 2004; 110: 3068-3074.
6) Pitha J, Kovar J, Blahova T. Fasting and nonfasting triglycerides in cardiovascular and other diseases. Physiol Res 2015; 64: S323-330.
7) Corona G, Cipriani S, Rastrelli G, Sforza A, Mannucci E, Maggi M. High triglycerides predicts arteriogenic erectile dysfunction and major adverse cardiovascular events in subjects with sexual dysfunction. J Sex Med 2016; 13: 1347-1358.
8) Egeberg A, Gislason GH, Hansen PR. Risk of major adverse cardiovascular events and all-cause mortality in patients with hidradenitis suppurativa. JAMA Dermatol 2016; 152: 429-434.
9) Cohn JN. Slowing the progression of cardiovascular disease. J Am Coll Cardiol 2016; 67: 1698-1700.
10) Kuipers F, Jong MC, Lin Y, Eck M, Havinga R, Bloks V, Verkade HJ, Hofker MH, Moshage H, Berkel TJ, Vonk RJ, Havekes LM. Impaired secretion of very low density lipoprotein-triglycerides by apolipoprotein E-deficient mouse hepatocytes. J Clin Invest 1997; 100: 2915-2922.
11) Austin MA, Rodriguez BL, McKnight B, McNeely MJ, Edwards KL, Curb JD, Sharp DS. Low-density lipoprotein particle size, triglycerides, and high-density lipoprotein cholesterol as risk factors for coronary heart disease in older Japanese-American men. Am J Cardiol 2000; 86: 412-416.
12) Lozano P, Henrikson NB, Dunn J, Morrison CC, Nguyen M, Blasi PR, Anderson ML, Whitlock EP. Lipid screening in childhood and adolescence for detection of multifactorial dyslipidemia: evidence report and systematic review for the US preventive services task force. JAMA 2016; 316: 634-644.
13) Morita SY. Metabolism and modification of apolipoprotein b-containing lipoproteins involved in dyslipidemia and atherosclerosis. Biol Pharm Bull 2016; 39: 1-24.
14) Dragica IL, Biserka BM, Ksenija K, Josipa K, Davorka V, Jasna V. Diversity of metabolic syndrome criteria in association with cardiovascular diseases – a family medicine-based investigation. Med Sci Monit 2013; 19: 571-578.
15) van den Berg MJ, van der Graaf Y, de Borst GJ, Kappelle LJ, Nathoe HM, Visseren FL. Low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, triglycerides, and apolipoprotein B and cardiovascular risk in patients with manifest arterial disease. Am J Cardiol 2016; 118: 804-810.
16) Liu ZH, Sun XP, Zhou SL, Wang HX. Research on the relations between the variation of miRNA-184 before and after treatment of acute myocardial infarction and prognosis. Eur Rev Med Pharmacol Sci 2017; 21: 843-847.
17) Garg R, Aggarwal S, Kumar R, Sharma G. Association of atherosclerosis with dyslipidemia and co-morbid conditions: a descriptive study. J Nat Sci Biol Med 2015; 6: 163-168.
18) Mora S, Glynn RJ, Hsia J, MacFadyen JG, Genest J, Ridker PM. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. Circulation 2010; 121: 1069-1077.
19) Stojakovic T, Scharnagl H, Marz W, Winkelmann BR, Boehm BO, Schmut O. Low density lipoprotein triglycerides and lipoprotein(a) are risk factors for retinal vascular occlusion. Clin Chim Acta 2007; 382: 77-81.