Original Article

Triglyceride glucose index for predicting cardiovascular outcomes in patients with coronary artery disease

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Background: Triglyceride glucose (TyG) index is a novel marker for metabolic disorders and recently it has been reported to be associated with cardiovascular disease (CVD) risk in apparently healthy individuals. However, the prognostic value of TyG index in patients with stable coronary artery disease (CAD) is not determined.

Methods: We conducted a nested case-control study among 3,745 patients with stable CAD. Patients were followed up for 11,235 person-years. The cardiovascular events (CVEs) were defined as all-cause death, non-fatal myocardial infarction (MI), stroke and post-discharge revascularization [percutaneous coronary intervention (PCI) coronary artery bypass grafting (CABG)]. In total, 290 (7.7%) patients with CVEs and 1,450 controls were matched according to age, gender, previous history of PCI or CABG and the duration of follow-up. TyG index was calculated as formula: ln[fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2].

Results: Multivariable Cox proportional hazards models revealed that TyG index was positively associated with CVEs risk (hazard ratio: 1.364, 95% confidence interval: 1.100–1.691, P=0.005). The Kaplan-Meier analysis indicated that patients within the highest quartile of TyG index presented the lowest event-free survival (P=0.029). Moreover, a 1-standard deviation (SD) increment in TyG index was associated with 23.2% [hazard ratio (HR): 1.232, 95% confidence interval (95% CI): 1.084–1.401] higher risk of CVEs, which was superior to other triglyceride or glycemic related markers.

Conclusions: The present study, firstly, showed that TyG index was positively associated with future CVEs, suggesting that TyG may be a useful marker for predicting clinical outcomes in patients with CAD.

Keywords: Triglyceride glucose index (TyG index); stable coronary artery disease; outcome

Submitted Jun 01, 2018. Accepted for publication Sep 30, 2018.
doi: 10.21037/jtd.2018.10.79
View this article at: http://dx.doi.org/10.21037/jtd.2018.10.79

Introduction

It has been well recognized that the development of cardiovascular disease (CVD) is driven by multiple contributing factors including glycemic abnormality and lipid disorder (1,2). Hypertriglyceridemia (HTG) is a common dyslipidemia and the association of triglyceride (TG) with CVD risk remains controversial (3,4). However, judging from a credible body of evidence, we can conclude that HTG is an independent risk factor of developing glucose metabolism disorders (5). Plasma TG levels are strongly associated with raised glucose levels because of the interactions between fat, muscle and function of pancreatic β-cells (6,7). Moreover, accumulation of TG in the liver may cause fatty liver disease, which can increase the risk of type 2 diabetes mellitus (T2DM) (8). Prospective studies have revealed that plasma TG is an independent risk factor for developing T2DM (9,10). Additionally, it has been demonstrated that lowering TG, such as fibrates do, can significantly attenuate the process of developing insulin resistance (11). Furthermore, it also has been reported that both fasting glucose and TG within the high normal range may predict CVD risk (12,13). Hence, evaluating the joint value of TG and fasting glucose in patients with stable coronary artery disease (CAD) may be clinically in need.

Triglyceride glucose (TyG) index is a novel marker, which has been demonstrated to have a high sensitivity and specificity in identifying metabolic syndrome (14). Previous studies have shown that TyG index is associated with carotid atherosclerosis, coronary artery calcification and high risk of CVD. Unfortunately, no data is currently available with regard to the effects of TyG index on clinical outcomes in patients with stable CAD (15-17). Therefore, the primary objective of the study was to investigate the prognostic role of TyG index in a large Chinese cohort with stable CAD.

Methods

Study design and population

Our study complied with the Declaration of Helsinki and was approved by the hospital's ethical review board (Fu Wai Hospital & National Center for Cardiovascular Diseases, Beijing, China, approval number: 2013–442). Informed written consents were obtained from all patients enrolled in this study.

As described in *Figure 1*, from March 2011 to October 2014, 5,437 consecutive patients were scheduled for coronary

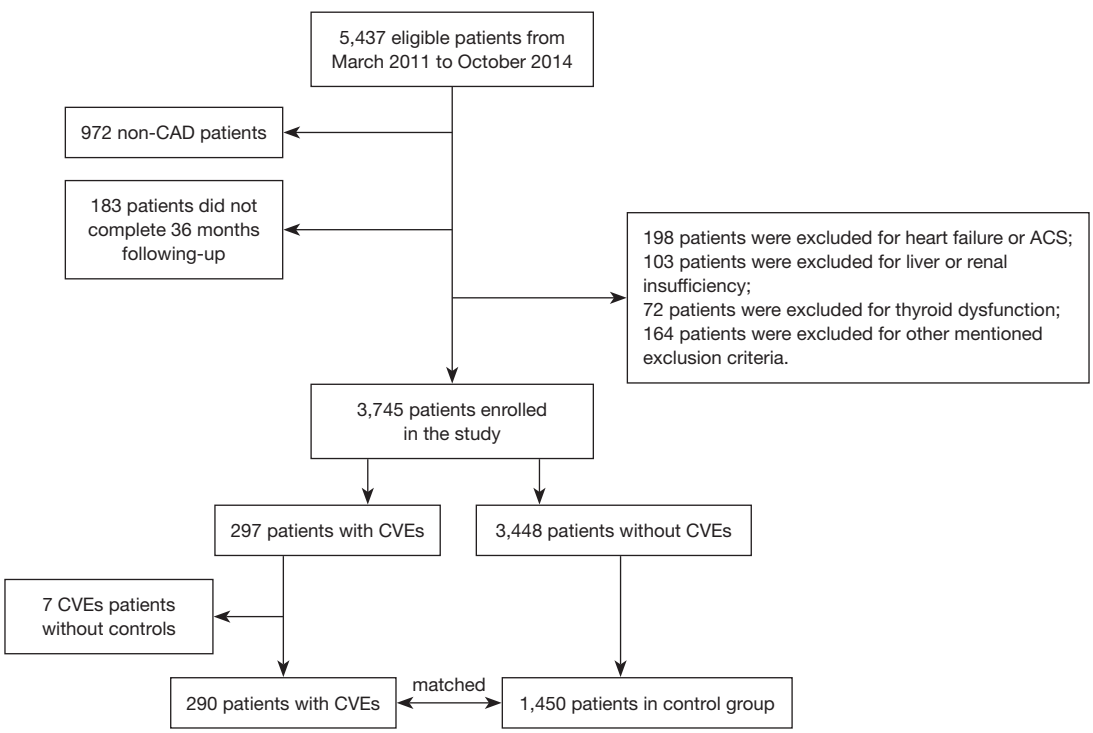

Figure 1 Flowchart of the study. CAD, coronary artery disease; ACS, acute coronary syndrome; CVEs, cardiovascular events.

angiography because of angina-like chest pain and/or positive treadmill exercise test or clinically suspected CAD in our division. Among these patients, 972 were excluded because they were not angiography-proven CAD. Patients with acute coronary syndrome (ACS), heart failure (left ventricular ejection fraction, LVEF <45%), severe liver and/or renal insufficiency, thyroid dysfunction, malignant disease, extreme body mass index (BMI >45 kg/m^2), suspected familial HTG [plasma TG ≥500 mg/dL (5.65 mmol/L) or more than one first-degree relative with TG ≥500 mg/dL] were also excluded. Patients were prospectively followed up at 6, 12, 24, 36 months by means of interviewing directly or using telephone conducted by trained nurses or doctors who were blinded to the clinical data. The cardiovascular events (CVEs) were all-cause death, non-fatal myocardial infarction (MI), stroke and post-discharge revascularization [percutaneous coronary intervention (PCI) coronary artery bypass grafting (CABG)]. Cardiovascular death was defined as death primarily caused by acute MI, congestive heart failure, stroke, malignant arrhythmia and other structural or functional cardiac diseases. Non-fatal MI was diagnosed as positive cardiac troponins along with typical chest pain or typical electrocardiogram serial changes. Stroke was diagnosed by the presence of typical symptoms or imaging. Finally, we identified 3,745 patients with stable CAD who completed our follow-up for the present analysis. During a follow-up of per 11,235 person-years, 297 CVEs occurred and individually matched to 5 randomly selected controls on age, gender, previous history of PCI and CABG, and the duration of follow-up.

Hypertension was defined as a self-reported hypertension, currently taking anti-hypertensive drugs or recorded systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg for three or more consecutive times. T2DM was defined as fasting serum glucose ≥7.0 mmol/L or the 2-h serum glucose of the oral glucose tolerance test ≥11.1 mmol/L or currently using hypoglycaemic drugs or insulin. BMI was calculated as weight divided by height squared. Information of other disease, family history and current therapy of every patient was collected from self-reported medical history.

Laboratory analysis

Blood samples were obtained from each patient from the cubital vein after at least 12-h fasting. Concentrations of total cholesterol (TC), TG, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) were measured using automatic biochemistry analyzer (Hitachi 7150, Japan) in an enzymatic assay. Non-HDL-C was calculated as TC minus HDL-C. The concentrations of glucose were measured by enzymatic hexokinase method. HbA1c was measured using Tosoh Automated Glycohemoglobin Analyser (HLC-723G8, Tokyo, Japan). TyG index was calculated as formula: ln[fasting TG (mg/dL) × fasting plasma glucose (mg/dL)/2].

Statistical analysis

The values were expressed as the mean ± standard deviation (SD) or median (Q1–Q3 quartiles) for the continuous variables and the number (percentage) for the categorical variables. The differences of clinical characteristics between groups were analyzed using Student *t*-test, $\chi 2$-tests, and Fisher's exact test where appropriate. Univariate and multivariate Cox regression analyses were performed to estimate the association TyG index with CVEs. We electively included traditional risk factors [hypertension, DM, lipid, family history of CAD, smoke, BMI, hsCRP (high sensitive C-reactive protein)] and clinical factors with significant differences between CVEs and control group. A P value <0.05 was considered statistically significant. The statistical analysis was performed with SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA).

Results

Cardiovascular events during follow-up

During a follow-up of per 11,235 person-years, 297 CVEs occurred. Each patient experienced CVEs was matched to 5 randomly selected controls on age (±2 years), gender, previous history of PCI and CABG, and the duration of follow-up. 7 patients with CVEs were excluded because they were without matched controls. Among 290 patients with CVEs, 35 (12.07%) died, 70 (24.14%) had stroke, 41 (14.13%) developed non-fatal MI and 144 (49.66%) underwent unplanned PCI or CABG. Patients who experienced non-fatal MI and underwent PCI or CABG were analyzed as one single event.

Baseline characteristics

As presented in *Table 1*, patients in CVEs group had higher levels of TyG index compared to the control group.

Table 1 Baseline characteristics of studied patients

Variables	Control group, N=1,450	CVEs group, N=290	P
Clinical factors			
Age, years	59.5±10.8	59.4±10.0	0.836
Male, n (%)	1,045 (72.1)	209 (72.1)	0.999
BMI (kg/m^2)	25.8±3.2	25.5±3.3	0.187
HT, n (%)	921 (63.5)	207 (71.4)	0.010
DM, n (%)	368 (25.4)	100 (34.5)	0.002
DM duration	5.7±4.8	6.5±5.3	0.149
Family history of CAD, n (%)	200 (13.8)	40 (13.8)	0.942
Current Smoker, n (%)	770 (54.5)	158 (53.1)	0.667
Drinking, n (%)	417 (28.2)	81 (28.9)	0.807
PrePCI, n (%)	310 (21.4)	62 (21.4)	1
PreCABG, n (%)	25 (1.7)	5 (1.7)	1
PreMI, n (%)	422 (29.1)	97 (33.4)	0.140
Laboratory factors			
Glucose (mmol/L)	5.6±1.5	5.9±2.0	0.001
HbA1c (%)	6.4±1.1	6.6±1.3	<0.001
ALT (IU/L)	23.0 (17.0–33.0)	24.0 (17.0–34.0)	0.115
AST (IU/L)	17.0 (14.0–22.0)	18.0 (14.0–23.0)	0.077
Creatinine (μmol)	75.8±16.8	77.3±16.4	0.141
UA (μmol/L)	351.3±87.5	365.3±95.6	0.022
hsCRP (μmol/L)	1.42 (0.72–3.13)	1.63 (0.83–3.30)	0.250
TC (mmol/L)	4.13±1.19	4.20±1.15	0.338
HDL-C (mmol/L)	1.06±0.28	1.07±0.30	0.825
LDL-C (mmol/L)	2.53±1.04	2.50±0.92	0.673
Non-HDL-C (mmol/L)	3.14±1.10	3.07±1.16	0.348
TG (mmol/L)	1.46 (1.09–2.03)	1.57 (1.15–2.18)	0.014
Lp(a) (mg/L)	158.6 (64.7–363.8)	363.8 (77.5–431.4)	0.369
TyG index	8.80±0.57	8.91±0.66	0.002
TG/HDL-C	1.44 (0.96–2.22)	1.56 (1.01–2.47)	0.046
LVEF (%)	63.7±7.6	61.8±9.0	0.001
Medications, n (%)			
Lipid lowering agents	1,109 (74.7)	218 (73.4)	0.644
ACEIs/ARBs	205 (14.1)	35 (12.1)	0.351
β-blockers	410 (28.2)	78 (26.9)	0.396
Aspirin	1,421 (98.0)	282 (97.2)	0.414
Antidiabetic drug, n (%)			
OADs	207 (14.3)	52 (17.9)	0.110
Insulin	103 (7.1)	24 (8.3)	0.484

Data were expressed as median ± SD, 25th and 75th percentile or n (%). BMI, body mass index; HT, hypertension; DM, diabetes mellitus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UA, uric acid; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; hsCRP, high sensitive C-reactive protein; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; Lp(a), lipoprotein (a); TyG index, triglyceride glucose index; LVEF, left ventricular ejection fraction; ACEIs, angiotensin-converting enzymes; ARBs, angiotensin receptor blocker.

Table 2 TyG index and cardiovascular risk factors

Variables	I quart, n=429 (<8.40)	II quart, n=444 (8.41–8.78)	III quart, n=434 (8.79–9.16)	IV quart, n=433 (>9.17)	P
Male, n (%)	311 (72.5)	334 (75.2)	298 (68.7)	311 (71.8)	0.191
Age, years	61.2±9.4	60.2±9.6	58.2±9.9	57.7±10.1	<0.001
BMI (kg/m^2)	24.5±3.3	25.6±3.2	26.3±3.1	26.6±2.9	<0.001
Family history of CAD, n (%)	63 (14.7)	54 (12.2)	66 (15.3)	57 (13.2)	0.753
Current Smoker, n (%)	231 (53.8)	237 (53.4)	219 (50.5)	241 (55.7)	0.489
HT, n (%)	251 (58.5)	278 (62.6)	276 (63.6)	323 (74.6)	<0.001
DM, n (%)	60 (14)	80 (18.1)	114 (26.3)	214 (49.7)	<0.001
UA (μmol/L)	330.8±80.5	351.0±81.3	356.4±87.1	377.4±98.6	<0.001
hsCRP (mg/L)	1.1 (0.55–2.24)	1.3 (0.72–2.97)	1.6 (0.78–3.37)	1.8 (0.98–4.29)	<0.001
HDL–C (mmol/L)	1.18±0.29	1.09±0.27	1.03±0.26	0.95±0.23	<0.001
LDL-C (mmol/L)	2.23±1.00	2.52±1.14	2.63±0.89	2.71±0.99	<0.001
Non-HDL-C (mmol/L)	2.52±0.97	2.90±0.90	3.23±1.28	3.66±1.09	<0.001
LVEF (%)	63.1±7.5	62.9±8.5	63.1±7.2	63.5±8.2	0.571
PrePCI, n (%)	99 (23.1)	89 (20.0)	100 (23.0)	84 (19.4)	0.403
PreCABG, n (%)	3 (0.7)	8 (1.8)	10 (2.3)	9 (2.1)	0.277
Events, n (%)	69 (16.1)	57 (12.8)	76 (17.5)	88 (20.3)	0.027

Data were expressed as mean ± SD, 25th and 75th percentile or n (%). BMI, body mass index; HT, hypertension; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; UA, uric acid; hsCRP, high sensitive C-reactive protein; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Patients in CVEs group also showed higher proportions of hypertension (71.4% *vs.* 63.5%, P=0.010) and diabetes (34.5% *vs.* 25.4%, P=0.002), elevated concentrations of plasma glucose, TG, HbA1C but lower levels of LVEF (all P<0.05). There were no significant differences in TC, HDL-C, LDL-C, lipoprotein (a), hsCRP, the proportions of current smoking, and family history of CAD between the two groups (all P>0.05).

Cardiovascular risk factors according to quartiles of TyG index

We also analyzed the distribution of cardiovascular risk factors according to quartiles of TyG index (I quart n=429, II quart n=444, III quart n=434, IV quart n=433). As shown in *Table 2*, TyG index was positively associated with BMI, UA, hsCRP, HDL–C, LDL-C, DM and hypertension while it was negatively related to age (all P<0.05).

Predictive role of TyG index on cardiovascular events

In the present study, univariate Cox proportional hazard regression analysis showed that TyG index was associated with CVEs (hazard ratio: 1.356, 95% confidence interval: 1.123–1.639, P=0.002, *Table 3*). Hypertension, DM and UA were also risk factors of CVEs (P<0.05) while LVEF played a protective role. In multivariate Cox proportional hazard regression analysis, we further examined the independent risk value of TyG index on CVEs (*Table 3*). After adjustment of BMI, LVEF, hypertension, DM, UA, smoke, hsCRP, HDL-C and LDL-C, TyG index was independently associated with CVEs [hazard ratio (HR): 1.364, 95% confidence interval (95% CI): 1.100–1.691, P=0.005]. The Kaplan–Meier analysis revealed that the patients within the highest quartile of TyG index presented the lowest event-free survival (P=0.029, *Figure 2*). In addition, a 1-SD increment in TyG index was associated with 23.2%

Table 3 Univariate and multivariate Cox proportional hazards regression analysis of the events

Variables	Univariate Cox regression		Multivariate Cox regression	
	HR (95% CI)	P	HR (95% CI)	P
BMI	0.975 (0.940–1.012)	0.187	–	
LVEF	0.975 (0.962–0.987)	<0.001	0.976 (0.963–0.989)	<0.001
HT	1.410 (1.092–1.812)	0.008	1.317 (1.004–1.727)	0.047
DM	1.479 (1.161–1.885)	0.020	1.350 (1.040–1.777)	0.025
hsCRP	1.010 (0.983–1.050)	0.339	–	–
UA	1.002 (1.001–1.003)	0.013	1.002 (1.001–1.003)	0.007
Smoke	1.056 (0.838–1.331)	0.646	–	–
HDL-C	1.031 (0.685–1.552)	0.882	–	–
LDL-C	0.973 (0.866–1.092)	0.638	–	–
TyG index	1.356 (1.123–1.639)	0.002	1.364 (1.100–1.691)	0.005

HR, hazard ratio; 95% CI, 95% confidence intervals; BMI, body mass index; LVEF, left ventricular ejection fraction; HT, hypertension; DM, diabetes mellitus; hsCRP, high sensitive C-reactive protein; UA, uric acid; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; UA, uric acid; TyG index, triglyceride glucose index.

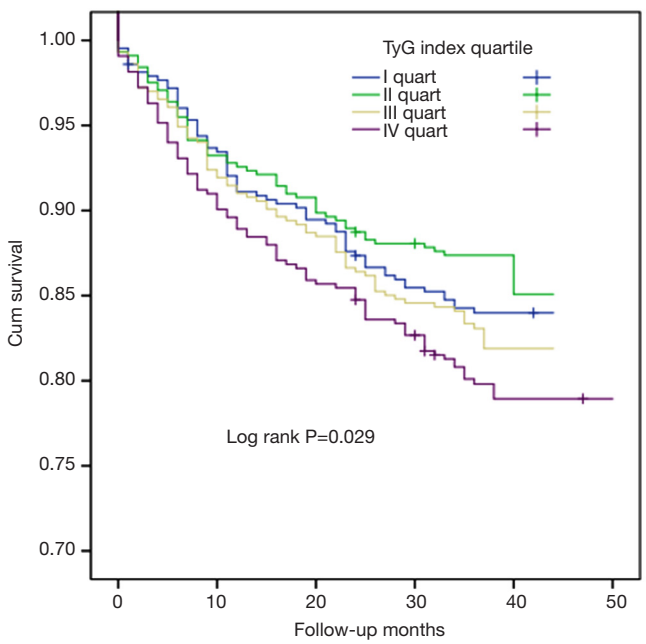

Figure 2 The event-free survival analysis according to the quartiles of TyG index. TyG index, triglyceride glucose index.

(HR: 1.232, 95% CI: 1.084–1.401, P<0.05) higher risk of CVEs, which was superior to other TG or glycemic related markers [TG: HR per 1-SD increment 1.104 (95% CI: 1.006–1.212), P<0.05; TG/HDL-C: HR per 1-SD increment 1.105 (95% CI: 0.955–1.227), P>0.05; HbA1c: HR per 1-SD increment 1.211 (95% CI: 1.093–1.341), P<0.05; glucose: HR per 1-SD increment 1.183 (95% CI: 1.074–1.303), P<0.05, *Figure 3A*]. Furthermore, TyG index was also positively associated with CVEs in subgroup analysis according to the different status of DM and LVEF [DM group: adjusted HR 1.574 (95% CI: 1.090–2.272), P<0.05; non-DM group: 1.434 (95% CI: 1.039–1.979), P<0.05; low LVEF group: adjusted HR 1.396 (95% CI: 1.036–1.882), P<0.05; high LVEF group: adjusted HR 1.521 (95% CI: 1.079–2.143), P<0.05; *Figure 3B,C*]. Finally, the predictive value of TyG index remained significant after adjustment of HbA1c in the multivariate model [adjusted HR 1.282 (95% CI: 1.006–1.634), P<0.05, *Figure 3D*].

Discussion

TyG index has been reported to be associated with CVD risk in apparently healthy individuals (17). However, the prognostic value of TyG index in patients with stable CAD remains undetermined. Using nested case-control analysis, the data suggested that TyG index was higher in patients who experienced CVEs. In addition, TyG index was found to be positively related to cardiovascular risk factors and presented the lowest event-free survival in its top quartered group. To our knowledge, the present study firstly demonstrated that TyG index was an independent

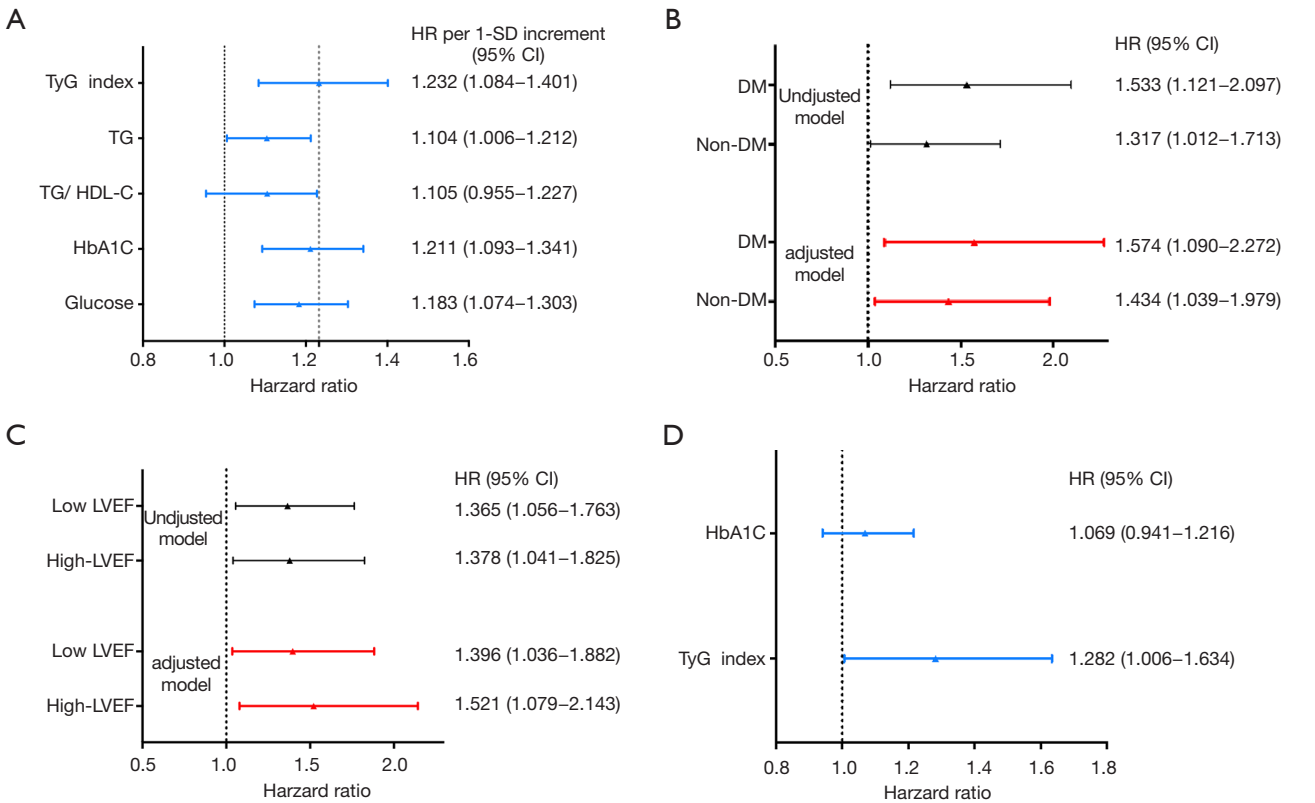

Figure 3 Predictive value of TyG index for CVEs in the different models. (A) HR for cardiovascular events risk elevation associated with 1-SD increment in triglyceride or glycemic related markers; (B) predictive value of TyG index for CVEs in diabetic and non-diabetic patients; (C) predictive value of TyG index for CVEs in patients with high and low LVEF; (D) predictive value of TyG index for CVEs after adjusting for HbA1c and other confounding variables. Adjusted model included BMI, smoking, hypertension, non-LDL-C, hs-CRP, UA (age, sex, DM and LVEF when appropriate). TyGindex, triglyceride glucose index; CVEs, cardiovascular events; HR, hazard ratio; LVEF, left ventricle ejection fraction; LDL-C, low density lipoprotein cholesterol; DM, diabetes mellitus.

risk marker for evaluating future CVEs in patients with stable CAD.

TyG index was firstly studied as a marker of identifying insulin resistance with a high sensitivity and specificity (18-20). It was demonstrated that TyG index was a useful predictor of type 2 diabetes and metabolic syndrome which contributed to cardiometabolic risk (21,22). Subsequently, several studies were conducted and found a positive relationship between TyG index and CVD. Two of such studies demonstrated that TyG index was associated with the presence of cardiovascular risk factors (23,24). Moreover, Irace *et al.* evaluated the association between carotid atherosclerosis and TyG index in two different cohorts and provided consistent, positive results (15). In addition to this, a study enrolled 4,319 Korean adults also indicated that TyG index was significantly associated with the presence of coronary calcification (16). Furthermore, a study including 888 asymptomatic type 2 diabetic patients showed that the higher TyG index was associated with increased risk of coronary stenosis (25). Of the note, studies mentioned above did not evaluated the prognostic value of TyG index in CVD risk.

In fact, a few prospective studies were conducted on the link between TyG index and CVEs. Vega *et al.* firstly investigated the relation of TyG index to mortality from cardiovascular causes, CAD, or CVD in 39,447 men and proved that TyG index did not predict CVD mortality (26). Apparently, this study was limited by gender selection. Another study enrolled 5,014 apparently healthy individuals and identified that the higher level of TyG index was significantly associated with an increased risk of developing CVD (17). They also developed a new model containing the TyG index in addition to Framingham variables and resulted in a higher predictive efficiency in the risk of developing

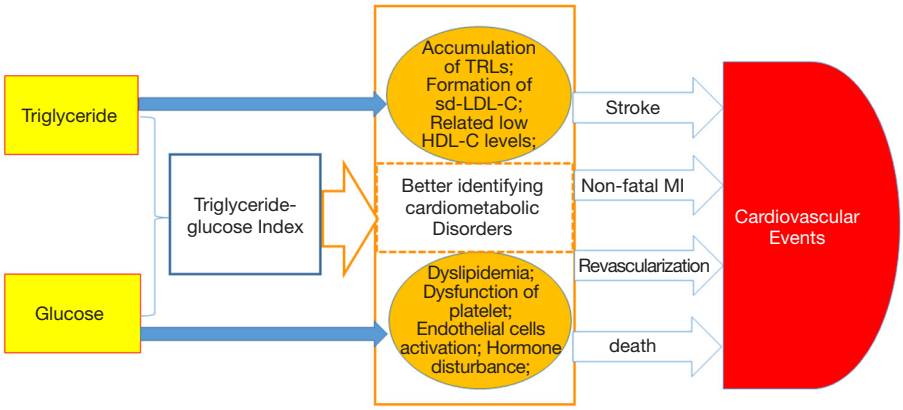

Figure 4 Mechanism of TyG index associated with cardiovascular outcomes. TyGindex, triglyceride glucose index; TRLs, triglyceride-rich lipoproteins; sd-LDL-C, small dense LDL-C; MI, myocardial infarction.

CVD. However, their study focused only on the healthy individuals. Consequently, determination of the prognostic role of TyG index in patients with CAD might be greatly of interest. That was the reason why we performed such study. As shown in the tables and figures, our study, for the first time, indicated that TyG index was significantly higher in patients with CVEs and had better predictive value than TG or glucose alone, suggesting that TyG index might be a simple, easy-to-use, reliable parameter in predicting the prognosis in patients with stable CAD. Moreover, we also compared the prognostic value of TyG index with HbA1c. As we well known, plasma HbA1c, the most reliable marker in evaluating long term glycemic control, had similar HR to TyG index in our study. To our knowledge, both markers were associated with insulin resistance in certain patients and only the predictive value of TyG index stayed significant when the two markers were in the same model (*Figure 3D*).

The exact mechanism underlying the relationship between the TyG index and CVEs has not been fully elucidated. The formula of TyG index is composed of TG and glucose. Although the association of TG with CVD risk is still under debate (3,4), a body of recent evidence has proved that TG and TG-rich lipoproteins are causal factors of CVD (27). Additionally, the concurrence of HTG also promotes the formation of small dense LDL particles (28). Despite the fact that most studies evaluate the CVD risk of TG only in HTG patients, a few studies have demonstrated that plasma TG within high normal range also predict CVEs. In fact, glucose disorder is another CVD risk factor frequently coexisting with HTG. Achievement of favorable goal in plasma TG by means of losing weight or drugs often helps improve glycemic control (29,30). Genetic polymorphisms affecting TG metabolism may also be associated with higher fasting plasma glucose (31). The Prospective Urban Rural Epidemiology (PURE) study demonstrated that high carbohydrate intake, which might increase plasma TG and glucose, was associated with greater risk of the total mortality (32). Therefore, using TyG index may better interpret their joint roles in CVD risk prediction. As we previously described, TyG index was also a useful marker in identifying metabolic disorder (22,23). Notably, inflammatory markers causing atherosclerotic plaque instability, including tumor necrosis factor-α, interleukins, leukocytes and fibrinogen, also played a crucial role in metabolic syndrome and related disorders (33,34). Therefore, TyG index might be a better marker of cardiometabolic risk estimation (*Figure 4*).

There were several limitations in the present study. Firstly, the sample size might be not large enough and the follow-up time might be not long enough. Secondly, the measurements of TG and fasting glucose had unavoidable intra-individual biological variation and changed over time. Previous studies demonstrated that increment in TyG index over time could predict the incidence of diabetes and was positively related to the value of TyG index at first measurement (35,36). We measured TG and fasting glucose only at the baseline and did not evaluate the predictive value of the changes in TyG index for CVEs. Moreover, other confounding factors such as exercise habit, participation to cardiac rehab program and cardiorespiratory fitness were not included in the model. Finally, we did not assess the relationship between TyG index and all metabolic factors

including waist circumstance due to a lack of data. Hence, larger sample and long-term studies are needed to confirm our findings.

Conclusions

Although previous studies indicated an association of TyG with the cardiovascular risk, the present study firstly reported that TyG index was associated with future CVEs in patients with stable CAD using nested case-control study.

Acknowledgements

Funding: This work was partially supported by the Capital Health Development Fund (201614035) and CAMS Major Collaborative Innovation Project (2016-I2M-1-011) awarded to Dr. Jian-Jun Li, MD, PhD.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: Our study complied with the Declaration of Helsinki and was approved by the hospital's ethical review board (Fu Wai Hospital & National Center for Cardiovascular Diseases, Beijing, China, approval number: 2013–442). Informed written consents were obtained from all patients enrolled in this study.

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Cite this article as: Jin JL, Cao YX, Wu LG, You XD, Guo YL, Wu NQ, Zhu CG, Gao Y, Dong QT, Zhang HW, Sun D, Liu G, Dong Q, Li JJ. Triglyceride glucose index for predicting cardiovascular outcomes in patients with coronary artery disease. J Thorac Dis 2018;10(11):6137-6146. doi: 10.21037/jtd.2018.10.79

