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ORIGINAL RESEARCH

γ-Glutamyl Transferase and Long-Term Survival in the SYNTAXES Trial: Is It Just the Liver?

Kai Ninomiya, MD; Patrick W. Serruys, MD, PhD; Scot Garg, MD, PhD; Shigetaka Kageyama, MD; Nozomi Kotoku, MD; Shinichiro Masuda, MD; Pruthvi C. Revaiah, MD; Neil O'leary, PhD; Arie Pieter Kappetein, MD, PhD; Michael J. Mack, MD, PhD; David R. Holmes, MD; Piroze M. Davierwala, MD; Friedrich W. Mohr, MD, PhD; Daniel J. F. M. Thuijs, MD, PhD; Yoshinobu Onuma, MD, PhD; for the SYNTAX Extended Survival (SYNTAXES) Investigators

BACKGROUND: Recently, machine learning algorithms have identified preprocedural γ-glutamyl transferase (GGT) as a significant predictor of long-term mortality after coronary revascularization in the SYNTAX (Synergy Between PCI [Percutaneous Coronary Intervention] With Taxus and Cardiac Surgery) trial. The aim of the present study is to investigate the impact of preprocedural GGT on 10-year all-cause mortality in patients with complex coronary artery disease after revascularization.

METHODS AND RESULTS: The SYNTAX trial was a randomized trial comparing PCI with coronary artery bypass grafting in 1800 patients with complex coronary artery disease. The present report is a post hoc subanalysis of the SYNTAXES (Synergy Between PCI With Taxus and Cardiac Surgery Extended Survival) trial, an investigator-driven extended 10-year follow-up of the SYNTAX trial. The association between preprocedural GGT and 10-year all-cause mortality was investigated. The mean values of GGT for men and women were 43.5 (SD, 48.5) and 36.4 (SD, 46.1) U/L, respectively. In multivariable Cox regression models adjusted by traditional risk factors, GGT was an independent predictor for all-cause death at 10-year follow-up, and each SD increase in log-GGT was associated with a 1.24-fold risk of all cause death at 10-year follow-up (95% CI, 1.10–1.40). According to previously reported sex-related GGT thresholds, patients with higher GGT level had a 1.74-fold risk of all-cause death at 10-year follow-up (95% CI, 1.32–2.29) compared with patients with lower GGT level.

CONCLUSIONS: Preprocedural GGT is an independent predictor of 10-year mortality after coronary revascularization in patients with complex coronary artery disease. In patients with elevated GGT, strong secondary prevention may be required after revascularization and must be studied prospectively.

REGISTRATION: URL: https://clinicaltrials.gov/study/NCT03417050.

Key Words: biological marker ■ γ-glutamyl transferase ■ long-term clinical outcomes ■ machine learning

The serum measurement of γ-glutamyl transferase (GGT) is an accurate, low-cost, highly sensitive, frequently used laboratory test that is considered to be an index of hepatobiliary dysfunction and alcohol abuse. The GGT activity is determined by genes and age, and there is still a remarkable between-sex difference, with women having lower values in normal physiology than men.[1]

Over the past decade, epidemiology and pathology studies have suggested that GGT has an independent role in the pathogenesis and clinical evolution of cardiovascular diseases associated with atherosclerosis.[2–5]

Correspondence to: Yoshinobu Onuma, MD, PhD, Interventional Cardiology, University of Galway, Medical Director CORRIB Core Lab (Cardiovascular Imaging and Atherosclerosis), University Road, Galway H91 TK33, Ireland. Email: yoshinobuonuma@gmail.com and Patrick W. Serruys, MD, PhD, Interventional Medicine and Innovation, University of Galway, University Road, Galway H91 TK33, Ireland. Email: patrick.w.j.c.serruys@gmail.com

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CLINICAL PERSPECTIVE

What Is New?

- A machine learning model was developed to predict long-mortality in the SYNTAX (Synergy Between PCI [Percutaneous Coronary Intervention] With Taxus and Cardiac Surgery) trial, and γ-glutamyl transferase (GGT) has been identified as a significant predictor of long-term mortality after coronary revascularization.
- According to sex-related GGT thresholds, patients with higher GGT level had a 1.64- to 1.74-fold risk of all cause death at 10-year follow-up compared with patients with lower GGT level in multivariable models.

What Are the Clinical Implications?

- Despite existing evidence, the clinical implications of measuring GGT before revascularization remain unclear and limited.
- Patients with elevated preprocedural GGT had significantly higher long-term mortality even after revascularization. Therefore, those patients may require strong postrevascularization therapies that must be studied prospectively.
- GGT is a low-cost, frequently used laboratory test marker that should be collected before revascularization as it can be considered as a risk factor predictive of long-term mortality.

Nonstandard Abbreviations and Acronyms

GGT	γ-glutamyl transferase
ML	machine learning
SYNTAXES	Synergy Between PCI With Taxus and Cardiac Surgery Extended Survival

In 2004, Paolicchi et al reported the GGT activity was present in histologic samples of atherosclerotic coronary plaques and was likely to be involved in promoting the oxidation of low-density lipoprotein.[2]

Despite existing evidence, the underlying mechanism remains unclear, as are the clinical implications of measuring it in patients with cardiovascular disease (CVD). Furthermore, no specific data are available on the impact of preprocedural GGT on long-term mortality in patients with complex coronary artery disease (CAD) after percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The predictive thresholds of preprocedural GGT on long-term mortality in patients receiving PCI or CABG are also unknown.

The SYNTAXES (Synergy Between PCI With Taxus and Cardiac Surgery Extended Survival) study obtained vital status up to 10 years in patients with 3-vessel disease or left main disease randomized in the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial.[6] Recently, in addition to past findings, a machine learning (ML) algorithm was applied to the SYNTAXES study database, and GGT was identified as a significant predictor of long-term mortality (Figure S1).[7] Age, CRP (C-reactive protein), left ventricular ejection fraction, and mental and physical status quantified using the 36-Item Short Form Health Survey.[8] The present subanalysis of the SYNTAXES study aimed to investigate the impact of preprocedural GGT on 10-year all-cause mortality in patients with complex CAD undergoing PCI or CABG.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patient Population

The present study is a post hoc subgroup analysis of the SYNTAXES study (NCT 03417050), an investigator-driven extended 10-year follow-up of the SYNTAX trial (NCT00114972).[6] The SYNTAX trial was a multicenter, randomized controlled trial that adopted an "all-comer" design with minimum exclusion criteria. A total of 1800 patients with de novo 3-vessel disease or left main CAD were randomized in a 1:1 manner to receive either PCI, with the default use of paclitaxel drug-eluting stents (TAXUS Express, Boston Scientific Corporation, Marlborough, MA) or CABG. The main result of the SYNTAXES study in terms of vital status up to 10 years has already been reported.[6] The median duration of follow-up was 11.2 years (interquartile range, 7.7–12.1 years) overall and 11.9 years in survivors. The SYNTAX trial and SYNTAXES study were approved by the ethics committees at each investigating center, and all patients provided written informed consent before participation in the SYNTAX trial. Follow-up was performed in accordance with local law and regulations of each participating institution and complied with the Declaration of Helsinki

End Points and Definitions

Before revascularization, blood samples were taken for GGT as well as other biological markers, such as CRP, hemoglobin A1c and fasting glucose, fasting total cholesterol, triglycerides, high-density lipoprotein cholesterol, and alanine aminotransferase (ALT), and analyzed by an independent central chemistry laboratory (Labcorp Drug Development, Geneva, Switzerland, and Indianapolis, IN).

The primary end point was all-cause mortality at 10 years. In the SYNTAXES study, vital status at 10 years was confirmed by contact with medical care personnel or using electronic health care record review and national death registries. Patients with missing vital status were included in the analysis but censored at the point they were lost to follow-up. Five patients in 2 institutes who did not participate in the SYNTAXES study for the 10-year extended follow-up were censored at 5 years. Major adverse cardiac and cerebrovascular events (MACEs) at 5 years (a composite of all-cause death, cardiac death, myocardial infarction, and stroke) were adjudicated by an independent clinical events committee.

Statistical Analysis

The changes in hazard for all-cause mortality at 10 years over serum GGT level were modeled using restricted cubic spline functions (3 knots) in a Cox regression model adjusted by age, sex, and body mass index. Hazard ratios (HRs) with 95% CIs for all-cause mortality were determined on the basis of Cox proportional hazards regression, adjusted for the following baseline variables: model 1: age, sex, body mass index, treatment arm, and metabolic syndrome; and model 2: all covariates in model 1 plus ALT, total cholesterol, medically treated diabetes, history of congestive heart failure, previous myocardial infarction, anatomic SYNTAX trial score, treatment arm, and CRP. Serum GGT was naturally logarithmically transformed to normalize the skewed distribution (Figure S2).

Serum GGT was also modeled as a binary variable according to sex-specific GGT thresholds of <32 and ≥32 U/L for women and <64 and ≥64 U/L for men, in accordance with prior studies.[9] The cumulative incidence of all-cause death was calculated using the Kaplan-Meier method. To determine the associations of GGT with CRP and established biological risk markers, such as triglycerides, total cholesterol, high-density lipoprotein cholesterol, glucose, and hemoglobin A1c, correlation coefficients adjusted for age and sex were calculated.

Continuous variables were expressed as mean (SD) or median with 25th to 75th percentile and were compared using the Student *t* test or Mann-Whitney *U*-test. Categorical variables were reported as percentages (numbers) and were compared using the χ^2 test or Fisher exact test. A 2-sided $P<0.05$ was considered statistically significant. Analyses were performed using R, version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

Of 1800 patients enrolled in the SYNTAX trial between March 2005 and April 2007, 167 (9.3%) did not have a GGT value available at baseline and were excluded. Consequently, 1633 (90.7%) patients were included in the present study (Figure 1).

In the whole population, the median value of the GGT was 29 (19–47) U/L, with median values for men and women of 31 (21–50) and 23 (16–36) U/L, respectively. The distribution of GGT between sexes is shown in Figure 2. After logarithmic transformation, the median (interquartile range) and mean (SD) log GGT were 1.46 (1.28–1.67) and 1.50 (0.30), respectively.

The baseline characteristics of patients stratified by a threshold value of 32 U/L for women and 64 U/L for men are presented in Table 1. Among men, patients with higher GGTs were younger than those with lower GGTs, whereas among women, there was no significant difference. Male and female patients with higher GGTs had higher body mass index. Among men, the prevalence of metabolic syndrome and a history of congestive heart failure was higher in patients with higher GGT than those with lower GGT.

Correlation Between GGT and Coronary Risk Factors and Biological Markers

Table 2 shows various correlations of GGT with other biological makers for CVD. When the biomarkers were treated as categorical variables, patients with higher GGT had a higher level of ALT, triglycerides, total cholesterol, glucose, hemoglobin A1c, and CRP than patients with lower GGT. There was no significant difference in high-density lipoprotein cholesterol level between patients with higher versus lower GGT. GGT significantly correlated with other biological markers, with the strongest age- and sex-adjusted correlation observed between GGT and ALT (r=0.44); other positive correlations were seen with triglycerides (r=0.23), CRP (r=0.19), and total cholesterol (r=0.10), whereas high-density lipoprotein cholesterol (r=−0.07) had a negative correlation.

Impact of Preprocedural GGT on Clinical Outcomes

The association between preprocedural GGT and mortality at 10 years is shown with cubic spline curves (Figure 2). In the age-, sex-, and body mass index–adjusted Cox model, each SD increase in log-GGT was associated with a 1.23-fold risk of all cause death at 10 years (95% CI, 1.12–1.35; P<0.001) and a 1.23-fold risk of MACE at 5 years (95% CI, 1.10–1.37; P<0.001; Table 3). Preprocedural serum GGT was an independent factor for both 5-year MACE and 10-year death after additional adjustment for metabolic syndrome. Additional adjustment for ALT, total cholesterol, medically treated diabetes, history of congestive heart failure, previous myocardial infarction, anatomic SYNTAX trial score, and CRP also did not change the results (HR per SD increase in log GGT, 1.24 [95% CI, 1.10–1.40] for all-cause death at 10 years; Table 3).

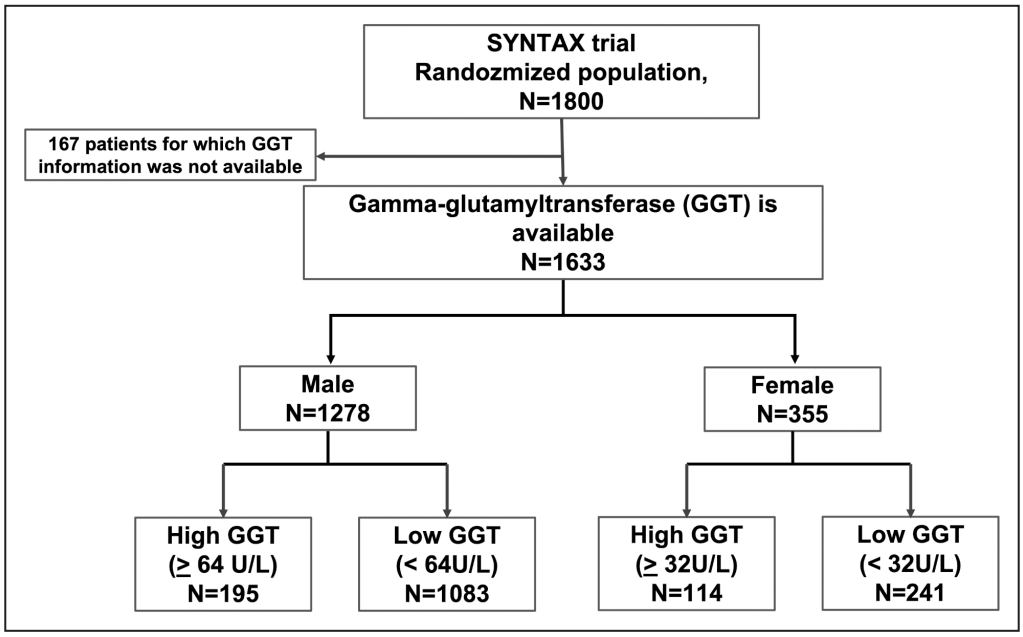

Figure 1. Study flowchart.
GGT indicates γ-glutamyl transferase; and SYNTAX indicates Synergy Between PCI [Percutaneous Coronary Intervention] With Taxus and Cardiac Surgery.

Similar findings were seen when GGT was treated as a categorical variable. Cumulative incidence curves demonstrated a greater risk of all-cause death in patients with higher GGT compared with those with lower GGT (Figure 3A). In multivariable models, patients with higher GGT had a 1.64- to 1.74-fold risk of all-cause death at 10 years compared with those with lower GGT (model 1: 95% CI, 1.28–2.10; model 2: 95% CI, 1.32–2.29; Table 3). Although 10-year mortality was highest with 39.5% among women with higher GGT (Figure 3B), there was no statistically significant sex-by-GGT interaction in multivariable Cox regression model for all-cause mortality (*P* for interaction=0.133). The analysis for each component of MACE is shown in Table 3. Notably, patients with higher GGT had a 2.29- to 2.67-fold risk of cardiac death at 5 years compared with those with lower GGT, whereas there was no significant difference in terms of noncardiac death at 5 years (Table 3). There was no treatment-by-subgroup interaction with treatment arm in both continuous and categorical models (*P* interaction=0.450 and 0.185, respectively).

DISCUSSION

To our knowledge, for the first time, the present study reports on the long-term impact of GGT on cardiovascular outcomes in patients with complex CAD randomized to PCI and CABG. The main findings of our study are as follows:

1. Preprocedural GGT was an independent factor of all-cause death at 10 years and 5-year MACE after myocardial revascularization, and each SD increase in log-GGT was associated with a 1.20- to 1.24-fold risk of all-cause death at 10 years in multivariable models.
2. According to sex-related GGT thresholds, patients with higher GGT level had a 1.64- to 1.74-fold risk of all-cause death at 10 years compared with patients with lower GGT level in multivariable models. Notably, patients with higher GGT had a 2.21- to 2.67-fold risk of cardiac death at 5 years compared with those with lower GGT.
3. These findings corroborate the recent report on prognostic factors identified through ML algorithms in patients with complex CAD.

GGT and CVD

An increasing number of studies have evaluated the relationship between serum GGT activity and mortality, following Conigrave et al's observation in 1993 that GGT has a predictive value for mortality, irrespective of hepatic disease or alcohol consumption. The prospective study by Lee et al included 28 838 Finnish men and women between the ages of 25 and 74 years and assessed their risk of coronary heart disease in the 25th, 50th, 75th, and 90th sex-specific percentiles of serum GGT. After adjustment for traditional cardiovascular risk factors, compared with the lowest GGT category (<25th percentile), the HRs for the risk of coronary heart disease in the other 4 groups ranged from 1.15 to 1.57 in men and from 1.03 to 1.44 in women (*P*<0.01 for trend).[9]

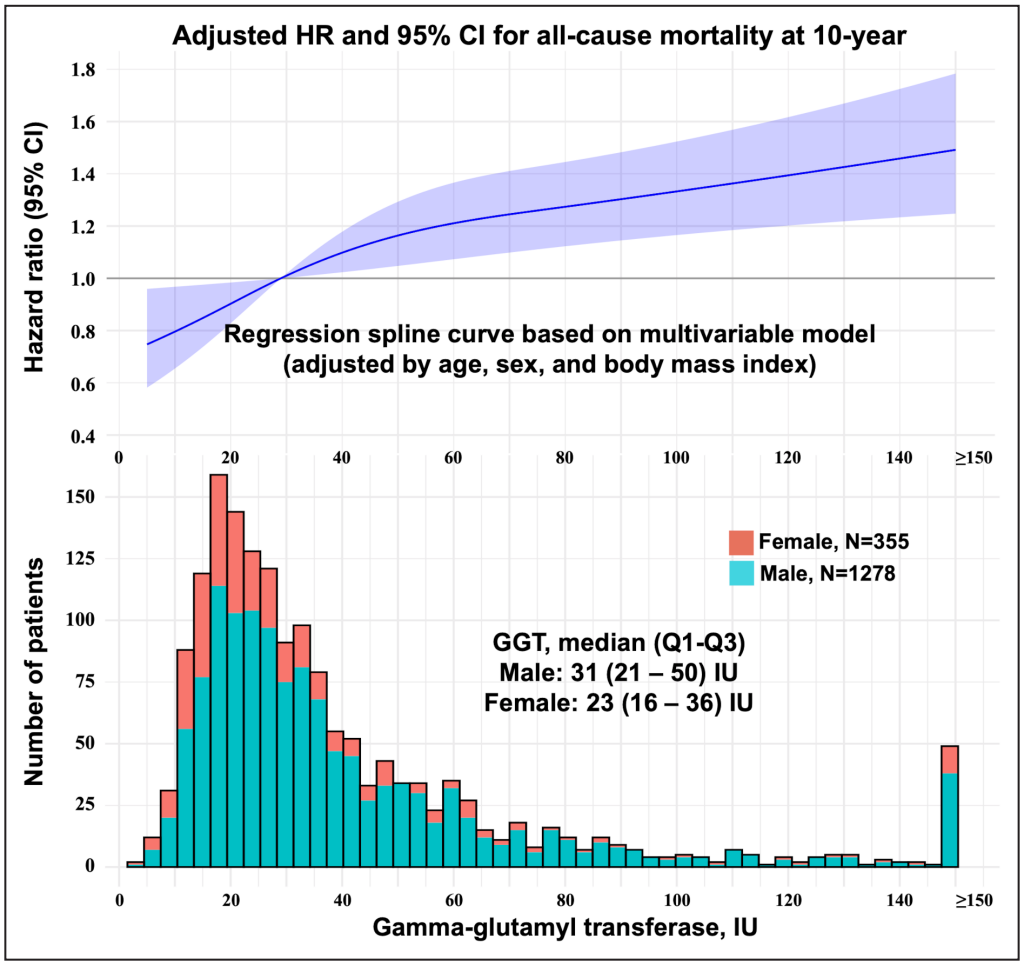

Figure 2. Regression spline curve for 10-year all-cause death according to GGT at preprocedure. The association between preprocedural GGT and mortality at 10 years is shown with cubic spline curves (adjusted for age, sex, and body mass index). Q1 indicates quartile 1; and Q3, quartile 3. GGT indicates γ-glutamyl transferase.

Ruttmann et al assessed the association of GGT with the risk of CVD-related mortality in a cohort of 163 944 Austrian adults, monitored for up to 17 years, and showed that a high GGT was significantly associated with CVD-related mortality, with adjusted HRs per log GGT of 1.66 (95% CI, 1.40–1.98) in men and 1.64 (95% CI, 1.36–1.97) in women.[3] Normal values of GGT vary because of age and sex, and some studies report that there are significant interactions between sex, level of GGT, and CVD mortality. An Asian study suggests a stronger association between GGT and CVD-related mortality and stroke in women than men.[5] Our study population consists of a larger number of patients with higher GGT levels than the general population, and elevation of preprocedural GGT was associated with long-term mortality in patients with complex CAD after myocardial revascularization, especially in women. Notably, patients with higher GGT had a 2.21- to 2.67-fold risk of cardiac death at 5 years compared with those with lower GGT.

Mechanisms of GGT Association With CVD and Future Treatment Options

Atherogenic Metabolic Risk Factors and Fatty Liver Disease

Previous studies demonstrated that elevation of GGT is a marker of the presence of metabolic syndrome, fatty liver, and greater risk for developing type 2 diabetes with insulin resistance. Metabolic syndrome is characterized by an increase of systemic inflammation, which results in multiorgan disease and increased risk of CVDs and mortality.[10]

Nonalcoholic fatty liver disease is associated with elevated GGT and is 1 manifestation of end-organ damage of the metabolic syndrome. In patients with nonalcoholic fatty liver disease, systemic inflammation, endothelial dysfunction, hepatic insulin resistance, oxidative stress, and altered lipid metabolism are considered to be mechanisms of increased risk of CVD and mortality.[11] Furthermore, there is growing interest to use GGT to predict the development of heart failure or its

Table 1. Baseline Characteristics

Characteristic	Men (n=1278)			Women (n=355)		
	High GGT (n=195)	Low GGT (n=1083)	*P* value	High GGT (n=114)	Low GGT (n=241)	*P* value
Age, y	61.6±9.6	64.6±9.5	<0.001	68.5±9.3	68.4±9.7	0.957
Body mass index, kg/m^2	28.8±4.4	27.8±4.4	0.002	29.5±5.6	28.0±5.6	0.020
Diabetes	26.7 (52/195)	21.6 (849/1083)	0.135	34.2 (39/114)	33.2 (80/241)	0.904
On insulin	11.3 (22/195)	8.7 (94/1083)	0.278	16.7 (19/114)	13.7 (33/241)	0.521
Metabolic syndrome	59.6 (93/156)	38.9 (362/931)	<0.001	64 (64/100)	58.6 (123/210)	0.387
Hypertension	67.7 (132/195)	65.7 (711/1083)	0.623	71.1 (81/114)	72.6 (175/241)	0.800
Dyslipidemia	75.1 (145/193)	78.7 (845/1074)	0.298	78.1 (89/114)	78.6 (187/238)	0.971
Current smoking	25.8 (50/194)	21.3 (230/1080)	0.187	16.7 (19/114)	14.2 (34/240)	0.528
Previous MI	38.5 (74/192)	32.9 (353/1072)	0.136	37.5 (42/112)	27.7 (66/238)	0.082
Previous stroke	6.2 (12/192)	4.4 (48/1080)	0.269	3.5 (4/113)	3.3 (8/240)	0.999
Peripheral vascular disease	11.3 (22/195)	9.1 (99/1083)	0.353	7.9 (9/114)	12.9 (31/241)	0.209
COPD	5.1 (10/195)	8.2 (89/1083)	0.148	11.4 (13/114)	10.0 (24/241)	0.711
Creatinine clearance, mL/min	81.5±20.0	80.4±17.8	0.435	72.7±19.8	74.4±19.7	0.446
LVEF, %	57.3±14.9	59.1±12.8	0.155	57.7±13.7	59.3±11.6	0.353
Congestive heart failure	7.3 (14/191)	3.4 (37/1073)	0.025	7.3 (8/110)	5.9 (14/238)	0.639
Disease type			0.748			0.212
LMCAD	38.5 (75/195)	37.2 (403/1083)		42.1 (48/114)	49.4 (119/241)	
3VD	61.5 (120/195)	62.8 (680/1083)		57.9 (66/114)	50.6 (122/241)	
SYNTAX trial score	30.7±12.1	29.1±11.0	0.058	28.0±11.9	26.5±12.3	0.257

Values are percentage (number/total) or mean±SD. 3VD indicates 3-vessel disease; COPD, chronic obstructive pulmonary disease; GGT, γ-glutamyl transferase; LMCAD, left main coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and SYNTAX, Synergy Between PCI [Percutaneous Coronary Intervention] With Taxus and Cardiac Surgery.

prognosis because the biochemical profiles of liver dysfunction are more clearly delineated.[12] In line with previous studies, the present study showed that increases in GGT were associated with metabolic syndrome, other atherogenic metabolic risk factors, and congestive heart failure. More important, although the information on fatty liver is not available in the present study, the elevated GGT was an independent factor of long-term mortality in multivariable analysis adjusted by those factors.

Triggering Oxidative Stress

Catalytically active GGT has been found within atherosclerotic carotid and coronary plaques from autopsy studies and surgical endarterectomies, colocalized with oxidized density lipoproteins (low-density lipoproteins) and CD68$^+$ foam cells.[2] The possible association between GGT and inflammatory processes stems from the fact that GGT has a key role in the interconversion of the glutathione-containing

Table 2. Correlation Between GGT and Other Biological Markers

Marker	Low GGT	High GGT	*P* value*	Correlation coefficient	*P* value†
ALT, U/L	29±25	45±32	<0.001	0.44	<0.001
Triglycerides, mg/dL	137±69	173±109	<0.001	0.23	<0.001
Total cholesterol, mg/dL	165±40	174±43	<0.001	0.10	<0.001
HDL cholesterol, mg/dL	43±12	44±13	0.627	−0.07	0.005
Glucose, mg/dL	119±43	128±50	<0.001	−0.01	0.662
HbA1c, %	6.1±1.0	6.3±1.2	0.018	0.03	0.262
CRP, mg/dL	0.84±1.68	1.47±2.41	<0.001	0.19	<0.001

Data are given as mean±SD unless otherwise indicated. ALT indicates alanine aminotransferase; CRP, C-reactive protein; GGT, γ-glutamyl transferase; HbA1c, hemoglobin A1c; and HDL, high-density lipoprotein.

*Two-sided *P* values against the null hypothesis of no difference in the means between the 2 groups.

†*P* value for correlation coefficient.

Table 3. Clinical Outcomes

Outcome	Age-, sex-, and BMI-adjusted model		Multivariable model 1*		Multivariable model 2†	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Numerical model, log GGT per SD increment						
Death, all cause, at 10 y	1.23 (1.12–1.35)	<0.001	1.20 (1.08–1.33)	<0.001	1.24 (1.10–1.40)	<0.001
Death, stroke, or MI at 5 y	1.23 (1.10–1.37)	<0.001	1.21 (1.07–1.37)	0.002	1.24 (1.08–1.42)	0.003
Death, all cause, at 5 y	1.35 (1.19–1.54)	<0.001	1.28 (1.11–1.48)	<0.001	1.39 (1.18–1.64)	<0.001
Cardiac death at 5 y	1.49 (1.26–1.76)	<0.001	1.41 (1.17–1.70)	<0.001	1.58 (1.28–1.96)	<0.001
Noncardiac death at 5 y	1.18 (0.96–1.46)	0.124	1.15 (0.92–1.45)	0.226	1.28 (0.98–1.67)	0.070
Stroke at 5 y	1.09 (0.81–1.46)	0.578	1.08 (0.79–1.48)	0.621	1.10 (0.77–1.58)	0.591
MI at 5 y	1.09 (0.90–1.32)	0.376	1.12 (0.91–1.38)	0.276	1.03 (0.81–1.31)	0.806
Categorical model, low GGT vs high GGT						
Death, all cause, at 10 y	1.64 (1.30–2.06)	<0.001	1.63 (1.27–2.09)	<0.001	1.72 (1.30–2.26)	<0.001
Death, stroke, or MI at 5 y	1.65 (1.26–2.17)	<0.001	1.59 (1.18–2.13)	0.002	1.60 (1.15–2.22)	0.005
Death, all cause, at 5 y	1.94 (1.41–2.67)	<0.001	1.85 (1.31–2.60)	<0.001	2.03 (1.38–2.97)	<0.001
Cardiac death at 5 y	2.24 (1.48–3.39)	<0.001	2.21 (1.41–3.45)	<0.001	2.56 (1.57–4.18)	<0.001
Noncardiac death at 5 y	1.52 (0.88–2.63)	0.135	1.46 (0.82–2.61)	0.204	1.62 (0.84–3.13)	0.147
Stroke at 5 y	1.16 (0.55–2.45)	0.705	0.96 (0.42–2.23)	0.929	0.92 (0.36–2.34)	0.858
MI at 5 y	1.42 (0.90–2.24)	0.137	1.43 (0.87–2.37)	0.158	1.22 (0.69–2.13)	0.493

BMI indicates body mass index; GGT, γ-glutamyl transferase; and MI, myocardial infarction.
*Multivariable model 1 was adjusted by age, sex, BMI, and metabolic syndrome.
†Multivariable model 2 was adjusted for all covariates in model 1 plus alanine aminotransferase, medically treated diabetes, history of congestive heart failure, previous MI, anatomic SYNTAX (Synergy Between PCI [Percutaneous Coronary Intervention] With Taxus and Cardiac Surgery) trial score, and CRP (C-reactive protein).

inflammatory mediator leukotriene C4 into leukotriene D4.[13]

In the extracellular milieu, GGT is the only enzyme responsible for the catabolism of glutathione. The GGT-mediated reactions have been shown to catalyze the oxidation of low-density lipoproteins, likely contributing to systemic oxidative stress,[14] which could then play a relevant role in the progression of atherosclerotic plaque and its destabilization: apoptosis of cellular elements of the lesion, plaque erosion and rupture, enhanced platelet

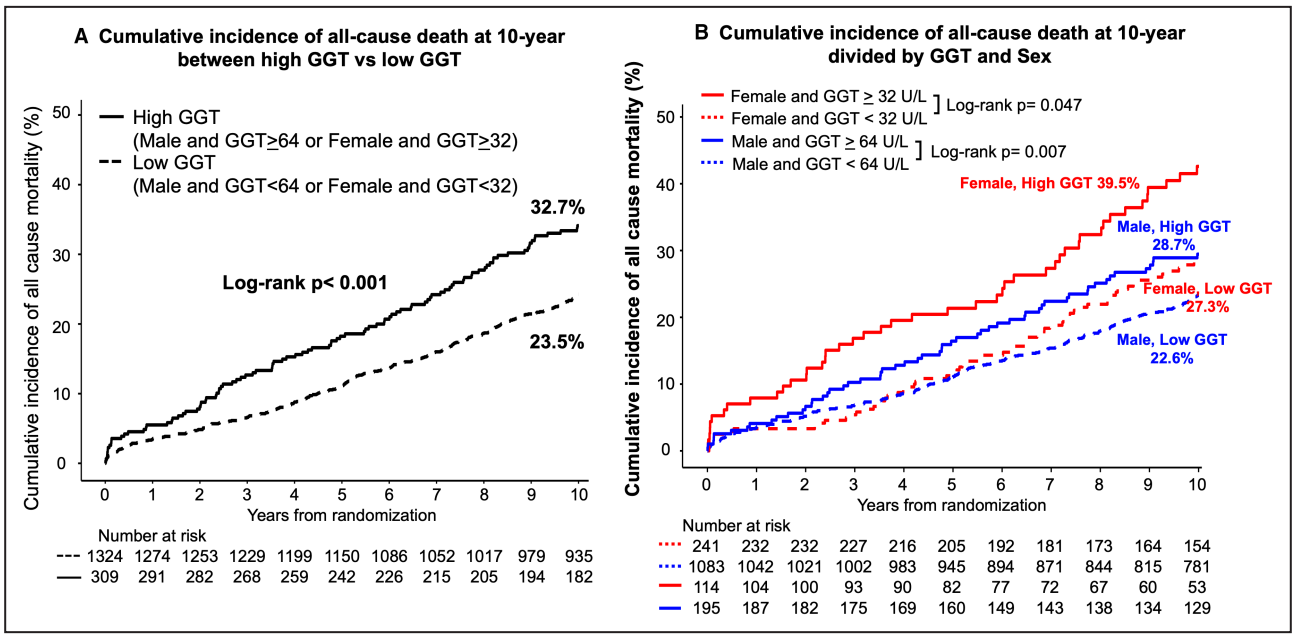

Figure 3. Cumulative incidence of all-cause death at 10 years according to sex-related GGT thresholds.
A, Cumulative incidence of all-cause death at 10 years between higher GGT vs lower GGT group. **B**, Cumulative incidence of all-cause death at 10 years in 4 groups according to sex-related GGT thresholds. GGT indicates γ-glutamyl transferase.

aggregation, and thrombosis.[15,16] Overexpression of glutathione peroxidase in apolipoprotein E mice blunts atherogenesis by inhibiting lipid peroxidation and vascular cell sensitivity to oxidized lipids.[17]

More recently, Aimo et al reported that big GGT, the highest-molecular-weight fraction of GGT, was associated with a composite of cardiovascular death or acute coronary syndrome requiring urgent coronary revascularization and epicardial fat volume, all of which is related to plaque inflammation.[18] In the present study, there was a significant positive linear trend between GGT and CRP, a marker of inflammation (r=0.16; P<0.001). Our results support previous findings that GGT activity is a surrogate of systemic inflammation. GGT itself may not be a determinant but is a conduit for atherosclerosis and inflammation that provides not only the mechanism but moreover the need for strong postrevascularization therapies that must be studied prospectively. Therapies targeting inflammation or the immune system[19] might potentially be effective for patients with CAD with elevated GGT.

Predictive Impact of GGT on Mortality in Patients With Complex CAD

The impact of preprocedural GGT on long-term mortality was incidentally revealed by ML approach. At variance from previous statistical approaches, ML and penalized regression can handle large numbers of anatomic, biological, and even psychologic parameters. Recently, Ninomiya et al reported undiscovered potentially important factors for predicting long-term mortality after PCI or CABG by applying ML algorithms to the SYNTAX trial database.[7] Surprisingly, in the ML model, GGT was identified as a more important prognostic factor to predict long-term mortality than conventional predictors, such as diabetes, chronic obstructive pulmonary disease, or smoking, a finding endorsed by the present study. Our findings on GGT in the present analysis have corroborated the ML findings on prognostic factors. Although the ML model including GGT showed helpful discrimination at cross-validation,[11] this model needs further confirmation using an external validation data set. However, limited data on 10-year outcomes after PCI or CABG are available and variables, such as GGT, mental/physical status, or CRP, are not always collected in the clinical trials; hence, external validation of our model might be not feasible in the context of a clinical trial. A "mega-analysis" based on large randomized or nonrandomized data, the so-called "big data," may be warranted to confirm these findings.

Limitations

First, as this is a post hoc analysis, all findings must be interpreted with caution and regarded as hypothesis generating because of the inherent limitations of post hoc analysis, including multiple testing.[20] The risk of the overestimation bias attributable to the data-driven search should be considered. Second, the number of individuals with high GGT in this cohort was small and may not have enough power for subgroup analyses, especially in women. Third, GGT levels were not collected during follow-up, but decision-making between PCI and CABG is inherently only based on baseline characteristics. Fourth, the absence of B-type natriuretic peptide and novel inflammatory markers makes it difficult to fully elucidate the detailed mechanisms.

CONCLUSIONS

Preprocedural GGT is a low-cost, frequently used laboratory test marker that can be considered a prognostic risk factor predictive of long-term mortality in patients with complex CAD even after revascularization. In patients with elevated GGT, strong secondary prevention may be required after revascularization and must be studied prospectively. The external validation of our ML model incorporating GGT will prove the predictive value of GGT in the future.

ARTICLE INFORMATION

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Affiliations

Department of Cardiology, University of Galway, Ireland (K.N., P.W.S., S.K., N.K., S.M., P.C.R., N.O., Y.O.); National Heart and Lung Institute, Imperial College London, London, United Kingdom (P.W.S.); Department of Cardiology, Royal Blackburn Hospital, Blackburn, United Kingdom (S.G.); Department of Cardiothoracic Surgery, Erasmus University Medical Centre, Rotterdam, the Netherlands (A.P.K., D.J.T.); Department of Cardiothoracic Surgery, Baylor University Medical Center, Dallas, TX (M.J.M.); Department of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, Rochester, MN (D.R.H.); University Department of Cardiac Surgery, Heart Centre Leipzig, Leipzig, Germany (P.M.D., F.W.M.); Division of Cardiovascular Surgery, Peter Munk Cardiac Centre, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada (P.M.D.); Department of Surgery, University of Toronto, Canada (P.M.D.); and Galway University Hospital, Galway, Ireland (Y.O.).

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Disclosures

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Supplemental Material

Data S1
Figures S1–S2

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