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ORIGINAL ARTICLE
Coronary artery disease

Triglyceride-glucose index predicts outcome in patients with chronic coronary syndrome independently of other risk factors and myocardial ischaemia

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Aims The triglyceride-glucose (TyG) index, a surrogate marker of insulin resistance (IR), is a prognostic risk factor in the general population. We aimed to assess whether it is an independent predictor of outcome also in patients with chronic coronary syndrome (CCS).

Methods and results TyG index was evaluated in 1097 consecutive patients (75% men, median age 72 years) with known (26%) or suspected coronary artery disease (CAD), undergoing stress-rest myocardial perfusion scintigraphy, and coronary angiography and followed up for a median of 4.5 years. Moderate/severe perfusion abnormalities during stress (summed stress score >7) were documented in 60% of patients, obstructive CAD in 74%, and 36% underwent early revascularization. TyG index was 8.9 (median, interquartile interval 8.6–9.2). Cardiac death or myocardial infarction occurred in 103 patients and all-cause death in 65. After correction for clinical risk factors, LV function and common bio-humoral variables, TyG index (HR 2.42, 95% CI 1.57–3.72, $P < 0.001$), and moderate/severe stress perfusion abnormalities (hazard ratio (HR) 2.17, 95% confidence interval (CI) 1.25–3.77, $P < 0.001$) independently predicted cardiac events. TyG index (HR 3.64, 95%CI 2.22–5.96, $P < 0.001$) and high-sensitivity C-reactive protein (HR 1.11, 95% CI 1.04–1.19, $P = 0.002$) independently predicted all-cause death.

Conclusion In patients with CCS, the TyG index identifies a cardiometabolic profile associated with an additional risk of cardiac events, over the presence of myocardial ischaemia and independently of other clinical, common bio-humoral or imaging risk determinants.

Keywords Triglycerides • Glucose • C-reactive protein • Prognosis • Coronary artery disease • Chronic coronary syndrome

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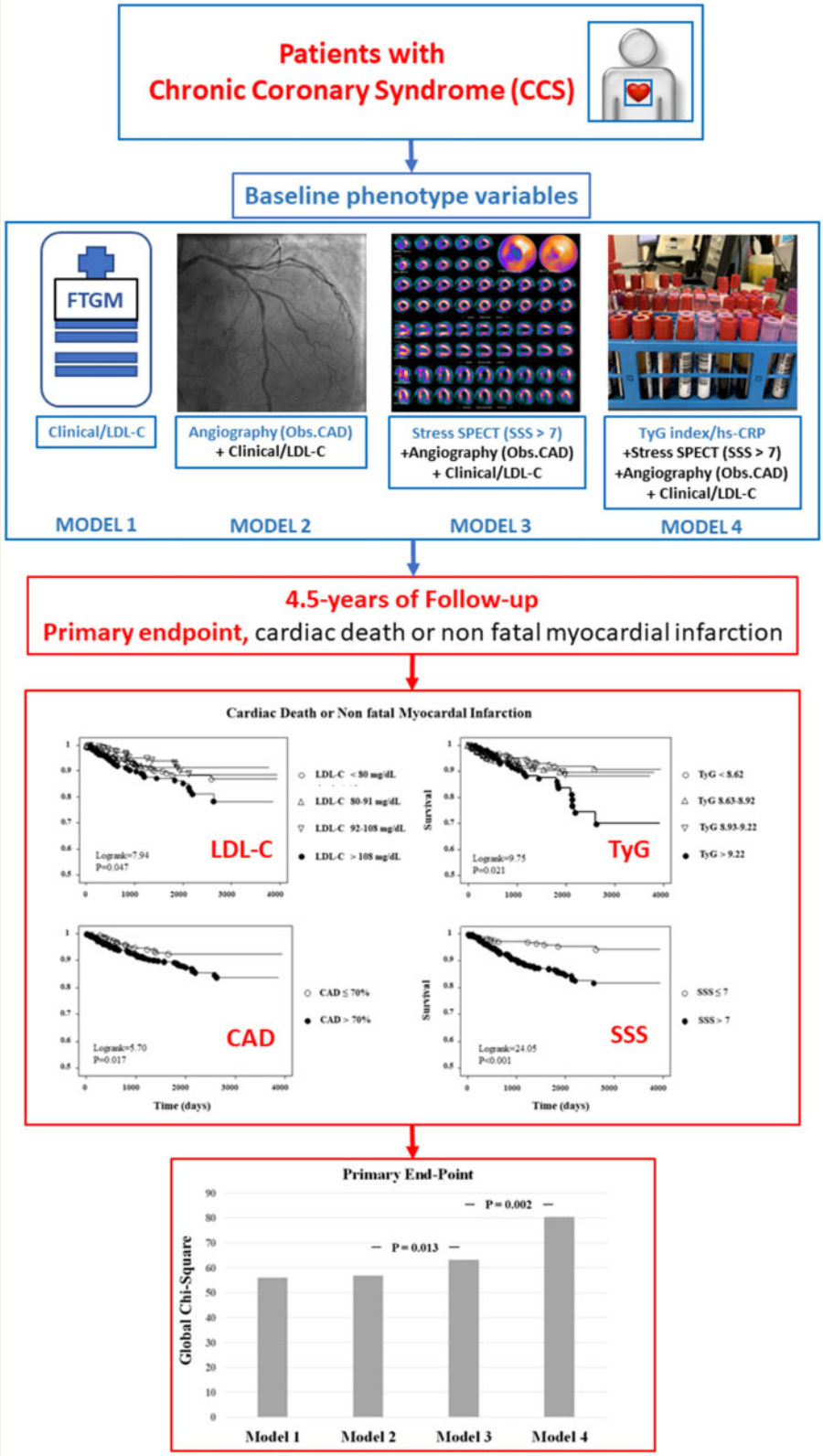
Graphical Abstract



Patients with chronic coronary symptoms were characterized by clinical variables, risk factors and common bio markers. They underwent diagnostic screening by functional and anatomical cardiac imaging and followed-up for 4.6 years. LDL cholesterol, obstructive coronary artery disease, moderate–severe myocardial ischaemia and the trygliceride-glucose index stratified the risk of cardiac events. The multivariable predictive model including tryglicer-ide-glucose index and high-sensitivity C-reactive protein outperformed all other models.

Introduction

In patients with stable angina or equivalent symptoms and intermediate-to-high probability of obstructive coronary artery disease (CAD), stress imaging is indicated for diagnostic and risk stratification purposes.[1] At myocardial perfusion scintigraphy (MPS), patients with a perfusion deficit involving >10% of the left ventricular (LV) myocardium have a high risk of adverse cardiac events and are commonly referred to invasive coronary angiography (ICA) and coronary revascularization with the goal to improve their symptoms and outcome.[2] This strategy has been challenged by the recent finding that myocardial ischaemia may not independently predict outcome in patients with chronic coronary syndromes (CCS),[3,4] and that revascularization of obstructive CAD may not be superior to optimal medical therapy (OMT) even in patients with documented ischaemia.[5] In parallel, robust evidence has been gathered on the efficacy of OMT, particularly with low-density lipoprotein (LDL) cholesterol lowering drugs, to improve the outcome of patients with CAD.[6–8]

Besides LDL cholesterol, plasma triglycerides (TGs) may contribute to the atherosclerosis process.[9] Higher TGs levels have been associated with type 2 diabetes mellitus, obesity and high fasting plasma glucose (FPG)[9] as well as with cardiac events in the general populations,[10,11] and in patients on statins after an acute coronary syndrome (ACS).[12] A TG-glucose (TyG) index, proposed as a surrogate marker of insulin resistance (IR),[13] predicted cardiac events in the general population,[14] and the progression of coronary atherosclerosis in patients with known disease,[15] irrespective of other risk factors or cholesterol levels. It is not known whether this marker is also a predictor of outcome in patients with CCS independently of the presence and extent of coronary disease.

Accordingly, we assessed the prognostic role of the TyG index in patients with CCS enrolled in a prospective single-center registry and fully characterized by circulating biomarkers, evaluation of inducible ischaemia by MPS and of coronary anatomy.

Methods

Patient population

The current study population was identified within the cohort of the Analysis of Myocardial Ischemia by Cadmium-zinc-telluride: accuracy and Outcome (AMICO) study.[16] Briefly, AMICO was a prospective, non-randomized, single-center study including consecutive patients with known or suspected stable CAD, referred for stress-rest myocardial perfusion scintigraphy (MPS) and then to coronary angiography at the Fondazione Toscana Gabriele Monasterio (FTGM) in Pisa between January 2010 and June 2019. Patients with acute or recent (<3 months) myocardial infarction (MI), unstable angina, non-ischaemic cardiomyopathy, moderate-to-severe heart valve disease, end-stage renal disease, or active malignancy were excluded.

All patients underwent a thorough clinical evaluation, an MPS study by a cadmium zinc telluride (CZT) camera and, within 1 month, an ICA, in those with abnormal MPS, or a coronary computed tomography angiography (CCTA), in those with uncertain MPS who were referred to ICA whether CCTA had shown or could not exclude obstructive CAD. All patients were then managed according to the current clinical practice and entered a long-term clinical follow up. Within the AMICO population ($n = 1464$), patients with available biomarkers of lipid/glucose metabolism and inflammation were included in the present study ($n = 1097$, 75% of the whole cohort). These patients did not display significant differences from the other patients ($n = 367$; data not shown).

All participants gave written informed consent. The study conformed to the Declaration of Helsinki and was approved by the institution's human research committee.

Myocardial perfusion scintigraphy and coronary angiography

The MPS, CCTA, and ICA protocols were described elsewhere.[16,17] At MPS, the summed stress score (SSS), summed rest score (SRS), the summed difference score (SDS), and the LV ejection fraction (LVEF) were calculated. Myocardial perfusion during stress was defined normal or minimally abnormal by SSS <4[16] and moderately/severely abnormal by SSS >7 (involving >10% of LV myocardium).[5] The readers were blinded to clinical data and coronary anatomy.

For both CCTA and ICA obstructive CAD was defined by the presence of >70% luminal diameter reduction in at least one epicardial coronary artery or >50% in the left main coronary artery. In the presence of obstructive CAD at CCTA the final diagnosis had to be confirmed at ICA.

Clinical management

Patients underwent coronary revascularization at the discretion of interventional cardiologists and referring cardiologists, by percutaneous coronary angioplasty or coronary artery bypass grafting according to contemporary recommendations.[1] Early coronary revascularization was defined as a revascularization procedure performed within 90 days from MPS exam or within 30 days from ICA. All patients received OMT for secondary prevention.[1]

Clinical and laboratory characterization

All patients underwent a thorough clinical and laboratory characterization within 1 month from MPS, as previously described.[16] Clinical evaluation was focused on cardiovascular risk factors, symptoms, and the history of CAD. The pre-test probability was calculated retrospectively according to 2019 European Society of Cardiology guidelines.[1] Blood samples were drawn in the morning after overnight fasting. TGs, total and high-density lipoprotein (HDL) cholesterol, and fasting plasma glucose (FPG) were measured through methods that were previously standardized in the core laboratory regarding sensitivity, accuracy, reproducibility, and working range (determination of analytes with an imprecision <10%). The operators who analysed the blood samples were blinded to all other patient data. LDL cholesterol was estimated using the Friedwald formula, which could be used in all cases as no patients had TG levels ≥400 mg/dL.[18] Close correlations existed between LDL cholesterol and non-HDL cholesterol ($r = 0.972$) and between LDL cholesterol and total cholesterol ($r = 0.929$). The TyG index was calculated as Ln (TG*FPG/2).[19] Estimated glomerular filtration rate was calculated through the Chronic Kidney Disease Epidemiology Collaboration equation.[20]

Follow-up

Patients were followed over time in a dedicated outpatient clinic and managed as clinically indicated. Follow-up data were retrieved in May 2020 from electronic health records and phone calls to patients or their relatives. For patients who died in a hospital or at home, the cause of death was retrieved from the medical records or the local physician who signed the death certificate. The attribution of cardiac death required documentation of significant arrhythmias or cardiac arrest, or death attributable to heart failure or MI in the absence of any other precipitating

factor. The primary end-point was the composite of cardiac death or non-fatal MI, and the secondary end-point was all-cause death. When multiple events occurred, patients were censored at the time of the first event. Late revascularization procedures (performed >90 days from enrolment MPS or >30 days from ICA) were also recorded. Follow-up events were adjudicated by an independent trained investigator, blinded to MPS data and coronary anatomy. No patient was lost at follow-up.

Statistical analysis

The statistical analysis was carried out using SPSS version 25.0 (IBM Corp., Armonk, NY) and R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Normal distribution was assessed using the Kolmogorov-Smirnov test; continuous variables were expressed as mean and 95% confidence interval, and non-normally distributed variables as median and interquartile interval (25–75° percentiles). Differences between groups were evaluated through the one-way Anova test. Categorical variables were compared by the Chi-square test with Yates correction. Estimates of the cumulative event rate were calculated by the unadjusted Kaplan–Meier method with the log-rank method to test for differences between curves. The model for multivariable Cox regression analysis was created by searching univariable predictors of the primary and/or secondary end-points (with $P < 0.05$) among the following variables: age, gender, family history of CAD, previous MI and/or coronary revascularization, current smoking status, hypertension, diabetes, obesity, LDL and HDL cholesterol, TyG index, high-sensitivity C-reactive protein (hs-CRP), LVEF, obstructive CAD (defined as above), SSS >7, and early revascularization. We defined incremental models for each end-point according to the results of the univariable analysis. Model 1 included male gender, previous MI and/or coronary revascularization, LDL cholesterol, and LVEF; Model 2 was Model 1 plus obstructive CAD; Model 3 was Model 2 plus SSS >7; and Model 4 was Model 3 plus hs-CRP and TyG. Multicollinearity between individual components of multivariate models was searched by calculating the Variance Inflation Factor, with a conservative threshold of 2.5. The one-in-ten event rule was followed for the primary end-point (103 events, 8 variables). The added prognostic value was evaluated in terms of Chi-square values from Cox regression analysis using the likelihood ratio test. Two-tailed *P*-values <0.05 were considered statistically significant.

Results

Study population

Our cohort included 1097 patients, whose baseline characteristics are reported in *Table 1*. Patients were more often males (75%), had a median age of 72 years (interquartile interval 64–77), and complained of typical angina in 45% of cases. Twenty-six percent of patients had a history of MI and/or coronary revascularization and 26% were in NYHA class II–III. Hypertension (61%), hypercholesterolaemia (52%), family history of CAD (46%), and diabetes (39%) were the most common cardiovascular risk factors. At enrolment, 50% of patients received statins and 34% had LDL cholesterol >100 mg/dL. The median TyG value was 8.9 (8.6–9.2). Twenty-seven percent of patients had LVEF <50%, 60% had SSS >7, 74% had obstructive CAD, and early revascularization was performed in 36%.

The frequency of family history of CAD, previous MI, and/or coronary revascularization and the prevalence of hypercholesterolaemia and diabetes increased in parallel with TyG quartiles, as well as total and LDL cholesterol, non-HDL cholesterol and the percentages of patients on aspirin, statins, beta-blockers, and diuretics. On the other hand, HDL cholesterol significantly decreased across TyG quartiles (Supplementary material online, *Table S1*). The percentages of patients with SSS >7, obstructive CAD, and multivessel disease increased from the first to the fourth TyG quartile (Supplementary material online, *Table S2*).

Over a median 4.4-year follow-up (interquartile interval 2.5–5.9), 103 events of cardiac death or MI were recorded and 65 all-cause deaths over 4.5 years (2.6–6.0). Furthermore, 150 patients (14%) underwent late coronary revascularization for reasons other than an acute MI. Rate of adverse events increased across TyG quartiles and this increment was significant for all-cause death (Supplementary material online, *Table S2*). Patients subsequently experiencing cardiac death or non-fatal MI were more often men, more symptomatic for dyspnoea, and more likely to be obese and had more commonly a history of MI and/or coronary revascularization and significantly higher TyG: 9.0 (8.7–9.5) vs. 8.9 (8.6–9.2), $P = 0.006$. The difference in TyG was even more pronounced between patients who died during follow-up and those who survived: 9.3 (8.9–10.0) vs. 8.9 (8.6–9.2), $P < 0.001$. Patients meeting the primary end-point were double as likely to have LVEF <50% and had higher SSS, SRS, and SDS and more frequently obstructive and extensive CAD. Broadly similar results were found for the secondary end-point. Conversely, there were no significant differences in the rates of revascularization at the end of the diagnostic workup (*Table 1*).

Survival analysis

At Kaplan–Mayer analysis, TyG and LDL cholesterol quartiles significantly stratified the risk of cardiac death or MI (*Figure 1*, upper panels). Similarly, SSS > 7 and obstructive CAD (>70% stenosis in at least one major vessel) significantly stratified the risk of the primary end-point (*Figure 1*, lower panels). Similar results were found when considering non-HDL cholesterol instead of LDL cholesterol or SSS >8 to define ischaemia.[16]

Incremental multivariable Cox prognostic models for the primary and the secondary end-points were defined based on the search for significant univariable predictors (Supplementary material online, *Table S3*) and are reported in *Table 2*. Previous myocardial infarction or revascularization, LDL cholesterol, and LVEF were independent predictors among clinical and routine biohumoral variables (Model 1), while SSS > 7, but not the presence of obstructive CAD, was an additional predictor among imaging variables (Models 2 and 3). In the final model, the TyG index was a strong predictor of the primary end-point (HR 2.41, 95% CI 1.55–3.75, $P < 0.001$), together with SSS > 7 and LVEF, outperforming other clinical and biohumoral variables. The TyG index (HR 3.88, 95% CI 2.35–6.40, $P < 0.001$), together with hs-CRP and LVEF, was also a strong independent predictor of the secondary end-point (all-cause death). The models including the TyG index showed an incremental prognostic power over models including clinical and imaging variables for both the primary and secondary end-points (*Figure 2*).

Discussion

We report that the TyG index is a strong independent predictor of future cardiac events in patients with CCS, together with LV systolic function and the presence of moderate–severe myocardial perfusion

Table 1 Patients characteristics

	Whole cohort, *n* = 1097	Cardiac death or non-fatal MI		*P*	All-cause death		*P*
		Yes, *n* = 103 (9%)	No, *n* = 994 (91%)		Yes, *n* = 65 (6%)	No, *n* = 1032 (94%)	
Clinical characteristics and risk factors							
Age (years)	72 (64–77)	71 (64–79)	72 (64–77)	0.929	73 (67–78)	71 (64–77)	0.929
Males, *n* (%)	821 (75)	87 (85)	734 (74)	0.018	51 (79)	770 (75)	0.488
NYHA class I, II, III, n (%)	803, 279, 15 (73, 25, 1)	61, 38, 4 (59, 37, 4)	742, 241, 11 (75, 24, 1)	0.001	30, 31, 4 (46, 48, 6)	773, 248, 11 (75, 24, 1)	<0.001
Typical angina, n (%)	493 (45)	42 (41)	451 (45)	0.372	29 (45)	464 (45)	0.957
Family history of CAD, n (%)	500 (46)	40 (39)	460 (46)	0.149	23 (35)	477 (46)	0.089
Previous MI and/or coronary revascularization, n (%)	284 (26)	49 (48)	235 (24)	0.001	35 (54)	249 (24)	<0.001
Current smoker, n (%)	302 (28)	24 (23)	278 (28)	0.578	14 (22)	288 (28)	0.265
Hypertension, n (%)	666 (61)	68 (66)	598 (60)	0.247	42 (65)	624 (61)	0.506
Hypercholesterolaemia, n (%)	571 (52)	61 (59)	510 (51)	0.126	38 (59)	533 (52)	0.286
Diabetes, n (%)	430 (39)	43 (42)	387 (39)	0.578	31 (48)	399 (39)	0.148
Obesity, n (%)	315 (29)	41 (40)	274 (28)	0.009	21 (32)	294 (29)	0.509
BMI (kg/m^2)	28 (25–31)	28 (26–33)	28 (25–31)	0.012	28 (26–32)	28 (25–31)	0.012
Atrial fibrillation, n (%)	144 (13)	18 (18)	126 (13)	0.170	17 (26)	127 (12)	0.001
eGFR (mL/min/1.73 m^2)	69 (54–84)	72 (57–85)	69 (54–84)	0.380	68 (56–84)	69 (54–84)	0.380
Lipid/glucose profile and inflammation							
Total cholesterol (mg/dL)	186 (167–198)	187 (167–200)	184 (169–197)	0.086	196 (166–210)	184 (169–197)	0.086
LDL cholesterol (mg/dL)	92 (80–109)	94 (78–115)	92 (80–108)	0.358	105 (82–123)	91 (80–108)	0.358
Non-HDL cholesterol (mg/dL)	121 (104–141)	125 (100–149)	120 (104–140)	0.253	141 (106–160)	120 (103–140)	0.253
HDL cholesterol (mg/dL)	60 (54–67)	60 (53–67)	60 (54–67)	0.718	58 (50–61)	60 (54–67)	0.718
Triglycerides (mg/dL)	143 (113–171)	151 (118–180)	142 (113–170)	0.085	159 (117–189)	142 (113–168)	0.085
Fasting plasma glucose (mg/dL)	105 (91–131)	110 (99–145)	104 (90–130)	0.001	120 (109–268)	103 (90–130)	0.001
TyG index	8.9 (8.6–9.2)	9.0 (8.7–9.5)	8.9 (8.6–9.2)	0.006	9.3 (8.9–10.0)	8.9 (8.6–9.2)	<0.001
hs-CRP (mg/L)	0.3 (0.1–0.8)	0.5 (0.1–1.3)	0.3 (0.1–0.8)	0.064	0.6 (0.2–4.0)	0.3 (0.1–0.8)	0.064
Therapy at baseline							
Statins, n (%)	524/1,057 (50)	53/101 (53)	471/956 (49)	0.540	32 (49)	492/992 (50)	0.954
Aspirin, n (%)	847/1,057 (80)	90/101 (89)	757/956 (79)	0.017	57 (88)	790/992 (80)	0.115
Beta-blockers, n (%)	664/1,057 (63)	74/101 (73)	590/956 (62)	0.022	51 (79)	613/992 (62)	0.007
CCBs, n (%)	186/1,057 (18)	14/101 (14)	172/956 (18)	0.300	7 (11)	179/992 (18)	0.136
ACEi/ARB, n (%)	742/1,057 (70)	70/101 (69)	672/956 (71)	0.120	44 (68)	698/992 (70)	0.542
Nitrates, n (%)	111/1,057 (11)	9/101 (9)	102/956 (11)	0.584	8 (12)	103/992 (10)	0.624
Diuretics, n (%)	481/1,057 (46)	64/101 (63)	417/956 (44)	<0.001	51 (79)	430/992 (43)	<0.001
MPS							
Exercise/dipyridamole, n (%)	748/351 (68/32)	64/39 (62/38)	685/309 (69/31)	0.168	43/22 (66/34)	706/326 (68/32)	0.720
Workload (W)	100 (100–125)	100 (100–125)	100 (75–125)	0.695	100 (100–125)	100 (75–125)	0.707
LVEF rest (%)	59 (48–66)	51 (31–63)	60 (50–67)	<0.001	35 (26–56)	60 (50–67)	<0.001
LVEF <50%, n (%)	293 (27)	50 (49)	143 (24)	<0.001	43 (66)	250 (24)	<0.001
SSS	8 (5–12)	12 (8–18)	8 (4–12)	<0.001	14 (9–20)	8 (5–12)	<0.001
SRS	2 (0–5)	4 (1–13)	2 (0–5)	<0.001	7 (2–15)	2 (0–5)	<0.001
SDS	5 (3–8)	6 (4–8)	5 (3–7)	0.021	5 (2–8)	5 (3–7)	0.899
SSS >7, n (%)	660 (60)	86 (84)	574 (58)	<0.001	54 (83)	606 (59)	<0.001
Coronary angiography							
Obstructive CAD, n (%)	813 (74)	85 (82)	728 (73)	0.041	52 (80)	761 (74)	0.264
0, 1, 2, 3 vessel disease, n (%)	284, 437, 247, 129 (26, 40, 22, 12)	18, 40, 23, 22 (18, 39, 22, 21)	266, 397, 224, 107 (27, 40, 22, 11)	0.007	13, 23, 11, 18 (20, 35, 17, 28)	271, 414, 236, 111 (26, 40, 23, 11)	0.001
Early revascularization, n (%)	395 (36)	37 (36)	358 (36)	0.985	25 (39)	370 (38)	0.671

See Methods for definition.

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCBs, calcium-channel blockers; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LM, left main coronary artery; LVEF, left ventricular ejection fraction; MPS, myocardial perfusion scintigraphy; NYHA, New York Heart Association; SDS, summed difference score; SRS, summed rest score; SSS, summed stress score; TyG index, triglyceride-glucose index.

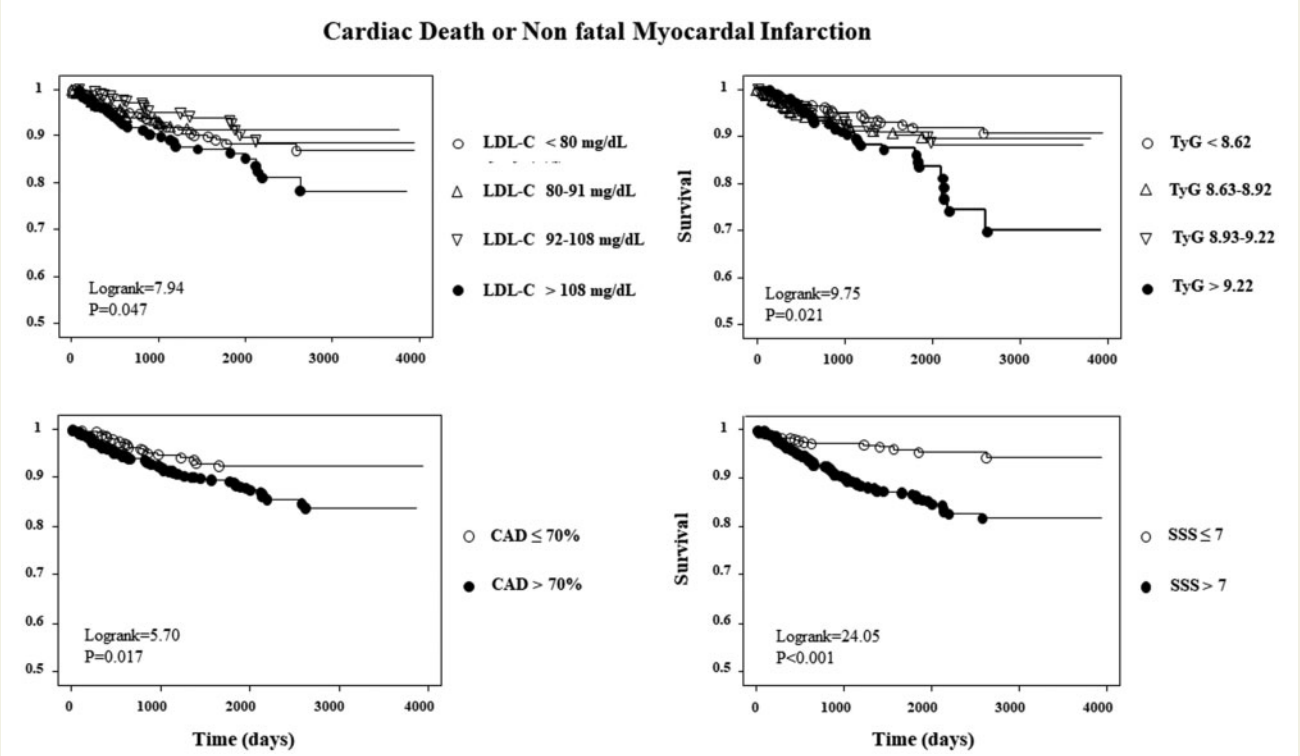


Figure 1 Event-free survival curves based on triglyceride-glucose index quartiles, LDL-C quartiles and Imaging findings. Unadjusted Kaplan–Meier curves were constructed to assess differences in event-free survival among patient groups defined by: (*A*) the triglyceride-glucose index quartiles; (*B*) the LDL cholesterol quartiles; (*C*) presence/absence of obstructive coronary artery disease defined by >70% stenosis in at least one major coronary vessel at coronary angiography; and (*D*) presence/absence of moderate–severe stress perfusion defect (summed stress score > 7) at myocardial perfusion scintigraphy.

defects during stress. The TyG index is also a strong independent predictor of all-cause death, together with LV systolic function and hs-CRP. The present results suggest that in patients with CCS, the presence and severity of IR, as expressed by the TyG index, can stratify the individual risk of events beyond other clinical and imaging prognostic determinants (*Graphical abstract*). Patients carrying this specific additional risk pattern could potentially benefit more from treatments targeted to improve metabolic dysregulation[21,22] and to counteract the effects of enhanced systemic inflammation.[23,24]

Serum TGs and the TyG index have been associated with the presence and extent of coronary atherosclerosis,[25,26] as well as with its progression over time and with patient outcomes.[15] Elevated TGs are often associated with small-dense LDL particles, low and dysfunctional HDL cholesterol particles. This pattern has pro-atherogenic and pro-inflammatory effects[9,27] and is often found before the development of overt hyperglycaemia.[28] The TyG index might identify such atherogenic cardio-metabolic risk profile before the onset of overt diabetes. In the present study, patients with higher TyG values at enrolment had an increased risk of cardiac events over an almost 5-year follow-up independently of the presence of diabetes, cholesterol levels, known CAD, and myocardial dysfunction. Interestingly, in this population at relative high risk of cardiac events (~10% at 5 years), the presence of moderate–severe stress perfusion abnormality at MPS but not the presence of obstructive CAD at coronary angiography or early revascularization retained an independent prognostic power.

In the present study, we also explored the possible additional prognostic value of systemic inflammation. Chronic inflammation can promote plaque formation and expansion by acting synergistically with other cardiovascular risk factors.[29] In patients with a history of MI or CCS, the use of anti-inflammatory treatments caused a significant reduction in major adverse cardiovascular events despite no effects on the lipid profile.[23,30] In our study, systemic inflammatory activation as shown by higher values of hs-CRP, and the cardiometabolic risk expressed by a higher TyG index identified patients with higher risk of all-cause mortality. It is interesting to consider that a relationship between higher hs-CRP and risk of all-cause mortality has been consistently reported in patients with CAD[31] in particular in obese patients.[32]

Limitations

The AMICO study enrolled in a high-volume laboratory a large population of patients who underwent both an MPS study and an anatomical evaluation by CTCA and/or ICA. Since the enrolment started in 2010, the criteria for referring patients to coronary angiography may not completely conform to the current diagnostic flow chart for CCS.[1] Furthermore, there were no pre-established decisional criteria for the revascularization of coronary artery

Table 2 **Multivariable Cox regression analysis for primary and secondary end-points**

	Model 1				Model 2				Model 3				Model 4		
	P	HR	95% CI		*P*	HR	95% CI		*P*	HR	95% CI		*P*	HR	95% CI
Cardiac death or non-fatal MI															
Males	0.309	–	–	Males	0.349	–	–	Males	0.280	–	–	Males	0.208	–	–
MI/Rev	0.070	1.77	1.17–2.67	MI/Rev	0.013	1.71	1.12–2.60	MI/Rev	0.024	1.62	1.07–2.46	MI/Rev	0.069	–	–
LDL-C	0.026	1.01	1.00–1.01	LDL-C	0.041	1.01	1.00–1.01	LDL-C	0.048	1.01	1.00–1.01	LDL-C	0.873	–	–
LVEF	<0.001	0.97	0.95–0.98	LVEF	<0.001	0.97	0.95–0.98	LVEF	0.002	0.97	0.96–0.99	LVEF	0.003	0.98	0.96–0.99
				Ob CAD	0.396	–	–	Ob CAD	0.870	–	–	Ob CAD	0.438	–	–
								SSS > 7	0.014	2.12	1.17–3.84	SSS > 7	0.007	2.29	1.25–4.18
												hs-CRP	0.073	–	–
												TyG	<0.001	2.41	1.55–3.75
All-cause death															
Males	0.197	–	–	Males	0.188	–	–	Males	0.186	–	–	Males	0.411	–	–
MI/Rev	0.123	–	–	MI/Rev	0.167	–	–	MI/Rev	0.189	–	–	MI/Rev	0.814	–	–
LDL-C	<0.001	1.01	1.01–1.02	LDL-C	<0.001	1.01	1.01–1.02	LDL-C	<0.001	1.01	1.01–1.02	LDL-C	0.517	–	–
LVEF	<0.001	0.93	0.91–0.94	LVEF	<0.001	0.93	0.91–0.94	LVEF	<0.001	0.93	0.91–0.94	LVEF	<0.001	0.94	0.92–0.96
				Ob CAD	0.698	–	–	Ob CAD	0.743	–	–	Ob CAD	0.216	–	–
								SSS > 7	0.871	–	–	SSS > 7	0.305	2.29	1.25–4.18
												hs-CRP	<0.001	1.12	1.05–1.19
												TyG	<0.001	3.88	2.35–6.41

See Methods for definitions. Model 1: male gender, previous MI and/or coronary revascularization, LDL cholesterol, LVEF; Model 2: Model 1 + obstructive CAD; Model 3: Model 2 + SSS >7; Model 4: Model 3 + hs-CRP + TyG index.
CI, confidence interval; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI/Rev, Previous MI and/or coronary revascularization; Ob CAD, obstructive coronary artery disease; SSS, summed stress score; TyG index, triglyceride-glucose index.

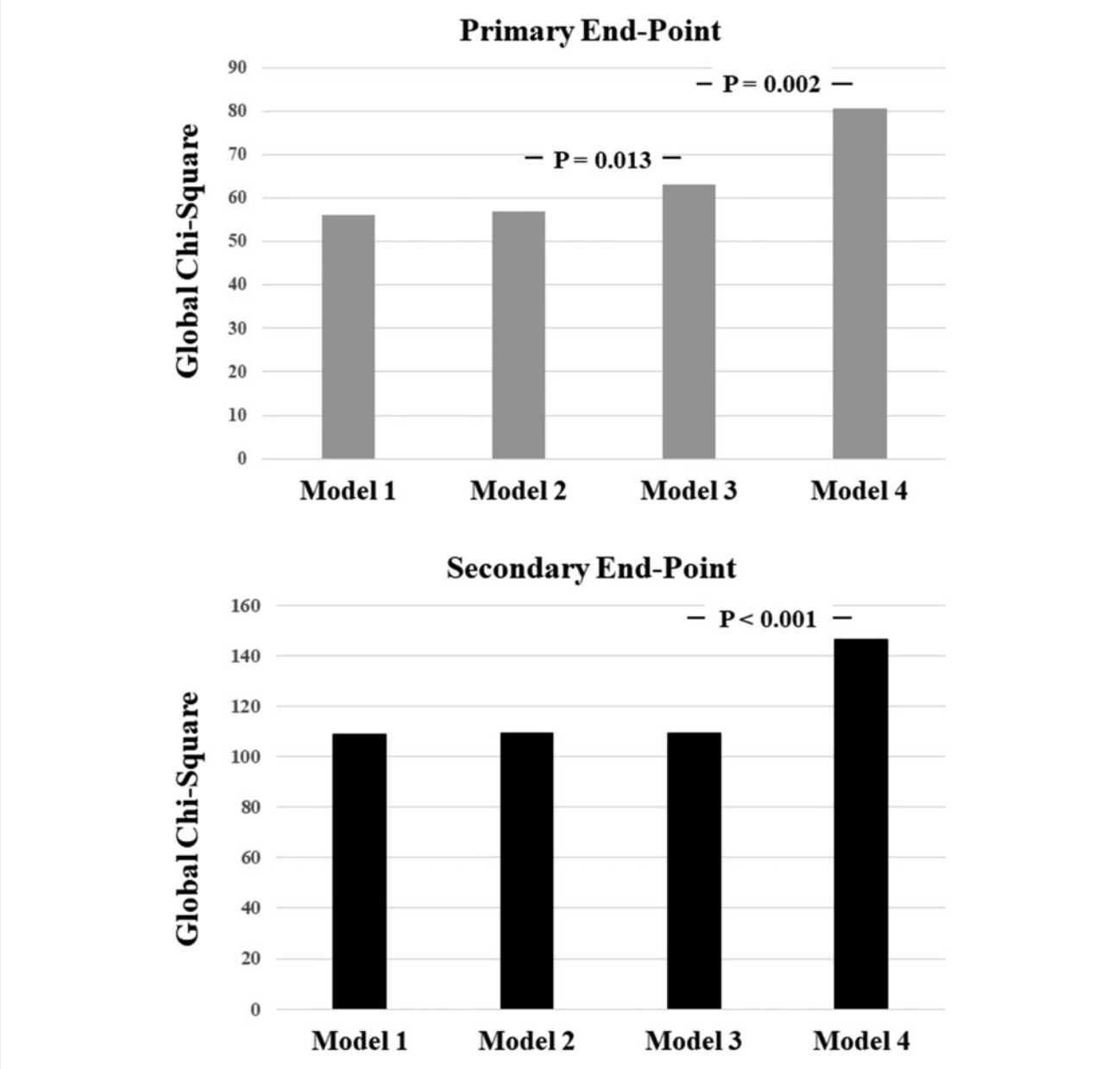


Figure 2 Incremental predictive models including triglyceride-glucose index and high-sensitivity C-reactive protein. At multivariable Cox regression analysis, the univariable predictors of the primary and/or secondary end-points were used to build incremental prognostic models. Chi-square values are reported for each of four models (see *Table 2* for model details) and for either the primary end-point (upper panel) or the secondary end-point (lower panel). The addition of the triglyceride-glucose index and high-sensitivity C-reactive protein to clinical and imaging variables (Model 4) significantly increased the prognostic power for cardiac events or all-cause death.

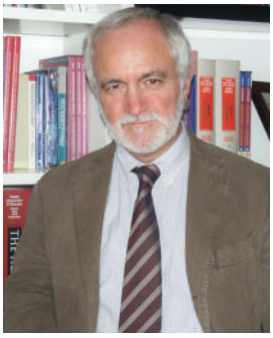
stenoses >70%, and the need for revascularization of single lesions was established by the interventional cardiologist taking into account results from the assessment of myocardial viability and ischaemia, according to common practice. The information on medical treatment was obtained at enrolment and reflected the clinical management before diagnostic evaluation. Details on medical treatment changes during the follow-up period which could have influenced outcome were not available.

Conclusions

In patients with CCS, the TyG index identifies a cardiometabolic profile associated with an additional risk of cardiac events, over the presence of myocardial ischaemia and independently of other clinical, common bio-humoral or imaging risk determinants. Together with systemic inflammation, it is also a strong predictor of all-cause death. Further studies would be needed to establish whether patients with a higher TyG index could benefit more from treatments targeted to

improve metabolic dysregulation and to counteract the effects of enhanced systemic inflammation.

Lead author biography



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Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Data availability statement

Raw data were generated at Fondazione CNR/Regione Toscana, Pisa, Italy. The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Declaration of Helsinki

The authors state that this study complies with the Declaration of Helsinki, that the locally appointed ethics committees have approved the research protocol and that informed consent has been obtained from the subjects (or their legally authorized representative).

Conflict of interest: none declared.

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