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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Patients with chronic coronary symptoms were characterized by clinical variables, risk factors and common biomarkers. 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 triglyceride-glucose index stratified the risk of cardiac events. The multivariable predictive model including triglyceride-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. 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. This strategy has been challenged by the recent finding that myocardial ischaemia may not independently predict outcome in patients with chronic coronary syndromes (CCS), and that revascularization of obstructive CAD may not be superior to optimal medical therapy (OMT) even in patients with documented ischaemia. 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.

Besides LDL cholesterol, plasma triglycerides (TGs) may contribute to the atherosclerosis process. Higher TGs levels have been associated with type 2 diabetes mellitus, obesity and high fasting plasma glucose (FPG) as well as with cardiac events in the general populations, and in patients on statins after an acute coronary syndrome (ACS). A TG-glucose (TyG) index, proposed as a surrogate marker of insulin resistance (IR), predicted cardiac events in the general population, and the progression of coronary atherosclerosis in patients with known disease, 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. 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. 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, and moderately/severely abnormal by SSS >7 (involving >10% of LV myocardium). 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. 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.

Clinical and laboratory characterization

All patients underwent a thorough clinical and laboratory characterization within 1 month from MPS, as previously described. 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 according to 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. 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/r). Estimated glomerular filtration rate was calculated through the Chronic Kidney Disease Epidemiology Collaboration equation.

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 conditions.
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 (25–75th 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.\(^\text{16}\)

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 I  Patients characteristics

| Clinical characteristics and risk factors | Whole cohort, \( n = 1097 \) | Cardiac death or non-fatal MI | All-cause death | \( P \) | \( P \) |
|------------------------------------------|-----------------|------------------|-----------------|------|------|
| Age (years)                              | 72 (64–77)      | 71 (64–79)       | 72 (64–77)      | 0.929 | 0.929 |
| Males, \( n \)                           | 821 (75)        | 87 (85)          | 734 (74)        | 0.018 | 0.488 |
| NYHA class I, II, III, \( n \)           | 803, 279, 15    | 61, 38, 4        | 742, 241, 11    | 0.001 | <0.001 |
| Typical angina, \( n \)                  | 493 (45)        | 42 (41)          | 451 (45)        | 0.372 | 0.957 |
| Family history of CAD, \( n \)           | 500 (46)        | 40 (39)          | 460 (46)        | 0.149 | 0.897 |
| Previous MI and/or coronary revascularization, \( n \) | 284 (26) | 49 (48) | 235 (24) | 0.001 | <0.001 |
| Current smoker, \( n \)                  | 302 (28)        | 24 (23)          | 278 (28)        | 0.578 | 0.265 |
| Hypertension, \( n \)                    | 666 (61)        | 68 (66)          | 598 (60)        | 0.247 | 0.506 |
| Hypercholesterolaemia, \( n \)           | 571 (52)        | 61 (59)          | 510 (51)        | 0.126 | 0.286 |
| Diabetes, \( n \)                         | 430 (39)        | 43 (42)          | 387 (39)        | 0.578 | 0.148 |
| Obesity, \( n \)                          | 315 (29)        | 41 (40)          | 274 (28)        | 0.009 | 0.509 |
| BMI (kg/m²)                               | 28 (25–31)      | 28 (26–33)       | 28 (25–31)      | 0.012 | 0.012 |
| Atrial fibrillation, \( n \)              | 144 (13)        | 18 (18)          | 126 (13)        | 0.170 | 0.001 |
| eGFR (mL/min/1.73 m²)                     | 69 (54–84)      | 72 (57–85)       | 69 (54–84)      | 0.380 | 0.380 |
| Statins, \( n \)                          | 524/1,057 (50)  | 53/101 (53)      | 471/956 (49)    | 0.086 | 0.954 |
| Aspirin, \( n \)                          | 847/1,057 (80)  | 90/101 (89)      | 757/956 (79)    | 0.017 | 0.115 |
| Beta-blockers, \( n \)                    | 664/1,057 (63)  | 74/101 (73)      | 590/956 (62)    | 0.022 | 0.007 |
| CCBs, \( n \)                             | 186/1,057 (18)  | 14/101 (14)      | 172/956 (18)    | 0.300 | 0.136 |
| ACEi/ARB, \( n \)                         | 742/1,057 (70)  | 70/101 (69)      | 672/956 (71)    | 0.120 | 0.542 |
| Nitrates, \( n \)                         | 111/1,057 (11)  | 9/101 (9)        | 102/956 (11)    | 0.584 | 0.624 |
| Diuretics, \( n \)                        | 481/1,057 (46)  | 64/101 (63)      | 417/956 (44)    | <0.001 | 0.001 |
| Exercise/dipyridamole, \( n \)            | 748/351 (68/32) | 64/39 (62/38)    | 685/309 (69/31) | 0.168 | 0.320 |
| Workload (W)                              | 100 (100–125)   | 100 (100–125)    | 100 (75–125)    | 0.695 | 0.707 |
| LVEF rest (%)                             | 59 (48–66)      | 51 (31–63)       | 60 (50–67)      | 0.001 | 0.001 |
| LVEF <50%, \( n \)                        | 293 (27)        | 50 (49)          | 143 (24)        | <0.001 | 0.250 |
| SSS                                       | 8 (5–12)        | 12 (8–18)        | 8 (4–12)        | <0.001 | 0.250 |
| SRS                                        | 2 (0–5)         | 4 (1–13)         | 2 (0–5)         | <0.001 | 0.001 |
| SDS                                        | 5 (3–8)         | 6 (4–8)          | 5 (3–7)         | 0.021 | 0.899 |
| SSS >7, \( n \)                            | 660 (60)        | 86 (84)          | 574 (58)        | <0.001 | 0.001 |
| Coronary angiography                      | 813 (74)        | 85 (82)          | 728 (73)        | 0.041 | 0.264 |
| Obstructive CAD, \( n \)                  | 284, 437, 247, 129 | 18, 40, 23, 22 | 266, 397, 224, 107 | 0.007 | 0.001 |
| Early revascularization, \( n \)          | 395 (36)        | 37 (36)          | 358 (36)        | 0.985 | 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.
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 and to counteract the effects of enhanced systemic inflammation.

Serum TGs and the TyG index have been associated with the presence and extent of coronary atherosclerosis, as well as with its progression over time and with patient outcomes. 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 and is often found before the onset of overt hyperglycaemia. 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. 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. 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 in particular in obese patients.

**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. 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 | Cardiac death or non-fatal MI | Cardiac death or non-fatal MI | Cardiac death or non-fatal MI |
| Males 0.309 – –          | Males 0.349 – –          | Males 0.280 – –          | Males 0.208 – –          |
| LDL-C 0.070 1.77 1.17–2.67 | LDL-C 0.013 1.71 1.12–2.60 | LDL-C 0.024 1.62 1.07–2.46 | LDL-C 0.069 – –          |
| LVEF <0.001 0.97 0.95–0.98 | LVEF <0.001 0.97 0.95–0.98 | LVEF <0.001 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 – –        | Ob CAD 0.873 – –        |
| MI/Rev 0.013 1.71 1.12–2.60 | MI/Rev 0.048 1.01 1.00–1.01 | 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 <0.001 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 – –        | Ob CAD 0.873 – –        |
| SSS > 7 0.014 2.12 1.17–3.84 | SSS > 7 0.014 2.12 1.17–3.84 | SSS > 7 0.014 2.12 1.17–3.84 | SSS > 7 0.014 2.12 1.17–3.84 |
| LVEF <0.001 0.97 0.95–0.98 | LVEF <0.001 0.97 0.95–0.98 | LVEF <0.001 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 – –        | Ob CAD 0.873 – –        |
| SSS > 7 0.014 2.12 1.17–3.84 | SSS > 7 0.014 2.12 1.17–3.84 | SSS > 7 0.014 2.12 1.17–3.84 | SSS > 7 0.014 2.12 1.17–3.84 |
| All-cause death          | All-cause death          | All-cause death          | 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 0.93 0.91–0.94 |
| Ob CAD 0.698 – –        | Ob CAD 0.743 – –        | Ob CAD 0.216 – –        | Ob CAD 0.873 – –        |
| SSS > 7 0.871 – –       | SSS > 7 0.871 – –       | SSS > 7 0.871 – –       | SSS > 7 0.871 – –       |
| hs-CRP <0.001 1.12 1.05–1.19 | hs-CRP <0.001 1.12 1.05–1.19 | hs-CRP <0.001 1.12 1.05–1.19 | hs-CRP <0.001 1.12 1.05–1.19 |
| TyG <0.001 3.88 2.35–6.41 | TyG <0.001 3.88 2.35–6.41 | TyG <0.001 3.88 2.35–6.41 | 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.
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

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

Lead author biography

Dr. Danilo Neglia is a cardiologist and a nuclear medicine specialist. He is a director of Multimodality Cardiovascular Imaging Program at Fondazione CNR/Regione Toscana in Pisa and a Faculty Member of the PhD Programme in Translational Medicine of Scuola Superiore Sant’Anna in Pisa. His research activity was recently focused on the applications of cardiovascular imaging in coronary artery disease with specific interest in the relationships between cardiovascular risk factors, biomarkers, coronary vascular function, and outcome. He coordinated national and international collaborative research projects in multimodal cardiac imaging such as the EVINCI study and the EURECA Registry within the ESC-EURObservational Research Programme.

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.

References

1. Knust J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Denton C, Cuijpers T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Sivil P, Glodar M, Hasiad D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407–477.
2. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetta U, Byrne RA, Collet J-P, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Sefirovic PM, Sibbing D, Stefani FF, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularisation. Eur Heart J 2019;40:87–165.
3. Hoffmann U, Ferenick M, Udelson JE, Picard MH, Truong QA, Patel MR, Huang M, DNC, Pencina M, Mark DB, Heitner JF, Fordyce CB, Pellikka PA, Tardif JC, Budoff MJ, Nkhasi G, Chow B, Kosinski AS, Lee KL, Douglas PS. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE Trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). Circulation 2017;135:2370–2372.
4. Neglia D, Liga R, Caselli C, Carpeggiani C, Lorenzi V, Sicari R, Lombardi M, Gaemperli O, Kauffman PA, Scholte Atha, Underwood SR, Knuuti J; EVINCI Study Investigators. Anatomical and functional coronary imaging to predict long-term outcome in patients with suspected coronary artery disease: the EVINCI-outcome study. Eur Heart J Cardiovasc Imaging 2020;21:1273–1282.
5. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O’Brien SM, Boden WE, Chairman BR, Senior R, López-Sendón J, Alexander KP, Lopes RD, Shaw LJ, Berger JS, Newman JD, Sithu MS, Goodman SG, Ruyzlo W, Gosselin G, Maggioni AP, White HD, Bhargava B, Min JK, Mancini GBJ, Berman DS, Picard MH, Kwon RY, Ali ZA, Mark DB, Speratus JA, Krishnan MH, Ehlazemi A, Moonrly N, Hue WA, Demkow M, Mavromatis K, Bockersia O, Peterso J, Miller TD, Siew H, Doerr R, Keltia M, Selvanayagam J, Steg PG, Held C, Kohsaka O, Mavromichalis S, Kirby R, Jeffries NO, Harrell FE, Rockhold FW, Broderick O, Ferguson TB, Williams DO, Harrington RA, Stone GW, Rosenberg Y. Initial invasive or conservative strategy for stable coronary disease. N Engl J Med 2020;382:1395–1407.
6. Adamson PD, Williams MC, Dweck MR, Mills NL, Boon NA, Daghmeh M, Bing R, Misaj Morgan K, Flather M, Forbes J, Hunter A, Nurrone J, Shah ASV, Timmis AD, van Beek EJ, Ahmed AA, Lepić J, Narula J, Newby DE, Radotić G, McAllister DA, Berry C. Guiding therapy by coronary CT angiography improves outcomes in patients with stable chest pain. J Am Coll Cardiol 2019;74:2058–2070.
7. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumthals RS, Braun LT, de Ferranti S, Faella-Tommasino J, Forman DE, Goldberg R, Hendebrink PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Nduume CE, O’Rinnge CE, Peralta CA, Saseen JI, Smith SC, Jr, Sperling L, Virani SS, Yehab Y. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;139:e1082–e1143.
8. Mach F, Baigent C, Catapano AL, Casas JP, Chadban SJ, Dammer EB, de Bruijn PC, de Groot I, de Zeeuw D, de Zeeuw P, Durrington PN, Egan B, Feenstra AR, Friedewald WT, Fruge AU, Goldfus AM, Halsey G, Hegele RA, Hishida T, Hongo T, Hukuhara T, Imai Y, Ikram MA, Janszky I, Januzzi JL, Jukema JW, Kollerits B, Knecht C, Kupel W, Lindermann T, Luscher TF, Mann JIF, Mancia G, Mbanya JC, Mehta RA, Micevski I, Moe CS, Mora S, Mustard EA, Niebauer J, Nicolosi A, Niskanen LA, Orchard TJ, O’Leary TW, Orsi J, Pajkrt E, Paterson A, Pedersen S, Peimoudi H, Prabhakaran D, Prinster J, Quasim J, Rolland V, Rubenfire M, Sacco RL, Schlett CL, Schimpf SS, Schuiteman A, Silapanaseth S, Sinaiko AR, Smit JH, Tsimi J, Volger M, Wallace RB, Wang TJ, Wang Y, Wilhem S, Williams K, Wilson PW, Yusuf S, Yusuf R, Zuberi K, Zamorano JL, Zhou J. 2018 ACC/AHA/ACP/EAP/AAPA/ABC/ACEP/ADA/AJPCNP/AMSA/ASPC/NLA/PCNA guideline on the management of dyslipidemia: lipid modification to reduce cardiovascular risk. J Am Coll Cardiol 2020;76:1111–1188.
9. Laufs U, Parhofer KG, Ginsberg HN, Hegele RA. Clinical review on triglycerides. Eur Heart J 2020;41:99–109c.
10. Castaño O, Pintó X, Subirana I, Amor AJ, Ros E, Hernández A, Martínez-González MA, Corella D, Salar-Salvador J, Estruch R, Lapetra J, Gómez-Graña E, Alonso-Gomez AP, Fiol M, Sierra-Majem L, Corbella E, Benajes D, Sorlí JV, Ruiz-Canela M, Badií N, Sierra-LT, Ortega E, Frisén M. Remnant cholesterol, not LDL cholesterol, is associated with incident cardiovascular disease. J Am Coll Cardiol 2020;76:2712–2724.
11. Burnett JR, Hooper AJ, Hegele RA. Remnant cholesterol and atherosclerotic cardiovascular disease risk. J Am Coll Cardiol 2020;76:2736–2739.
12. Schwartz GG, Abt M, Bao W, DeMicco D, Kallend D, Miller M, Mundh H, Olsson AG. Fasting triglycerides predict recurrent ischemic events in patients with acute coronary syndrome treated with statins. J Am Coll Cardiol 2015;65:2267–2275.
13. Guerrero-Romero F, Simental-Mendia LE, González-Ortiz M, Martínez-Abundis E, Ramos-Zavala MG, Hernández-González SO, Jacques-Camarena O, Davies-Jones G, Rodríguez-Morán M. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. J Clin Endocrinol Metab 2010;95:3347–3351.
14. Hong S, Han J, Park CY. The triglyceride glucose index is a simple and low-cost marker associated with atherosclerotic cardiovascular disease: a population-based study. BMC Med 2020;18:361.
15. Won K-B, Lee BK, Park H-B, Heo R, Lee S-E, Razi A, Lin FY, Kumar A, Hadaimitzky M, Kim Y-J, Sung JM, Comte E, Andreini D, Pontone G, Budoff MJ, Gottlieb I, Chun EJ, Cademartiri F, Maffei E, Marques H, de Araújo Gonçalves P, Leonardo JA, Shin S, Choi JH, Virrucci R, Sabadý H, Chinainan K, Ralf RG, Park CH, Berman DS, Narula J, Shaw LJ, Bax JJ, Min K, Chang HJ. Quantitative assessment of coronary plaque volume change related to triglyceride-glucose index;
The Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging (PARADIGM) registry. Cardiovasc Diabetol 2020;19:113.

16. Gimelli A, Pugliese NR, Buechel RR, Ccezani M, Clemente A, Kaufmann PA, Marzullo P. Myocardial perfusion scintigraphy for risk stratification of patients with coronary artery disease: the AMICO registry. *Eur Heart J Cardiovasc Imaging* 2020. 10.1093/ehjci/zej298.

17. Gimelli A, Sega R, Duce V, Kusch A, Clemente A, Marzullo P. Accuracy of myocardial perfusion imaging in detecting multivessel coronary artery disease: a cardiac CZT study. *J Nucl Cardiol* 2017;24:687–695.

18. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502.

19. Simental-Mendiá LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Met Syndr Rel Dis* 2008;6:299–304.

20. Levey AS, Stevens LA, Schmid CH, Zhang Y(L), Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lentie F, Greene T, Coresh J; for the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Int Med* 2009;150:604–612.

21. Samsoondar JP, Burke AC, Sutherland BG, Telford DE, Sawyez CG, Edwards JY, Pinkosky SL, Newton RS, Huff MW. Prevention of diet-induced metabolic dysregulation, inflammation, and atherosclerosis in Ldlr(-/-) mice by treatment with the ATP-citrate lyase inhibitor bempedoic acid. *Arter Tromb Vasc Biol* 2017;37:647–656.

22. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT, Juliano RA, Jiao L, Granowitz C, Tardif J-C, Ballantyne CM. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med* 2019;380:11–22.

23. Nidorf SM, Fiolet ATL, Mastorod A, Eikelboom JW, Schut A, Opstal TSJ. The SHK, Xuf X-F, Ireland MA, Lenderink T, Latchen D, Hoogslag P, Jerzemski A, Nierop P, Whelan A, Hendriks R, Swart J, Kuijper JGP, van Hessen MWJ, Schlaks P, Tan I, Thompson AG, Morton A, Judkins C, Bax WA, Dirkse M, Alings M, Hankey GJ, Budgeon CA, Tijsjen JGP, Cornel JH, Thompson PL. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020;383:1838–1847.

24. Aimo A, Pascual Figal DA, Bayes-Genis A, Erdin M, Georgiopoulos G. Effect of low-dose colchicine in acute and chronic coronary syndromes: a systematic review and meta-analysis. *Eur J Clin Invest* 2021;51:e13464.

25. Kim MK, Ahn CW, Kang S, Nam JS, Kim KR, Park JS. Relationship between the triglyceride glucose index and coronary artery calcification in Korean adults. *Cardiov Diabetol* 2017;16:108.

26. Won K-B, Kim YS, Lee BK, Heo R, Han D, Lee JH, Lee S-E, Sung JM, Cho I, Park H-B, Cho I-J, Chang H-J. The relationship of insulin resistance estimated by triglyceride glucose index and coronary plaque characteristics. *Medicine* 2018;e10726.

27. Welty PK. How do elevated triglycerides and low HDL-cholesterol affect inflammation and atherothrombosis? *Curr Cardiol Rep* 2012;14:400.

28. Sánchez－Ilgico L, Navarro-González D, Fernández-Montero A, Pastrana-Delgado J, Martinez JA. The TyG index may predict the development of cardiovascular events. *Eur J Clin Invest* 2016;46:189–197.

29. Lawler PR, Bhatt DL, Godoy LC, Lüscher TF, Bonow RO, Verma S, Ridker PM. Targeting cardiovascular inflammation: next steps in clinical translation. *Targeting cardiovascular inflammation: next steps in clinical translation. Eur Heart J* 2021;42:113–131.

30. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne CM, Fonseca F, Nicolau J, Keenig W, Anker SD, Kastelein JJP, Cornel JH, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Rather M, Shimokawa H, Oga H, Dillingberg M, Rossi PRF, Touquay RPT, Libby P, Glynn R. Antinflammatory therapy with canakinumab for atherosclerotic disease. *N Eng J Med* 2017;377:1119–1131. 10.1093/ehjci/zej298.

31. Luo F, Feng C, Zhou C. C-reactive protein and all-cause mortality in patients with stable coronary artery disease: a secondary analysis based on a retrospective cohort study. *Med Sci Mon* 2019;25:9820–9828.

32. Ding D, Wang M, Su D, Hong C, Li X, Yang Y, Zhang Y, Hu G, Ling W. Body mass index, high-sensitivity C-reactive protein and mortality in Chinese with coronary artery disease. *PLoS One* 2015;10:e0135713.