Rapid plaque progression is independently associated with hyperglycemia and low HDL cholesterol in patients with stable coronary artery disease: a PARADIGM study

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ORIGINAL ARTICLE

Rapid Plaque Progression Is Independently Associated With Hyperglycemia and Low HDL Cholesterol in Patients With Stable Coronary Artery Disease: A PARADIGM Study

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BACKGROUND: We assessed whether combinations of cardiometabolic risk factors independently predict coronary plaque progression (PP) and major adverse cardiovascular events in patients with stable coronary artery disease.

METHODS: Patients with known or suspected stable coronary artery disease (60.9±9.3 years, 55.4% male) undergoing serial coronary computed tomography angiographies (≥2 years apart), with clinical characterization and follow-up (N=1200), were analyzed from the PARADIGM study (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging). Plaque volumes measured in coronary segments (≥2 mm in diameter) were summed to provide whole heart plaque volume (mm^3) and percent atheroma volume (plaque volume/vessel volume×100; %) per patient at baseline and follow-up. Rapid PP was defined as a percent atheroma volume increase of ≥1.0%/y. Major adverse cardiovascular events included nonfatal myocardial infarction, death, and unplanned coronary revascularization.

RESULTS: In an interscan period of 3.2 years (interquartile range, 1.9), rapid PP occurred in 341 patients (28%). At multivariable analysis, the combination of cardiometabolic risk factors defined as metabolic syndrome predicted rapid PP (odds ratio, 1.51 [95% CI, 1.12–2.03]; *P*=0.007) together with older age, smoking habits, and baseline percent atheroma volume. Among single cardiometabolic variables, high fasting plasma glucose (diabetes or fasting plasma glucose >100 mg/dL) and low HDL-C (high-density lipoprotein cholesterol; <40 mg/dL in males and <50 mg/dL in females) were independently associated with rapid PP, in particular when combined (odds ratio, 2.37 [95% CI, 1.56–3.61]; *P*<0.001). In a follow-up of 8.23 years (interquartile range, 5.92–9.53), major adverse cardiovascular events occurred in 201 patients (17%). At multivariable Cox analysis, the combination of high fasting plasma glucose with high systemic blood pressure (treated hypertension or systemic blood pressure >130/85 mm Hg) was an independent predictor of events (hazard ratio, 1.79 [95% CI, 1.10–2.90]; *P*=0.018) together with family history, baseline percent atheroma volume, and rapid PP.

CONCLUSIONS: In patients with stable coronary artery disease, the combination of hyperglycemia with low HDL-C is associated with rapid PP independently of other risk factors, baseline plaque burden, and treatment. The combination of hyperglycemia with high systemic blood pressure independently predicts the worse outcome beyond PP.

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See Editorial by Matuck and Arbab-Zadeh

CLINICAL PERSPECTIVE

The results of the present study highlight the relevance of specific cardiometabolic risk conditions for the progression of coronary atherosclerosis and cardiovascular outcome in patients with suspected or known stable coronary artery disease. The combination of hyperglycemia (expressing insulin resistance even in the absence of established type-2 diabetes) and low HDL-C (high-density lipoprotein cholesterol) is associated with the extent of coronary plaque burden and, independently of other risk factors, strongly and specifically predicts rapid plaque progression despite current treatment. These findings underline the relevance of early and more aggressive control of prediabetic and diabetic states in patients with coronary artery disease through lifestyle and pharmacological interventions. They also suggest the need for more extensive research to elucidate the mechanisms by which hyperglycemia and low HDL-C interact to cause an adverse cardiometabolic profile prone to atherogenesis. Hyperglycemia, in combination with hypertension, is also associated with an increased risk of future coronary artery disease-related events beyond the progression of coronary atherosclerosis. The present results confirm the persisting prognostic relevance of impaired glycemic control and hypertension, underscoring the need for a more aggressive treatment of cardiometabolic profiles and blood pressure levels to reduce the residual risk of cardiovascular events. New large clinical studies could be needed to test whether specific new treatments addressed to lower glucose levels and improve HDL and endothelial function would be particularly relevant to reducing the residual global burden of atherosclerotic cardiovascular disease.

Nonstandard Abbreviations and Acronyms

ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
CAD	coronary artery disease
CCTA	coronary computed tomography angiography
CPV	calcified plaque volume
CVD	cardiovascular diseases
FPG	fasting plasma glucose
HDL-C	high-density lipoprotein cholesterol
HU	Hounsfield units
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiac events
MeS	metabolic syndrome
NCPV	noncalcified plaque volume
PARADIGM	Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging
PAV	percent atheroma volume
PP	coronary plaque burden progression
PV	plaque volume
SBP	systemic blood pressure

Cardiovascular diseases (CVD) are still the major cause of death, and among them, ischemic heart disease is still the most prevalent, accounting for 9 440 000 deaths per year worldwide and for an estimated 185 000 000 disability-adjusted life years (years of life lost due to premature mortality plus years lived with disability).[1]

Atherosclerotic cardiovascular disease (ASCVD) is still the major cause of CVD morbidity and mortality, and the current guidelines on CVD prevention in clinical practice concentrate principally on the prevention of ASCVD and of ASCVD-related risk (10-year risk of fatal and nonfatal CVD events).[2] Interestingly, both in the worldwide report on global burden of CVD and in the European CVD prevention guidelines, the main modifiable CVD and ASCVD risk factors include high apolipoprotein-B-containing lipoproteins, of which LDL-C (low-density lipoprotein cholesterol) is the most abundant, high systemic blood pressure (SBP), cigarette smoking, and high fasting plasma glucose (FPG; prediabetes and type-2 diabetes under treatment).[1,2] These are considered the main targets for lifestyle change and for optimal medical treatment in patients with suspected or known ASCVD.[2]

Among these risk factors, the prevalence of high FPG has increased steeply in middle- and high-income countries[3] and is one of the relevant components of the cardiometabolic risk condition known as metabolic syndrome (MeS), defined by a variable combination of high

FPG, high triglycerides, low HDL-C (high-density lipoprotein cholesterol), high SBP, and central obesity,[4] most of which have been associated with the residual CVD risk, that is, the risk persisting despite optimal medical treatment.[5,6]

The relative role of cardiometabolic risk factors, compared with other established risk factors, to predict the presence, extent, and progression of coronary atherosclerosis and major adverse cardiac events (MACE) in current populations of patients with known or suspected stable coronary artery disease (CAD) under optimal medical treatment is not completely understood. Such information is crucial to discriminate, among patients who will benefit from a global cardiovascular prevention addressing multiple risk factors, those individuals in whom additional treatment targeting more aggressively specific risk determinants would produce additional benefit.

The recent diffusion of coronary computed tomography angiography (CCTA) as a tool to quantify and characterize coronary atherosclerosis and its progression offers the opportunity to better define the relative role of risk factors in the atherosclerotic process. Large registry data have demonstrated the association of major cardiovascular risk factors with the prevalence, severity, and extent of CAD estimated at CCTA as well as the additional prognostic value of CCTA beyond all risk factors such as age and sex.[7] The PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) is the largest serial CCTA registry to date using rigorous quantification methodology of coronary plaques and with a long-term follow-up for events available.[8] Its design allowed to demonstrate the impact of baseline plaque characteristics and some of the established risk factors such as age, sex, diabetes, obesity, or the integrated ASCVD risk score on coronary plaque progression[9–11] as well as the predictors of statin nonresponse.[12]

The present study aimed to assess whether specific combinations of emerging cardiometabolic risk determinants are able to predict coronary atherosclerotic plaque burden, coronary plaque burden progression (PP), and MACE, independently from established CVD risk factors, in patients with known or suspected stable CAD from the PARADIGM study.

METHODS

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

Study Design, Population, and Baseline Clinical Characterization

The PARADIGM study is a prospective, open-label, international, multicenter observational registry designed to evaluate the association between changes in coronary atherosclerotic plaque, assessed by serial CCTA, and clinical risk profiles, as well as their impact on MACE in patients with known or suspected CAD. The study rationale and design have been previously described in detail.[8] The study population includes 2252 adults who underwent serial CCTA for evaluation of suspected angina symptoms over an interscan period of at least 24 months at 13 cardiovascular centers in 7 countries. This study was approved by institutional review boards at each site, and participants gave informed consent.

Of the initial 2252 patients, a total of 1200 were included in the present study after the exclusion of patients with CCTA with inadequate image quality for quantitative plaque analysis (n=492) or a lack of available information on clinical events at follow-up (n=235) and on risk factors, circulating lipid profile, and statin use (n=325; Figure 1). Risk factor profile, laboratory data, and medication use were collected at the time of the first CCTA scan. Laboratory and statin use data were also collected at the time of the follow-up CCTA scan. The recorded noncardiometabolic risk factors included age, sex, family history of CVD, history of previous CAD, and smoking habits (previous or current tobacco smoking). The modifiable cardiometabolic risk factors were defined according to current international standards for CVD risk assessment[1] and, for the MeS components, according to the International Diabetes Federation[13] and the American Heart Association/National Heart, Lung, and Blood Institute[14] clinical definitions, as later agreed upon.[4,15] Annotations were based on patients' clinical records plus annotated treatment and, when appropriate, on available clinical and bio-humoral measurements. High LDL-C was defined

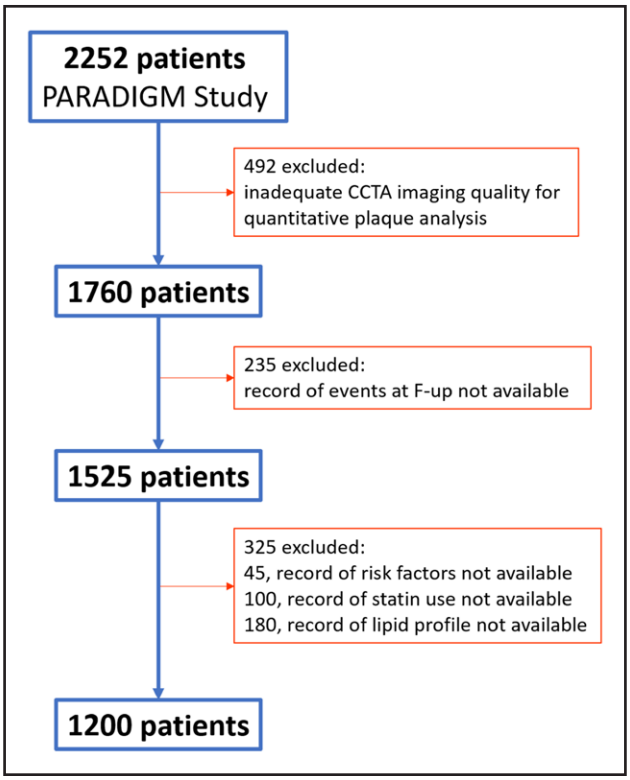

Figure 1. Patient flow chart.
Criteria for the selection of the present population of 1200 patients from the initial 2252 patients enrolled in the PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) study. CCTA indicates coronary computed tomography angiography; and F-up, follow-up.

as hypercholesterolemia under treatment with statins or other lipid-lowering drugs, or LDL-C >130 mg/dL. The MeS components included high SBP (hypertension under treatment or SBP >130/85 mm Hg), high FPG (FPG >100 mg/dL or diabetes, defined by treatment with hypoglycemic agents or insulin or FPG > 126 mg/dL), high body mass index (BMI; >30 kg/m^2), low HDL-C (<40 mg/dL in males and <50 mg/dL in females), and high triglycerides (>150 mg/dL). BMI was used instead of waist circumference, which was not available in the PARADIGM population. A BMI >25 kg/m^2 cutoff was also considered in a subanalysis to account for a more adequate threshold for the majority of patients enrolled in the PARADIGM study who were of East Asian ethnicity[16] and in line with the International Diabetes Federation guidelines underlying the difficulty of choosing cutoff values for waist measurements, and for BMI, in different ethnic groups.[4] The presence of MeS was defined by the combination in each patient of at least 3 of the following: high SBP, high BMI as a proxy for obesity, high FPG, high triglycerides, and low HDL-C.[4,15]

Coronary CCTA Data Measurements and Analysis

All data acquisition and postprocessing of CCTA exams were in accordance with the Society of Cardiovascular Computed Tomography guidelines.[17,18] Scans were performed using ≥64-detector row single- or dual-source scanners, with multiple vendors, using both prospective and retrospective gating. DICOM (Digital Imaging and Communications in Medicine) files from baseline and follow-up CCTAs were transferred to a Central Core Laboratory for blind analysis of coronary atherosclerosis as previously described.[19] Quantitative plaque analysis was performed by independent level III-experienced CCTA readers, blinded to the clinical results, using a semi-automated plaque analysis software, with manual correction (QAngioCT Research Edition v2.1.9.1, Medis Medical Imaging Systems, Leiden, the Netherlands), which has shown excellent intraobserver, inter-observer, and interscan reproducibility in previous studies[20,21] and in the PARADIGM population.[19] Per segment and per lesion analysis were performed for coronary plaque, lumen, and vessel in all coronary artery segments ≥2 mm in diameter from the coronary tree. The presence of atherosclerosis was defined as any tissue ≥1 mm^2 within or adjacent to the lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or lumen and identified in >2 planes.[17,22] Fiduciary landmarks were used for co-registration of segments and lesions as previously described.[19] Nonevaluable segments in either baseline or follow-up CCTAs were excluded pairwise for plaque progression analyses to obtain the same number of evaluated coronary segments at the 2 CCTA scans. Segments that had been stented between the 2 CCTAs were excluded in both scans. Segmental data were summed to per-patient level according to a modified 17-segment coronary tree model.[17] For the present analysis, only per-patient data were used. Regardless of the presence of atherosclerotic plaques, plaque volume (PV; mm^3) of every coronary segment (PV=vessel volume−lumen volume) was summed to generate the whole heart PV per patient. Coronary plaques were further classified by composition according to the predefined intensity cutoffs in Hounsfield units (HU) for calcified plaques (>350 HU), fibrous plaques (131–350 HU), fibro-fatty plaques (31–130 HU), and necrotic cores (−30 to 30 HU).[23,24] Noncalcified PV (NCPV) per patient was defined as the sum of PV of plaques with ≤350 HU and calcified PV per patient as the sum of PV of plaques >350 HU. Change in whole heart PV, NCPV, and calcified PV per patient was obtained as PVs at follow-up CCTA minus PVs at baseline CCTA. Annual change of PV, NCPV and calcified PV per patient (mm^3/y) was defined as PVs change divided by interscan period. For the present analysis, whole heart percent atheroma volume (PAV=PV/vessel volume×100) per patient was chosen as the primary index of atherosclerotic plaque burden according to a prior analysis showing the lowest variance of this measure.[25] Annual change of whole heart PAV (%/y) was defined as PAV divided by interscan period.

Study End Points

The first objective of the present analysis was to explore the relative role of single and combined cardiometabolic risk factors, in particular MeS and its components, together with other CVD risk factors as determinants of coronary plaque burden and its progression. To this aim, the first end point was chosen as an annual change in whole heart PAV ≥1%/y as an indicator of rapid PP.[10]

The second objective was to assess the relative impact of the same single and combined risk factors, together with plaque burden and rapid PP, on clinical outcome. To this aim, the outcome end point was MACE, defined as the occurrence of nonfatal myocardial infarction, death, or unplanned, symptom-driven revascularization. Unplanned revascularization was defined as a procedure performed >30 days from any CCTA exam. Patients experiencing events in the interscan period between the baseline and follow-up CCTA scans were not omitted from the main analysis.

Statistical Analysis

Continuous variables are expressed as mean±SD. Plaque data are expressed as median with interquartile range because of their left-skewed distribution. Categorical variables are presented as absolute values (percentage). In patient groups stratified for presence/absence of the MeS, continuous data were compared with the Mann-Whitney *U* test, or Kruskal-Wallis test for unpaired data, and Wilcoxon signed-rank test for paired data, as appropriate. Categorical variables were compared with χ^2 test or McNemar test, as appropriate. Univariate and multivariable linear regression analyses were performed to identify the association of single or combined cardiometabolic risk factors and other clinical risk factors with baseline plaque burden (PAV), while univariate and multivariable logistic regression analyses were used to estimate their independent predictive role in rapid PP. The selection of variables for the multivariate analysis was performed using a clinical criterium, considering all the CVD risk factors. All analyses were corrected for statin treatment at baseline. Supplementary analyses for predictors of rapid PP were also performed: (1) using BMI >25 kg/m^2 as a proxy for obesity; (2) in male or female patients; and (3) in patients without an established diagnosis of diabetes (as defined by treatment with hypoglycemic agents or insulin or FPG >126 mg/dL). Additional supplementary analyses for predictors of baseline PAV and of rapid PP were also performed, adjusting for all medical therapy at baseline and for statin treatment at follow-up CCTA, respectively.

The ability of the single cardiometabolic risk factors to predict patient outcome was assessed using Kaplan-Meier curves, and multivariable Cox analyses were performed to evaluate the independent predictive role of single or combined cardiometabolic risk factors and other clinical risk factors on MACE without or with the inclusion of baseline PAV and rapid PP in the models. All analyses were adjusted for statin treatment at baseline. The Statistical Package for the Social Sciences version 19 (SPSS, Chicago, IL) was used. A $P<0.05$ was considered statistically significant for all analyses.

RESULTS

Patients Characteristics

The mean age of the 1200 patients (665 males, 55%) was 60±9 years. Ethnicity was East Asian (92%) or White (8%). A family history of CVD was present in 26% of patients. The clinical presentation at the time of baseline CCTA included stable chest pain (84%), mainly atypical or noncardiac than typical (70% and 9% versus 5%), dyspnea (7%), while 9% of patients were asymptomatic. Among modifiable CVD risk factors, previous CAD was present in 16%, smoking habits in 40%, and high LDL-C in 29%. Among cardiometabolic CVD risk factors, which are also components of the MeS, high SBP and high FPG were the most frequent (62% and 53%, respectively), followed by low HDL-C, high triglycerides, and high BMI (37%, 34%, and 5%, respectively). The majority of patients were under medical treatment at the time of the baseline CCTA (79%), and, among treatments, aspirin and statins were the most frequent (50% and 48%, respectively), followed by antihypertensive drugs (ranging from 34% to 31%), antidiabetics (13%), nitrates (11%), and diuretics (10%).

The combination of at least 3 cardiometabolic risk factors identifying the MeS was observed in 366 patients (31%). The clinical characteristics, risk factors, medication use, and bio-humoral profiles in the whole population and in patients grouped according to presence/absence of MeS are presented in Table 1. Patients with MeS were older and more frequently female than patients without. They had a lower frequency of high LDL-C and a higher frequency of high SBP, high FPG, low HDL-C, high triglycerides, and high BMI, that is, all 5 components of the syndrome. Patients with MeS received more frequently any kind of medical treatment apart from nitrates, which were similarly administered in patients with or without MeS. Bio-humoral data confirmed the differences in cardiometabolic risk profile among the 2 groups and notably showed similar values of total-C, lower values of LDL-C, and higher values of non-HDL-C and Remnant-C in patients with the MeS as compared with patients without.

Changes in statin treatment, bio-humoral profiles, and other measurable risk factors from the time of baseline CCTA to that of follow-up CCTA are shown in Figure 2. At follow-up, statin treatment was more frequent

Table 1. Baseline Clinical Characteristics of the Study Population

	Whole population, N=1200	Metabolic syndrome (−), n=834	Metabolic syndrome (+), n=366	*P* value
Nonmodifiable CVD risk factors				
Age, y	60±9	60±9	62±9	<0.001
Sex male	665 (55)	488 (59)	177 (48)	0.001
Ethnicity East Asian	1107 (92)	762 (91)	345 (94)	0.084
Ethnicity White	93 (8)	72 (9)	21 (6)	
Family history	306 (26)	210 (25)	96 (26)	0.148
Symptoms				
Typical chest pain	59 (5)	42 (5)	17 (5)	0.640
Atypical/noncardiac chest pain	952 (79)	659 (79)	293 (80)	
Dyspnea	85 (7)	55 (7)	30 (8)	
Asymptomatic	104 (9)	78 (9)	26 (7)	
Modifiable CVD risk factors				
Previous CAD	187 (16)	131 (16)	56 (15)	0.850
Smoking	482 (40)	325 (39)	157 (43)	0.201
High LDL-C	350 (29)	260 (31)	90 (25)	0.021
High SBP*	741 (62)	416 (50)	325 (89)	<0.001
High FPG*	634 (53)	322 (39)	312 (85)	<0.001
Low HDL-C*	447 (37)	174 (21)	273 (75)	<0.001
High TG*	410 (34)	149 (18)	261 (71)	<0.001
High BMI*	59 (5)	18 (2)	41 (11)	<0.001
Medications				
Beta-blockers	378 (32)	237 (28)	141 (39)	<0.001
Calcium antagonists	376 (31)	222 (27)	154 (42)	<0.001
RAS inhibitors	403 (34)	241 (29)	162 (44)	<0.001
Nitrates	132 (11)	88 (11)	44 (12)	0.454
Diuretics	120 (10)	70 (8)	50 (14)	0.005
Anti-diabetic	159 (13)	71 (9)	88 (24)	<0.001
Aspirin	597 (50)	395 (47)	202 (55)	0.012
Statins	577 (48)	385 (46)	192 (52)	0.044
Laboratory data				
Total-C, mg/dL	183±39	184±39	181±40	0.206
LDL-C, mg/dL	112±35	114±35	107±34	0.001
FPG, mg/dL	111±35	105±29	124±42	<0.001
TG, mg/dL	143±81	119±66	196±88	<0.001
HDL-C, mg/dL	49±12	52±12	42±9	<0.001
Non-HDL-C, mg/dL	134±37	132±37	139±38	0.004
Remnant-C, mg/dL	22±19	18±16	32±22	<0.001
HbA1C, %	6.4±1.2	6.3±1.1	6.8±1.4	<0.001

Continuous variables are presented as mean±SD, categorical variables as absolute N and (%). Continuous data were compared with the Mann-Whitney *U* test and categorical variables with χ^2 test. $P<0.05$ show statistically significant differences. BMI indicates body mass index; CAD, coronary artery disease; CVD, cardiovascular diseases; FPG, fasting plasma glucose; HbA1C, hemoglobin A1c (measured in a subgroup of 548 patients); HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RAS, renin angiotensin system; Remnant-C, remnant cholesterol; SBP, systemic blood pressure; TG, triglycerides; and Total-C, total cholesterol.

*Modifiable CVD risk factors which are also components of the metabolic syndrome.

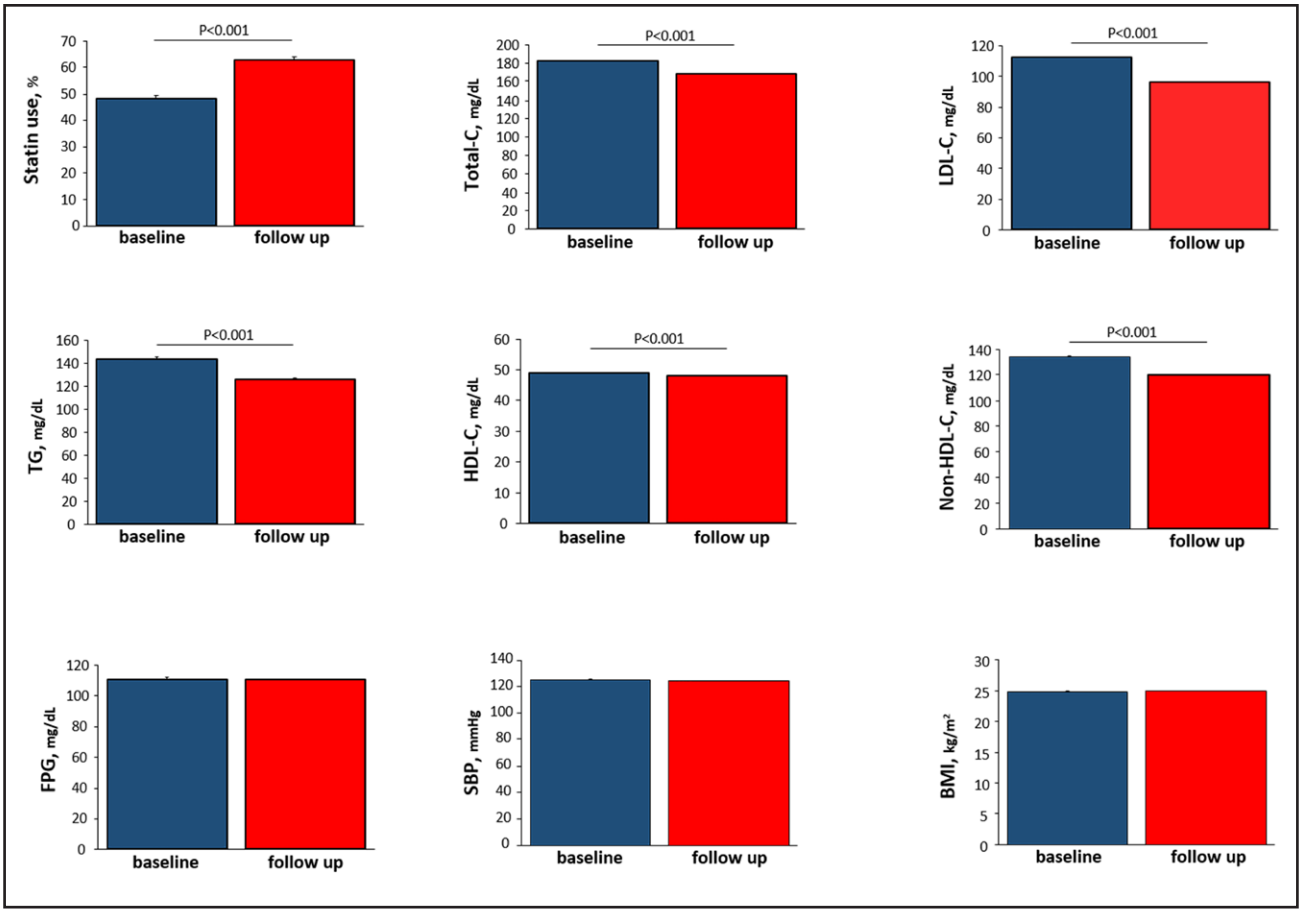

Figure 2. Changes in statin treatment, in bio-humoral profiles, and in other measurable risk factors from the time of baseline coronary computed tomography angiography (CCTA) to that of follow-up CCTA.
Bar graph representing statin use as well as blood lipids, fasting plasma glucose (FPG), systolic blood pressure (SBP), and body mass index (BMI), values (mean±SE) measured in the whole population at the time of baseline CCTA and of follow-up CCTA. Continuous data were compared with the Wilcoxon signed-rank test for paired data and categorical variables with McNemar test. HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; and Total-C, total cholesterol.

than at baseline, and most lipid biomarkers significantly decreased, more evidently for total-C (−14.9±1.2 mg/dL), LDL-C (−16.0±1.1 mg/dL), non-HDL-C (−14.6±41.4 mg/dL), and triglycerides (−17.9±2.4 mg/dL) than for HDL-C (−0.9±0.3 mg/dL), with a small increase in remnant-C (1.9±20.4). On the contrary, there were no significant changes in FPG (−0.33±32.1 mg/dL), systolic BP (−1.1±19.2 mm Hg), or BMI (0.02±0.8 kg/m^2).

Cardiometabolic Risk, Atherosclerotic Coronary Plaque Burden, and Progression

Plaque burden measurements at baseline and follow-up CCTA, as well as their annual changes, are described in the whole population and compared among patients grouped according to presence/absence of MeS in Table 2.

At baseline, patients with MeS had a higher whole heart plaque burden (PV and PAV), including both calcified and noncalcified volumes, than patients without MeS. The median interscan period was 3.6 (interquartile range, 1.4) years. At follow-up, all plaque burden parameters increased in the whole population and were higher in patients with MeS than in patients without MeS. Moreover, patients with MeS showed a higher annual increase in total, and in particular, calcified plaque burden than patients without MeS. Rapid coronary PP (delta PAV/y ≥1%) was observed in 341 (28%) participants and was more frequent in patients with MeS.

Univariable analyses of the association between clinical characteristics, medical therapy, and baseline PAV or rapid PP are reported in Tables S1 and S2. At multivariable linear regression analysis, age, sex male, previous CAD, smoking habits, and MeS were associated with baseline PAV (Table 3, model 1A). Among cardiometabolic risk factors, high FPG and low HDL-C were significantly associated with baseline PAV (Table 3, model 1B), in particular when combined (Table 3, model 1C). High SBP showed a weak association. At multivariable logistic regression analysis, age, smoking habits, and MeS were independent predictors of rapid PP, together with baseline PAV when included in the model (Table 4, models 2A and 2B). When MeS

Table 2. Coronary Atherosclerotic Plaque Burden, Plaque Progression, and Outcome

	Whole population, N=1200	Metabolic syndrome (−), n=834	Metabolic syndrome (+), n=366	*P* value
Plaque burden at baseline				
PV, mm³	47.56 (4.18–140.02)	39.13 (0–127.01)	69.81 (14.89–170.64)	<0.001
NCPV, mm³	30.00 (1.3194.47)	23.8–995 (0–83.13)	39.93 (9.29–126.26)	<0.001
CPV, mm³	6.78 (0–38.83)	4.97 (0–33.50)	12.25 (0.03–50.92)	<0.001
PAV, %	2.65 (0.18–7.99)	2.20 (0–7.37)	3.86 (0.97–9.58)	<0.001
NCPAV, %	1.70 (0.09–5.35)	1.35 (0–4.67)	2.31 (0.51–6.80)	<0.001
CPAV, %	0.37 (0–2.32)	0.26 (0–1.99)	0.70 (0–2.69)	0.001
Plaque burden at follow-up				
PV, mm³	85.24 (17.94–211.52)	72.42 (12.16–188.32)	120.94 (38.95–256.10)	<0.001
NCPV, mm³	43.32 (6.80–115.51)	34.15 (4.31–101.20)	57.76 (17.97–152.06)	<0.001
CPV, mm³	22.09 (1.65–80.67)	18.58 (0.34–72.31)	37.96 (3.94–101.86)	<0.001
PAV, %	4.68 (1.11–12.30)	3.88 (0.76–11.06)	6.60 (2.35–15.44)	<0.001
NCPAV, %	2.44 (0.48–6.47)	2.06 (0.28–5.62)	3.37 (1.03–8.21)	<0.001
CPAV, %	1.26 (0.09–5.00)	0.97 (0.02–4.64)	2.11 (0.21–5.36)	<0.001
Plaque burden annual change				
Delta PV/y, mm³	7.24 (0.19–20.74)	5.67 (0–18.89)	10.62 (1.90–28.01)	<0.001
Delta NCPV/y, mm³	0.93 (-0.37–8.70)	0.61 (-0.24–7.40)	1.51 (-0.74–12.04)	0.153
Delta CPV/y, mm³	3.45 (0.10–11.12)	1.78 (0.01–9.62)	5.44 (0.66–15.70)	<0.001
Delta PAV/y, %	0.41 (0.03–1.17)	0.33 (0–0.99)	0.59 (0.14–1.42)	<0.001
Delta NCPAV/y, mm³	0.05 (-0.03–0.47)	0.03 (-0.02–0.43)	0.10 (-0.04–0.63)	0.040
Delta CPAV/y, mm³	0.19 (0.01–0.69)	0.16 (0–0.59)	0.29 (0.03–0.86)	<0.001
Rapid plaque progression				
Delta PAV/y ≥1%	341 (28)	208 (25)	133 (36)	<0.001
Outcome				
MACE	201 (17)	124 (15)	77 (21)	0.008
Nonfatal MI	11 (1)	6 (1)	5 (1)	0.279
Any cause death	17 (1)	14 (2)	3 (1)	0.223
Unplanned revascularization	175 (15)	106 (13)	69 (19)	0.006

Coronary plaque variables are presented as median with interquartile range (IQR) and categorical variables as absolute N and (%). Continuous data were compared with the Mann-Whitney *U* test and categorical variables with χ^2 test. $P<0.05$ show statistically significant differences. Two patients without MeS had unplanned revascularization and later on a nonfatal MI. CPAV indicates calcified percent atheroma volume; CPV, calcified plaque volume; MACE, major adverse cardiovascular events; MeS, metabolic syndrome; MI, myocardial infarction; NCPAV, noncalcified percent atheroma volume; NCPV, noncalcified plaque volume; PAV, percent atheroma volume; and PV, plaque volume.

was substituted with individual cardiometabolic risk factors, only high FPG and low HDL-C remained independent predictors of rapid PP (Table 4, model 2C), in particular when combined and even when baseline PAV was included in the model (Table 4, models 2D and 2E). The independent predictive role of the combination of high FPG and low HDL-C for rapid PP (model 2E) was confirmed in sensitivity analyses performed in male or female patients, in patients without an established diagnosis of diabetes, and using a BMI >25 kg/m² as a proxy for obesity (Tables S3 through S6). Moreover, the independent predictive role of the combination of high FPG and low HDL-C for baseline PAV and rapid PP was also confirmed when adjusting for full medical therapy at baseline or for statin use at follow-up CCTA, respectively (Tables S7 and S8).

The individual and combined effects of high FPG and low HDL-C on plaque burden progression, expressed by the annual change of PAV, noncalcified percent atheroma volume, and calcified percent atheroma volume (%/y), in the whole population are shown in Figure 3. Both the individual and synergistic effects of high FGP and low HDL-C are evident in the progression of total plaque burden. Either high FPG or low HDL-C are associated with the progression of noncalcified percent atheroma volume, while only high FPG is associated with the progression of calcified percent atheroma volume.

Cardiometabolic Risk, Rapid Coronary Plaque Progression, and MACE

In a median follow-up period of 8.23 years (interquartile range, 5.92–9.53), MACE occurred in 201 patients

Table 3. Multivariable Linear Regression for the Association Between Baseline Clinical Characteristics and Baseline Percent Atheroma Volume

	Model 1A		Model 1B		Model 1C	
	Coefficient±SE	*P* value	Coefficient±SE	*P* value	Coefficient±SE	*P* value
Age, y	0.24±0.3	<0.001	0.23±0.03	<0.001	0.23±0.03	<0.001
Sex male	1.93±0.50	<0.001	2.03±0.51	<0.001	2.02±0.50	<0.001
Family history	−0.10±0.51	0.852	−0.09±0.51	0.861	−0.10±0.51	0.849
Previous CAD	3.41±0.65	<0.001	3.40±0.65	<0.001	3.41±0.65	<0.001
Smoking	1.04±0.50	0.037	1.01±0.50	0.042	1.06±0.50	0.033
High LDL-C	−0.11±0.50	0.827	0.12±0.50	0.807	0.07±0.50	0.888
MeS	1.34±0.49	0.006	…	…	…	…
High SBP	…	…	0.86±0.48	0.073	1.01±0.48	0.035
High FPG	…	…	1.12±0.46	0.015	…	…
High BMI	…	…	−0.62±0.49	0.550	−0.62±1.03	0.550
Low HDL-C	…	…	1.10±0.49	0.025	…	…
High TG	…	…	0.50±0.48	0.304	0.56±0.48	0.243
High FPG and Low HDL-C	…	…	…	…	1.72±0.56	0.002

P<0.05 show statistically significant differences. Models are adjusted for baseline statin therapy. BMI indicates body mass index; CAD, coronary artery disease; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MeS, metabolic syndrome; SBP, systemic blood pressure; and TG, triglycerides.

(17%), including unplanned coronary revascularizations in 175 (15%; Table 2). The 10-years event-free survival rate was significantly lower in patients with MeS than in those without MeS (85% versus 78%; *P*=0.012; Figure 4). Patients with either high FPG or high SBP had similarly reduced event-free survival rates as compared with patients with none of these 2 factors, while patients with the combination of high FPG and high SBP had the worst outcome (Figure 4).

The univariable analysis of the association between baseline clinical characteristics and MACE is reported in Table S9. At multivariable Cox analyses, age, family history, previous CAD, and MeS were independently associated with MACE (Table 5, model 3A). When baseline PAV and rapid PP were included in the model, previous CAD and MeS were no longer independent predictors of MACE (Table 5, model 3B). Among single cardiometabolic risk factors, high SBP and high FPG were the only independent predictors of MACE (Table 5, model 3C), in particular when combined and even when baseline PAV and rapid PP were included in the model (Table 5, models 3D and 3E).

DISCUSSION

In the current study, the analysis of a large cohort of patients with suspected or known stable CAD undergoing serial coronary CCTA allowed us to demonstrate that the specific cardiometabolic risk profile characterized by hyperglycemia and low HDL-C levels is associated with the presence and extent of coronary atherosclerosis and, most importantly, predicts a rapid progression of coronary plaque burden independently of other established risk factors and treatment. Even in the present population, characterized by a relatively low mortality rate, patients with a rapid progression of coronary plaque burden demonstrated a worse outcome, mainly due to the increased frequency of late, unplanned revascularizations. Importantly, high FPG, in combination with high SBP, was also able to further stratify patient risk of adverse cardiac events, besides the extent of coronary atherosclerosis and its rapid progression over time. The present results underline the relevance of a specific combination of cardiometabolic risk factors in the same patient as determinants of coronary atherosclerosis residual risk, that is, the risk persisting despite current treatments.

Cardiometabolic Risk, Progression of Coronary Atherosclerosis, and Outcome

A few studies have reported that the progression of coronary atherosclerosis, as measured by serial CCTA, is related to the globally estimated clinical risk of future cardiovascular events, in particular in diabetic patients.[26,27] In a previous PARADIGM study analysis, it has been shown that plaque progression measured by the annual rate of PAV, noncalcified percent atheroma volume, and calcified percent atheroma volume increase from baseline to follow-up CCTA was associated with increasing cumulative estimated ASCVD risk.[28] As in other studies, however, the prospective contribution of individual and combined cardiometabolic risk factors on rapid progression of coronary atherosclerosis and on actually measured future adverse cardiovascular events has not been explored.

Table 4. Multivariable Logistic Regression for the Association Between Baseline Clinical Characteristics and Rapid Plaque Progression

	Model 2A		Model 2B		Model 2C		Model 2D		Model 2E	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, y	1.05 (1.03–1.07)	<0.001	1.02 (1.01–1.04)	0.006	1.02 (1.01–1.04)	<0.001	1.05 (1.03–1.06)	<0.001	1.02 (1.01–1.04)	0.010
Sex male	1.22 (0.91–1.64)	0.192	0.98 (0.71–1.35)	0.885	0.98 (0.71–1.35)	0.053	1.34 (0.98–1.80)	0.068	1.06 (0.76–1.47)	0.727
Family history	1.17 (0.87–1.57)	0.315	1.19 (0.86–1.64)	0.295	1.16 (0.86–1.57)	0.336	1.27 (0.89–1.58)	0.328	1.17 (0.85–1.62)	0.331
Previous CAD	1.28 (0.90–1.84)	0.175	0.90 (0.60–1.36)	0.622	1.27 (0.88–1.83)	0.196	1.27 (0.86–1.83)	0.194	0.90 (0.59–1.36)	0.604
Smoking	1.66 (1.24–2.15)	<0.001	1.53 (1.11–2.10)	0.009	1.63 (1.21–2.19)	0.001	1.62 (1.20–2.18)	0.002	1.49 (1.08–2.05)	0.015
High LDL-C	0.97 (0.72–1.31)	0.856	0.99 (0.72–1.36)	0.975	1.07 (0.79–1.45)	0.652	1.07 (0.79–1.45)	0.670	1.08 (0.78–1.49)	0.663
MeS	1.63 (1.24–2.16)	<0.001	1.51 (1.12–2.03)	0.007	…	…	…	…	…	---
High SBP	…	…	…	…	1.18 (0.88–1.58)	0.259	1.08 (0.88–1.59)	0.254	1.08 (0.79–1.48)	0.636
High FPG	…	…	…	…	1.50 (1.14–1.98)	0.004	…	…	…	---
High BMI	…	…	…	…	1.08 (0.60–1.95)	0.798	1.08 (0.60–1.95)	0.799	1.20 (0.65–2.21)	0.561
Low HDL-C	…	…	…	…	1.82 (1.37–2.43)	<0.001	…	…	…	---
High TG	…	…	…	…	1.15 (0.86–1.52)	0.350	1.15 (0.87–1.53)	0.323	1.12 (0.82–1.52)	0.470
High FPG or low HDL-C	…	…	…	…	…	…	1.52 (1.09–2.12)	0.014	1.40 (0.98–2.00)	0.065
High FPG and low HDL-C	…	…	…	…	…	…	2.72 (1.84–4.02)	<0.001	2.37 (1.56–3.61)	<0.001
PAV, %	…	…	1.12 (1.10–1.15)	<0.001	…	…	…	…	1.12 (1.10–1.15)	<0.001

P<0.05 show statistically significant differences. Models are adjusted for baseline statin therapy. BMI indicates body mass index; CAD, coronary artery disease; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MeS, metabolic syndrome; OR, odds ratio; PAV, percent atheroma volume; SBP, systemic blood pressure; and TG, triglycerides.

Besides established ASCVD risk factors, the general combination of at least 3 cardiometabolic risk factors, described as MeS,[4,13–15] has received particular attention over the past decades due to its elevated prevalence and the consideration that it is projected to continuously increase in parallel with the prevalence of obesity and type-2 diabetes. In the general population, it has been shown that MeS is associated with a higher risk of the combined outcome end point of MACE as well as with cardiovascular and all-cause mortality, even if the effects of MeS were not in excess of those related to the presence of single components.[29] The possible association of specific combinations of cardiometabolic risk factors with coronary atherosclerosis progression and with major ASCVD-related events has not been explored.

The first relevant result of the present study is the demonstration for the first time that the combination of high FPG with low HDL-C levels, which is very frequent in diabetes and prediabetic states, is a strong and independent determinant of rapid coronary plaque progression, outperforming other cardiometabolic risk factors and even after adjustment for baseline plaque burden and statin treatment.

High FPG, including prediabetes and overt diabetes, is a major determinant of CVD-related outcomes in the general population,[1] and its relationship with progressive CAD has been clearly demonstrated. In previous PARADIGM analyses, either established type-2 diabetes or the triglyceride-glucose index, a surrogate index for insulin resistance, were shown as independent predictors of coronary plaque progression and adverse plaque features at CCTA.[10,27] In a recent post hoc analysis of trials involving serial coronary intravascular ultrasonography measurements in patients with or without diabetes, mainly testing aggressive treatment strategies for specific CVD risk factors on coronary plaque progression, greater (on-treatment) HbA1c levels were associated with annualized changes in PAV and with

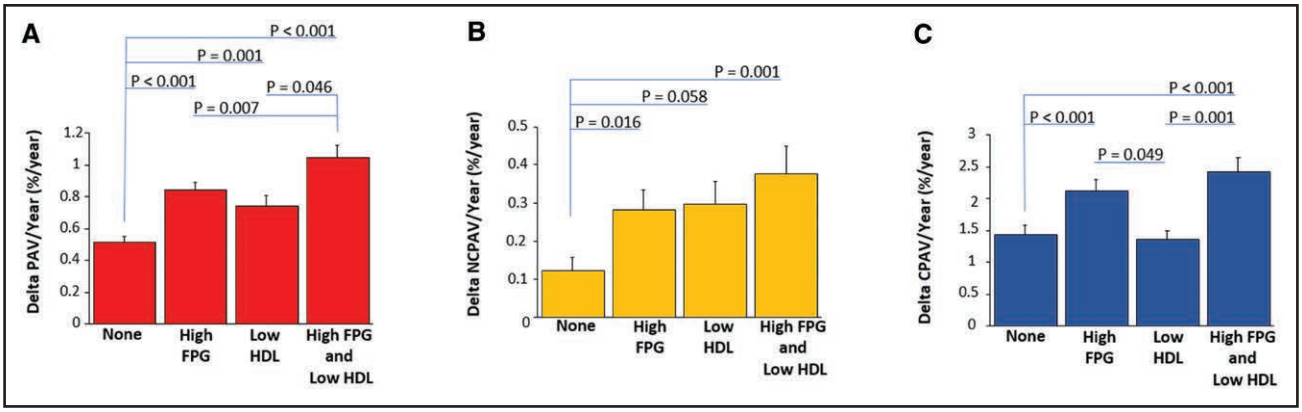

Figure 3. Individual and combined effects of high fasting plasma glucose (FPG) and low high-density lipoprotein cholesterol (HDL-C) on plaque burden progression, expressed by annual change of percent atheroma volume (PAV), noncalcified PAV (NCPAV), and calcified PAV (CPAV) (%/y) in the whole population.

Bar graph representing annual changes (delta) in whole heart PAV (%/y; **A**), whole heart NCPAV (%/y; **B**), and whole heart CPAV (%/y; **C**) for 4 groups: patients without high FPG and without low HDL-C (none), patients with only high FPG, patients with only low HDL-C, and patients with both high FPG and low HDL-C. Continuous data were compared with the Kruskal-Wallis test, and multiple comparisons were performed using Mann-Whitney *U* test with Bonferroni correction for *P* value.

MACE independently of achieved CVD risk factor control.[30] Similar results were obtained in a previous PARADIGM analysis in patients without baseline coronary plaque burden.[31]

Low levels of HDL-C have always been considered a relevant ASCVD risk determinant, but genetic studies and clinical trials have challenged the notion that HDL-C levels may be causally linked to CVD, independent of the cholesterol content in LDL particles. In particular, the failure of many cholesteryl ester transfer protein inhibitors to raise HDL-C levels raised doubts on the protective role of HDL. These findings have raised attention to the multiple biological functions of HDL beyond the so-called reverse cholesterol transport, including anti-inflammatory and anti-oxidative properties, which may be in turn involved in atherogenesis.[32]

Recent data indicate that HDL-C levels and HDL particle functionality are correlated with the pathogenesis and prognosis of type-2 diabetes. HDL is a complex macromolecular cluster of various components, such as apolipoproteins, enzymes, and lipids. Hyperglycemia leads to reduced HDL-C levels and deteriorated HDL functionality via various alterations in HDL particles' proteome and lipidome. In turn, reduced HDL-C levels and impaired HDL functionality impact the performance of key organs related to glucose homeostasis, such as pancreas and skeletal muscles. Thus, a bidirectional correlation between these 2 conditions exists, leading to a perpetual self-feeding cycle.[33] Experimental data underlined the impact of deficiency of apolipoprotein A1 and lecithin-cholesterol acyltransferase, key components of HDL structure, on glucose homeostasis in diet-induced obesity murine models.[34] These findings suggested that HDL structure, rather than adipose tissue, is responsible for the observed glucose metabolic abnormalities and, in turn, might have an effect on coronary plaque burden. Whichever the interaction is, recent results on the favorable prognostic impact of new glucose lowering drugs in patients with and without established diabetes underline the relevance of counteracting this cardiometabolic risk

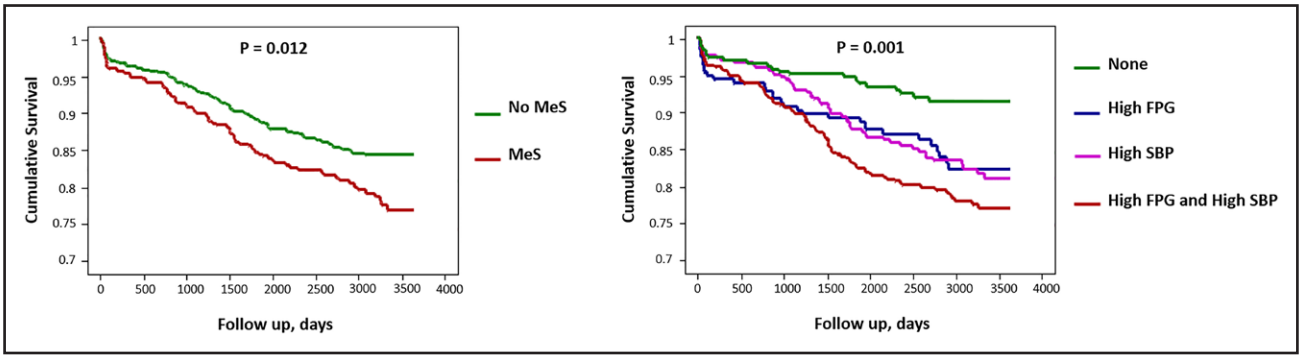

Figure 4. Survival analysis.

Kaplan-Meier curves for event-free survival in patients with no MeS (blue) and in patients with MeS (red; **A**). Kaplan-Meier curves for event-free survival in patients without high fasting plasma glucose (FPG) and without high systemic blood pressure (SBP; green), patients with only high FPG (blue), patients with only high SBP (yellow), and patients with both high FPG and high SBP (red; **B**). MeS indicates metabolic syndrome.

Table 5. Multivariable Cox Regression for the Association Between Baseline Clinical Characteristics, Rapid PP, and Major Adverse Cardiovascular Events

	Model 3A		Model 3B		Model 3C		Model 3D		Model 3E	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, y	1.03 (1.01–1.05)	<0.001	1.02 (1.00–1.03)	0.035	1.03 (1.01–1.04)	0.001	1.03 (1.01–1.04)	0.001	1.02 (1.00–1.03)	0.065
Sex male	1.36 (0.98–1.88)	0.064	1.25 (0.90–1.74)	0.179	1.31 (0.94–1.83)	0.107	1.30 (0.94–1.82)	0.117	1.20 (0.86–1.66)	0.295
Family history	1.51 (1.12–2.04)	0.007	1.52 (1.13–2.06)	0.006	1.54 (1.07–1.95)	0.005	1.54 (1.14–2.09)	0.005	1.55 (1.14–2.10)	0.005
Previous CAD	1.60 (1.17–2.23)	0.006	1.37 (0.97–1.93)	0.071	1.60 (1.14–2.23)	0.006	1.60 (1.15–2.23)	0.006	1.36 (0.97–1.92)	0.077
Smoking	1.25 (0.91–1.70)	0.163	1.18 (0.86–1.61)	0.298	1.27 (0.93–1.74)	0.130	1.27 (0.93–1.74)	0.127	1.20 (0.88–1.64)	0.252
High LDL-C	1.05 (0.77–1.44)	0.747	1.06 (0.77–1.44)	0.729	1.10 (0.80–1.51)	0.546	1.10 (0.81–1.51)	0.540	1.09 (0.80–1.50)	0.590
MeS	1.37 (1.03–1.83)	0.032	1.28 (0.96–1.72)	0.091	…	…	…	…	…	…
High SBP	…	…	…	…	1.39 (1.01–1.16)	0.045	…	…	…	…
High FPG	…	…	…	…	1.36 (1.01–1.82)	0.040	…	…	…	…
High BMI	…	…	…	…	0.68 (0.35–1.34)	0.270	0.68 (0.35–1.34)	0.263	0.73 (0.37–1.44)	0.366
Low HDL-C	…	…	…	…	1.08 (0.80–1.46)	0.599	1.07 (0.80–1.45)	0.641	1.01 (0.75–1.36)	0.965
High TG	…	…	…	…	1.07 (0.80–1.45)	0.641	1.07 (0.79–1.44)	0.654	1.05 (0.78–1.41)	0.752
High SBP or high FPG	…	…	…	…	…	…	1.65 (1.03–2.67)	0.039	1.54 (0.95–2.49)	0.079
High SBP and high FPG	…	…	…	…	…	…	2.06 (1.28–3.33)	0.003	1.79 (1.10–2.90)	0.018
PAV, %	…	…	1.03 (1.02–1.04)	<0.001	…	…	…	…	1.03 (1.01–1.04)	0.002
Rapid PP	…	…	1.44 (1.06–1.95)	0.018	…	…	…	…	1.42 (1.05–1.93)	0.024

P<0.05 show statistically significant differences. Models are adjusted for baseline statin therapy. BMI indicates body mass index; CAD, coronary artery disease; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MeS, metabolic syndrome; PAV, percent atheroma volume; PP, plaque progression; SBP, systemic blood pressure; and TG, triglycerides.

profile as a measure to prevent CVD and CAD-related events.[35]

Another relevant finding of the present study is the demonstration of the prognostic impact of the combination of high FPG and high SBP, underlying the additional role of hypertension over an atherogenic cardiometabolic profile in causing CAD-related events and, in particular, late revascularizations.

High SBP is currently the first, in ranking order, modifiable risk factor accounting for cardiovascular mortality and all-cause disability-adjusted life years lost.[1] Nevertheless, data on the relationship between hypertension and coronary atherosclerosis progression are scanty. In a small, low-risk population of patients with suspected CAD submitted to serial CCTA, hypertension was an independent determinant of noncalcified plaque progression but was not significantly associated with annual progression of total plaque burden (on a per-plaque and per-patient analysis).[36] On the contrary, the combination of established diabetes and hypertension predicted MACE risk in patients without obstructive CAD, even after adjustment for baseline extent of coronary atherosclerosis.[37] The present results extend and clarify previous findings demonstrating that in patients with suspected or known CAD, high FPG and high SBP, determined at a first diagnostic evaluation, persist at follow-up despite treatment. High FPG, even after exclusion of established diabetes, is a key determinant of the extent of coronary atherosclerosis and of its rapid progression, and, in combination with high SBP, it is also able to further stratify the risk of MACE beyond baseline coronary plaque burden and its progression over time.

Hypertension is associated with abnormal vasodilatory capacity, which plays a crucial role in CAD. Changes in signaling pathways in vascular endothelial and smooth muscle cells are key molecular mechanisms that trigger endothelial/vascular dysfunction, which characterizes hypertension. Among the complex molecular mechanisms involved, the nitric oxide– nitric oxide-sensitive guanylate cyclase-cGMP pathway is considered one of the most relevant.[38] In the context of the cardiometabolic risk profile described above, the presence of hypertension could thus express a relevant coexistent impairment of endothelial function able to reinforce the atherogenic process and, in particular, enhance the functional effects of coronary atherosclerosis such as myocardial ischemia. It is conceivable that the increased prevalence of MACE in the present population in patients with combined high FPG and high SBP, mainly driven by unplanned revascularizations, could be explained at least in part by a higher predisposition to recurrent ischemia and related symptoms, which could have promoted more frequent late revascularizations.

Other cardiometabolic risk factors, that is, obesity and hypertriglyceridemia, had no significant independent impact on coronary plaque progression and outcome in the PARADIGM population.

Obesity is an emergent risk factor for CVD, being closely associated with prediabetic and diabetic conditions.[1] In the general population, it has been associated with worse outcome,[1] particularly in men, independent of the presence of the MeS.[39] However, the relationship between high BMI and outcome in patients with CAD is more complex. In women with suspected CAD from the WISE study,[40] higher BMI values were not associated with significant CAD and MACE. On the contrary, in patients with stable CAD and a long-term follow-up, obesity, but not overweight, was independently associated with increased mortality.[41] In a recent report from the STABILITY trial in patients with stable CAD, all-cause and cardiovascular mortality were lowest in patients with a BMI between 25 and 35 kg/m^2, while very low or very high BMI values were strong markers of poor prognosis.[42,43]

In the present study, BMI >30 kg/m^2 was not independently associated with increased coronary plaque burden, rapid PP, or MACE. Since the present population included mainly patients of East Asian ethnicity, a different cutoff for a high BMI value (25 kg/m^2) was also used, but the results did not change. These results may indirectly confirm the few available data on the relationship between high BMI and coronary plaque progression, documenting that CAD progression and CAD-related outcomes seem to depend more on the associated metabolic phenotype[39] or visceral adiposity than on BMI itself.[44]

A potential causal role of triglycerides, triglyceride-rich lipoproteins, and their remnants in atherogenesis has been recently underlined.[6] As a matter of fact, high triglycerides are often associated with low HDL-C as determinants of a specific cardiometabolic risk profile, known as atherogenic dyslipidemia, which is independent of LDL-C, correlates with insulin resistance and incident diabetes, and is associated with ASCVD risk in general populations.[45–48] In patients with suspected or known CAD, this condition may specifically influence CAD-related events and responses to statin treatment.[49–52] High triglyceride levels are also associated with decreased HDL function, so that the proatherogenic properties of triglyceride-rich lipoproteins can be coupled with reduced antiatherogenic effects of HDL-C, both contributing to enhanced atherosclerotic plaque formation and progression.[53,54] In a previous study in patients with suspected or known stable CAD, the combination of high triglycerides with low HDL-C, as expressed by a high triglyceride/HDL-C ratio, was associated with a higher CCTA-derived risk score and was an independent predictor of the primary composite outcome end point of all-cause mortality and nonfatal myocardial infarction.[55] In a subgroup of this population in which coronary plaque burden progression could be evaluated by a second CCTA scan, a higher baseline triglyceride/HDL-C ratio was also associated with a higher increase in coronary plaque burden at follow-up.[55]

In the present study, patients with the MeS had higher values of triglycerides, non-HDL-C, and remnant-C as well as lower values of HDL-C. Nevertheless, high triglycerides were not independent determinants of coronary plaque burden and progression and were not associated with outcome. On the contrary, low HDL-C was an independent predictor of the extent of coronary atherosclerosis and of rapid PP, even if it was not independently related to outcome. Since the present results could have been influenced by the specific population analyzed, with a low prevalence of obesity and possible peculiar dietary habits, they cannot be extended to more general populations. Nevertheless, they may suggest that the impact of triglyceride-rich lipoproteins on ASCVD risk might be substantially mediated by indirect effects on other atherogenic mechanisms.

Limitations

The present analysis has several limitations. The selected population was at relatively low risk, being composed of patients with atypical chest pain and a low prevalence of severe CAD. The prevalent ethnicity was East Asian with a possible cardiometabolic risk profile and lifestyle and dietary habits not superimposable with other populations. Differences in nutritional habits may have reduced the relevance of some components, such as triglyceride levels, in the cardiometabolic risk profile shown to be associated with coronary plaque progression. The value of BMI, instead of waist circumference, was used to define obesity based on a cutoff value that mainly applies to European and US populations. Patients of East Asian ethnicity may have different associations between BMI, percentage of body fat, and CVD risks compared with European populations.[16] Nevertheless, even when a lower cutoff value for BMI was used in the analyses, the results did not change. There is a recognized difficulty in choosing cutoff values even for waist measurements in different ethnic groups,[4] and in any case, these parameters may be considered only as approximate indicators of visceral adiposity,[44] which should be determined by more accurate measurements not available in the present study. Moreover, LDL-C and Remnant-C were calculated and not directly measured. Finally, due to the observational design of the study, information on medical therapy was limited to the use of medical treatment at the time of the baseline CCTA and to the use of statins at the time of the second CCTA. Full data on dosages and adherence to treatment were not recorded. There was no control over optimal medical treatment, so some

patients could have been undertreated. In particular, it could not be assessed whether effective glycemic control was achieved since HbA1c data were available only in a minority of patients (n=548). Additionally, because only patients who had both a baseline and a follow-up CCTA scan were eligible, patients had a relatively low prevalence of obstructive CAD and event rate. Patients in whom coronary disease could have progressed more rapidly and, hence, could have been more likely to experience clinical events may not have been referred for a second coronary CCTA. Thus, some selection bias was inevitable, and the generalizability of the present results to higher-risk populations is not known.

Conclusions

In summary, this is the first prospective large study in which the relative independent role of established and emerging cardiometabolic risk factors could be tested in predicting both progressive coronary atherosclerosis and cardiovascular outcomes. The present results significantly expand previous knowledge by demonstrating that: (1) high circulating FPG (expressing insulin resistance even in the absence of established type-2 diabetes) and low HDL-C, both individually and in combination, are relevant determinants of the extent of coronary plaque burden and of its progression over time; (2) these 2 factors identify a specific cardiometabolic condition, independent of other risk factors, strongly and specifically associated with a more rapid PP persisting despite current treatment; (3) high SBP is able to condition, in association with high FPG, additional risk of future CAD-related events besides the progression of coronary atherosclerosis; and (4) among other modifiable risk factors, the independent and strong effects of smoking are confirmed, while the impact of LDL-C is possibly mitigated by the large current use of statins, which is further increased once coronary atherosclerosis is documented by CCTA.

Further clinical studies could be needed to confirm and expand the present results to larger multi-ethnic populations and to assess whether better control of the specific cardiometabolic condition identified by hyperglycemia and low HDL-C by lifestyle and pharmacological interventions could reduce coronary plaque progression and, together with a better control of hypertension,[56] could prevent adverse related events. The observed role of the combination of high FPG and low HDL-C to predict rapid coronary PP underlines the need to better elucidate the mechanisms by which these 2 factors may interact to cause an adverse cardiometabolic profile prone to atherogenesis.

Testing specific new treatments addressed to lower glucose levels to improve HDL and endothelial function would be particularly relevant to reducing the residual global burden of ASCVD.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S9

REFERENCES

1. Vaduganathan M, Mensah GA, Turco JV, Fuster V, Roth GA. The global burden of cardiovascular diseases and risk: a compass for future health. *J Am Coll Cardiol*. 2022;80:2361–2371. doi: 10.1016/j.jacc.2022.11.005
2. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, et al; ESC National Cardiac Societies. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42:3227–3337. doi: 10.1093/eurheartj/ehab484
3. Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D, Gale CP, Maggioni AP, Petersen SE, Huculeci R, et al. European society of cardiology: cardiovascular disease statistics 2021: executive summary. *Eur Heart J Qual Care Clin Outcomes*. 2022;8:377–382. doi: 10.1093/ehjqcco/qcac014
4. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC; International Diabetes Federation Task Force on Epidemiology and Prevention. International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart

Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640–1645. doi: 10.1161/CIRCULATIONAHA.109.192644

5. Sampson UK, Fazio S, Linton MF. Residual cardiovascular risk despite optimal LDL cholesterol reduction with statins: the evidence, etiology, and therapeutic challenges. *Curr Atheroscler Rep*. 2012;14:1–10. doi: 10.1007/s11883-011-0219-7
6. Ginsberg HN, Packard CJ, Chapman MJ, Borén J, Aguilar-Salinas CA, Averna M, Ference BA, Gaudet D, Hegele RA, Kersten S, et al. Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies-a consensus statement from the European Atherosclerosis Society. *Eur Heart J*. 2021;42:4791–4806. doi: 10.1093/eurheartj/ehab551
7. Naoum C, Berman DS, Ahmadi A, Blanke P, Gransar H, Narula J, Shaw LJ, Kritharides L, Achenbach S, Al-Mallah MH, et al. Predictive value of age- and sex-specific nomograms of global plaque burden on coronary computed tomography angiography for major cardiac events. *Circ Cardiovasc Imaging*. 2017;10:e004896. doi: 10.1161/CIRCIMAGING.116.004896
8. Lee SE, Chang HJ, Rizvi A, Hadamitzky M, Kim YJ, Conte E, Andreini D, Pontone G, Volpato V, Budoff MJ, et al. Rationale and design of the Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography IMaging (PARADIGM) registry: a comprehensive exploration of plaque progression and its impact on clinical outcomes from a multicenter serial coronary computed tomographic angiography study. *Am Heart J*. 2016;182:72–79. doi: 10.1016/j.ahj.2016.09.003
9. Won KB, Lee SE, Lee BK, Park HB, Heo R, Rizvi A, Lin FY, Kumar A, Hadamitzky M, Kim YJ, et al. Longitudinal assessment of coronary plaque volume change related to glycemic status using serial coronary computed tomography angiography: a PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) substudy. *J Cardiovasc Comput Tomogr*. 2019;13:142–147. doi: 10.1016/j.jcct.2018.12.002
10. Won KB, Lee BK, Park HB, Heo R, Lee SE, Rizvi A, Lin FY, Kumar A, Hadamitzky M, Kim YJ, et al. 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. doi: 10.1186/s12933-020-01081-w
11. Indraratna P, Khasanova E, Gulsin GS, Tzimas G, Takagi H, Park KH, Lin FY, Shaw LJ, Lee SE, Narula J, et al; PARADIGM investigators. Plaque progression: where, why, and how fast? A review of what we have learned from the analysis of patient data from the PARADIGM registry. *J Cardiovasc Comput Tomogr*. 2022;16:294–302. doi: 10.1016/j.jcct.2021.11.004
12. van Rosendael SE, van den Hoogen IJ, Lin FY, Andreini D, Al-Mallah MH, Budoff MJ, Cademartiri F, Chinnaiyan K, Choi JH, Conte E, et al. Clinical and coronary plaque predictors of atherosclerotic nonresponse to statin therapy. *JACC Cardiovasc Imaging*. 2023;16:495–504. doi: 10.1016/j.jcmg.2022.10.017
13. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome: a new worldwide definition. *Lancet*. 2005;366:1059–1062. doi: 10.1016/S0140-6736(05)67402-8
14. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, et al; American Heart Association. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112:2735–2752. doi: 10.1161/CIRCULATIONAHA.105.169404
15. Huang PL. A comprehensive definition for metabolic syndrome. *Dis Model Mech*. 2009;2:231–237. doi: 10.1242/dmm.001180
16. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;363:157–163. doi: 10.1016/S0140-6736(03)15268-3
17. Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ, Nieman K, Pontone G, Raff GL. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr*. 2014;8:342–358. doi: 10.1016/j.jcct.2014.07.003
18. Abbara S, Blanke P, Maroules CD, Cheezum M, Choi AD, Han BK, Marwan M, Naoum C, Norgaard BL, Rubinshtein R, et al. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee: endorsed by the North American Society for Cardiovascular Imaging (NASCI). *J Cardiovasc Comput Tomogr*. 2016;10:435–449. doi: 10.1016/j.jcct.2016.10.002
19. Lee SE, Chang HJ, Sung JM, Park HB, Heo R, Rizvi A, Lin FY, Kumar A, Hadamitzky M, Kim YJ, et al. Effects of statins on coronary atherosclerotic plaques: the PARADIGM study. *JACC Cardiovasc Imaging*. 2018;11:1475–1484. doi: 10.1016/j.jcmg.2018.04.015
20. Park HB, Lee BK, Shin S, Heo R, Arsanjani R, Kitslaar PH, Broersen A, Dijkstra J, Ahn SG, Min JK, et al. Clinical feasibility of 3D automated coronary atherosclerotic plaque quantification algorithm on coronary computed tomography angiography: comparison with intravascular ultrasound. *Eur Radiol*. 2015;25:3073–3083. doi: 10.1007/s00330-015-3698-z
21. Lee SE, Park HB, Xuan D, Lee BK, Hong MK, Jang Y, Chang HJ. Consistency of quantitative analysis of coronary computed tomography angiography. *J Cardiovasc Comput Tomogr*. 2019;13:48–54. doi: 10.1016/j.jcct.2018.09.012
22. Min JK, Shaw LJ, Devereux RB, Okin PM, Weinsaft JW, Russo DJ, Lippolis NJ, Berman DS, Callister TQ. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol*. 2007;50:1161–1170. doi: 10.1016/j.jacc.2007.03.067
23. de Graaf MA, Broersen A, Kitslaar PH, Roos CJ, Dijkstra J, Lelieveldt BP, Jukema JW, Schalij MJ, Delgado V, Bax JJ, et al. Automatic quantification and characterization of coronary atherosclerosis with computed tomography coronary angiography: cross-correlation with intravascular ultrasound virtual histology. *Int J Cardiovasc Imaging*. 2013;29:1177–1190. doi: 10.1007/s10554-013-0194-x
24. Achenbach S, Moselewski F, Ropers D, Ferencik M, Hoffmann U, MacNeill B, Pohle K, Baum U, Anders K, Jang IK, et al. Detection of calcified and non-calcified coronary atherosclerotic plaque by contrast-enhanced, submillimeter multidetector spiral computed tomography a segment-based comparison with intravascular ultrasound. *Circulation*. 2004;109:14–17. doi: 10.1161/01.CIR.0000111517.69230.0F
25. van Rosendael AR, Lin FY, Ma X, van den Hoogen IJ, Gianni U, Al Hussein O, Al'Aref SJ, Peña JM, Andreini D, Al-Mallah MH, et al. Percent atheroma volume: optimal variable to report whole-heart atherosclerotic plaque burden with coronary CTA, the PARADIGM study. *J Cardiovasc Comput Tomogr*. 2020;14:400–406. doi: 10.1016/j.jcct.2020.01.012
26. Nakanishi R, Ceponiene I, Osawa K, Luo Y, Kanisawa M, Megowan N, Nezarat N, Rahmani S, Broersen A, Kitslaar PH, et al. Plaque progression assessed by a novel semi-automated quantitative plaque software on coronary computed tomography angiography between diabetes and non-diabetes patients: a propensity–score matching study. *Atherosclerosis*. 2016;255:73–79. doi: 10.1016/j.atherosclerosis.2016.11.004
27. Kim U, Leipsic JA, Sellers SL, Shao M, Blanke P, Hadamitzky M, Kim YJ, Conte E, Andreini D, Pontone G, et al. Natural history of diabetic coronary atherosclerosis by quantitative measurement of serial coronary computed tomographic angiography: results of the PARADIGM study. *JACC Cardiovasc Imaging*. 2018;11:1461–1471. doi: 10.1016/j.jcmg.2018.04.009
28. Han D, Berman DS, Miller RJH, Andreini D, Budoff MJ, Cademartiri F, Chinnaiyan K, Choi JH, Conte E, Marques H, et al. Association of cardiovascular disease risk factor burden with progression of coronary atherosclerosis assessed by serial coronary computed tomographic angiography. *JAMA Netw Open*. 2020;3:e2011444. doi: 10.1001/jamanetworkopen.2020.11444
29. Guembe MJ, Fernandez-Lazaro CI, Sayon-Orea C, Toledo E, Moreno-Iribas C; RIVANA Study Investigators. Risk for cardiovascular disease associated with metabolic syndrome and its components: a 13-year prospective study in the RIVANA cohort. *Cardiovasc Diabetol*. 2020;19:195–209. doi: 10.1186/s12933-020-01166-6
30. Dykun I, Bayturan O, Carlo J, Nissen SE, Kapadia SR, Tuzcu EM, Nicholls SJ, Puri R. HbA1c, Coronary atheroma progression and cardiovascular outcomes. *Am J Prev Cardiol*. 2022;9:100317. doi: 10.1016/j.ajpc.2022.100317
31. Won KB, Lee BK, Lin FY, Hadamitzky M, Kim YJ, Sung JM, Conte E, Andreini D, Pontone G, Budoff MJ, et al. Glycemic control is independently associated with rapid progression of coronary atherosclerosis in the absence of a baseline coronary plaque burden: a retrospective case-control study from the PARADIGM registry. *Cardiovasc Diabetol*. 2022;21:239. doi: 10.1186/s12933-022-01656-9
32. Casula M, Colpani O, Xie S, Catapano AL, Baragetti A. HDL in atherosclerotic cardiovascular disease: in search of a role. *Cells*. 2021;10:1869. doi: 10.3390/cells10081869
33. Xepapadaki E, Nikdima I, Sagiadinou EC, Zvintzou E, Kypreos KE. HDL and type 2 diabetes: the chicken or the egg? *Diabetologia*. 2021;64:1917–1926. doi: 10.1007/s00125-021-05509-0
34. Xepapadaki E, Maulucci G, Constantinou C, Karavia EA, Zvintzou E, Daniel B, Sasson S, Kypreos KE. Impact of apolipoprotein A1- or lecithin:cholesterol

acyltransferase-deficiency on white adipose tissue metabolic activity and glucose homeostasis in mice. *Biochim Biophys Acta Mol Basis Dis*. 2019;1865:1351–1360. doi: 10.1016/j.bbadis.2019.02.003
35. He G, Yang G, Huang X, Luo D, Tang C, Zhang Z. SGLT2 inhibitors for prevention of primary and secondary cardiovascular outcomes: a meta-analysis of randomized controlled trials. *Heart Lung*. 2023;59:109–116. doi: 10.1016/j.hrtlng.2023.02.009
36. Smit JM, van Rosendael AR, El Mahdiui M, Neglia D, Knuuti J, Saraste A, Buechel RR, Teresinska A, Pizzi MN, Roque A, et al. Impact of clinical characteristics and statins on coronary plaque progression by serial computed tomography angiography. *Circ Cardiovasc Imaging*. 2020;13:e009750. doi: 10.1161/CIRCIMAGING.119.009750
37. van Rosendael AR, Bax AM, Smit JM, van den Hoogen IJ, Ma X, Al'Aref S, Achenbach S, Al-Mallah MH, Andreini D, Berman DS, et al. Clinical risk factors and atherosclerotic plaque extent to define risk for major events in patients without obstructive coronary artery disease: the long-term coronary computed tomography angiography CONFIRM registry. *Eur Heart J Cardiovasc Imaging*. 2020;21:479–488. doi: 10.1093/ehjci/jez322
38. Ma J, Li Y, Yang X, Liu K, Zhang X, Zuo X, Ye R, Wang Z, Shi R, Meng Q, et al. Signaling pathways in vascular function and hypertension: molecular mechanisms and therapeutic interventions. *Signal Transduct Target Ther*. 2023;8:168. doi: 10.1038/s41392-023-01430-7
39. Arnlöv J, Ingelsson E, Sundström J, Lind L. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. *Circulation*. 2010;121:230–236. doi: 10.1161/CIRCULATIONAHA.109.887521
40. Kip KE, Marroquin OC, Kelley DE, Johnson BD, Kelsey SF, Shaw LJ, Rogers WJ, Reis SE. Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) study. *Circulation*. 2004;109:706–713. doi: 10.1161/01.CIR.0000115514.44135.A8
41. Younis A, Younis A, Goldkorn R, Goldenberg I, Peled Y, Tzur B, Klempfner R. The association of body mass index and 20-year all-cause mortality among patients with stable coronary artery disease. *Heart Lung Circ*. 2019;28:719–726. doi: 10.1016/j.hlc.2018.02.015
42. Held C, Hadziosmanovic N, Aylward PE, Hagström E, Hochman JS, Stewart RAH, White HD, Wallentin L. Body mass index and association with cardiovascular outcomes in patients with stable coronary heart disease - a STABILITY substudy. *J Am Heart Assoc*. 2022;11:e023667. doi: 10.1161/JAHA.121.023667
43. Gao JW, You S, Liu ZY, Hao QY, Wang JF, Vuitton DA, Zhang SL, Liu PM. Different metabolic phenotypes of obesity and risk of coronary artery calcium progression and incident cardiovascular disease events: the CARDIA study. *Arterioscler Thromb Vasc Biol*. 2022;42:677–688. doi: 10.1161/ATVBAHA.122.317526
44. Antonio-Villa NE, Juárez-Rojas JG, Posadas-Sánchez R, Reyes-Barrera J, Medina-Urrutia A. Visceral adipose tissue is an independent predictor and mediator of the progression of coronary calcification: a prospective sub-analysis of the GEA study. *Cardiovasc Diabetol*. 2023;22:81. doi: 10.1186/s12933-023-01807-6
45. Murguía-Romero M, Jiménez-Flores JR, Sigrist-Flores SC, Espinoza-Camacho MA, Jiménez-Morales M, Piña E, Méndez-Cruz AR, Villalobos-Molina R, Reaven GM. Plasma triglyceride/HDL-cholesterol ratio, insulin resistance, and cardiometabolic risk in young adults. *J Lipid Res*. 2013;54:2795–2799. doi: 10.1194/jlr.M040584
46. Vega GL, Barlow CE, Grundy SM, Leonard D, DeFina LF. Triglyceride-to-high-density-lipoprotein-cholesterol ratio is an index of heart disease mortality and of incidence of type 2 diabetes mellitus in men. *J Invest Med*. 2014;62:345–349. doi: 10.2310/JIM.0000000000000044
47. Natali A, Baldi S, Bonnet F, Petrie J, Trifirò S, Tricò D, Mari A; RISC Investigators. RISC Investigators. Plasma HDL-cholesterol and triglycerides, but not LDL-cholesterol, are associated with insulin secretion in nondiabetic subjects. *Metabolism*. 2017;69:33–42. doi: 10.1016/j.metabol.2017.01.001
48. Chen Z, Chen G, Qin H, Cai Z, Huang J, Chen H, Wu W, Chen Z, Wu S, Chen Y. Higher triglyceride to high-density lipoprotein cholesterol ratio increases cardiovascular risk: 10-year prospective study in a cohort of Chinese adults. *J Diabetes Investig*. 2020;11:475–481. doi: 10.1111/jdi.13118
49. Ballantyne CM, Olsson AG, Cook TJ, Mercuri MF, Pedersen TR, Kjekshus J. Influence of low high density lipoprotein cholesterol and elevated triglyceride on coronary heart disease events and response to simvastatin therapy in 4S. *Circulation*. 2001;104:3046–3051. doi: 10.1161/hc5001.100624
50. Bittner V, Johnson BD, Zineh I, Rogers WJ, Vido D, Marroquin OC, Bairey-Merz CN, Sopko G. The triglyceride/high-density lipoprotein cholesterol ratio predicts all cause mortality in women with suspected myocardial ischemia: a report from the Women's Ischemia Syndrome Evaluation (WISE). *Am Heart J*. 2009;157:548–555. doi: 10.1016/j.ahj.2008.11.014
51. Bittner V, Johnson BD, Zineh I, Rogers WJ, Vido D, Marroquin OC, Bairey-Merz CN, Sopko G. Triglyceride and triglyceride/HDL (high density lipoprotein) ratio predict major adverse cardiovascular outcomes in women with non-obstructive coronary artery disease. *J Am Heart Assoc*. 2019;8:e009442. doi: 10.1161/JAHA.118.009442
52. Sultani R, Tong DC, Peverelle M, Lee YS, Baradi A, Wilson AM. Elevated triglycerides to high-density lipoprotein cholesterol (TG/HDL-C) ratio predicts long-term mortality in high-risk patients. *Heart Lung Circ*. 2020;29:414–421. doi: 10.1016/j.hlc.2019.03.019
53. Welty FK. How do elevated triglycerides and low HDL-cholesterol affect inflammation and atherothrombosis? *Curr Cardiol Rep*. 2013;15:400. doi: 10.1007/s11886-013-0400-4
54. Di Giorgi N, Michelucci E, Smit JM, Scholte AJHA, El Mahdiui M, Knuuti J, Buechel RR, Teresinska A, Pizzi MN, Roque A, et al. A specific plasma lipid signature associated with high triglycerides and low HDL cholesterol identifies residual CAD risk in patients with chronic coronary syndrome. *Atherosclerosis*. 2021;339:1–11. doi: 10.1016/j.atherosclerosis.2021.11.013
55. Caselli C, De Caterina R, Smit JM, Campolo J, El Mahdiui M, Ragusa R, Clemente A, Sampietro T, Clerico A, Liga R, et al. Triglycerides and low HDL cholesterol predict coronary heart disease risk in patients with stable angina. *Sci Rep*. 2021;11:20714. doi: 10.1038/s41598-021-00020-3
56. Saladini F, Palatini P. Is intensive blood pressure reduction a possible solution to counteract the development of diabetes mellitus? *Eur J Prev Cardiol*. 2023;30:986–987. doi: 10.1093/eurjpc/zwad150