JACC: CARDIOVASCULAR IMAGING VOL. 12, NO. 7, 2019

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

Plaque Morphology as Predictor of Late Plaque Events in Patients With Asymptomatic Type 2 Diabetes

A Long-Term Observational Study

David A. Halon, MB ChB,[a] Idit Lavi, MPH,[b] Ofra Barnett-Griness, PhD,[b] Ronen Rubinshtein, MD,[c] Barak Zafrir, MD,[d] Mali Azencot, PhD,[a] Basil S. Lewis, MD[a,c]

ABSTRACT

OBJECTIVES The authors used coronary computed tomography angiography (CTA) to determine plaque characteristics predicting individual late plaque events precipitating acute coronary syndromes (ACS) in a cohort of asymptomatic type 2 diabetic patients.

BACKGROUND In patients with coronary artery disease, CTA plaque characteristics may predict mid-term patient events.

METHODS Asymptomatic patients with diabetes 55 to 74 years of age with no history of coronary artery disease (N = 630) underwent baseline 64-slice CTA and detailed plaque level analysis. All subsequent clinical events were recorded and adjudicated. In patients who developed ACS, culprit plaque was identified at invasive angiography and its precursor located on the baseline CTA. Plaque characteristics predicting an ACS-associated culprit plaque event were analyzed by time to event accounting for inpatient clustering of plaques and competing events.

RESULTS Among 2,242 plaques in 499 subjects, 24 ACS culprit plaques were identified in 24 subjects during median follow-up of 9.2 years (interquartile range: 8.4 to 9.8 years). Plaque volume (upper vs. lower quartile hazard ratio [HR]: 6.9; 95% confidence interval [CI]: 1.6 to 30.8; p = 0.011), percentage of low-density plaque content <50 Hounsfield units (HR: 14.2; 95% CI: 1.9 to 108; p = 0.010), and mild plaque calcification (HR vs. all other plaques 3.3 [95% CI: 1.5 to 7.3]; p = 0.004) predicted plaque events univariately and after adjustment by clinical risk score. A culprit plaque event occurred in 13 of 376 (3.5%) high-risk plaques (HRP) (plaques with ≥2 risk predictors) versus 11 of 1,866 (0.6%) in non-HRPs (p < 0.0001), at 12 of 343 (3.5%) stenotic sites (≥50%) versus 12 of 1,899 (0.6%) nonstenotic sites (p < 0.0001) and in 7 of 131 (5.3%) HRP with stenosis (p < 0.0001 vs. all others). In 130 (20.6%) subjects, no coronary plaque was present on baseline CTA.

CONCLUSIONS In asymptomatic patients with type 2 diabetes, CTA plaque volume, percent low-density plaque content, and mild calcification predicted late plaque events. The additional presence of luminal stenosis increased the probability of an acute event. (J Am Coll Cardiol Img 2019;12:1353-63) © 2019 by the American College of Cardiology Foundation.

Diabetes mellitus (DM) is an independent risk factor for adverse atherosclerotic events (1). Several studies have examined the additional risk in this population afforded by an elevated coronary artery calcium (CAC) score and the additional prognostic information obtained by coronary arterial findings on cardiac computed tomography angiography (CTA) (2-5). The composition

From the [a]Cardiovascular Clinical Research Institute, Lady Davis Carmel Medical Center, Haifa, Israel; [b]Department of Community Medicine and Epidemiology, Lady Davis Carmel Medical Center, Haifa, Israel; [c]Ruth and Bruce Rappaport School of Medicine Technion-Israel Institute of Technology, Haifa, Israel; and the [d]Preventive Cardiology and Rehabilitation Service, Lady Davis Carmel Medical Center, Haifa, Israel. This study was supported by a research grant from the European Foundation for the Study of Diabetes. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received January 25, 2018; accepted February 23, 2018.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2018.02.025

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CABG = coronary artery bypass grafting

CAC = coronary artery calcium

CAD = coronary artery disease

CI = confidence interval

CTA = computed tomography angiography

DM = diabetes mellitus

HR = hazard ratio

HRP = high-risk plaque

HU = Hounsfield units

IQR = interquartile range

LDL-C = low-density lipoprotein cholesterol

PCI = percutaneous coronary intervention

of coronary arterial plaques in patients with diabetes is different to that of patients without diabetes and may be responsible for increased risk in this population (6). Although plaque characteristics have been related to outcome events in some patient populations (7–10), there are few long-term data relating baseline CTA plaque characteristics and morphology to a late plaque event (causing an acute coronary syndrome) in an initially asymptomatic diabetic population with no clinical history of coronary artery disease (CAD).

SEE PAGE 1364

METHODS

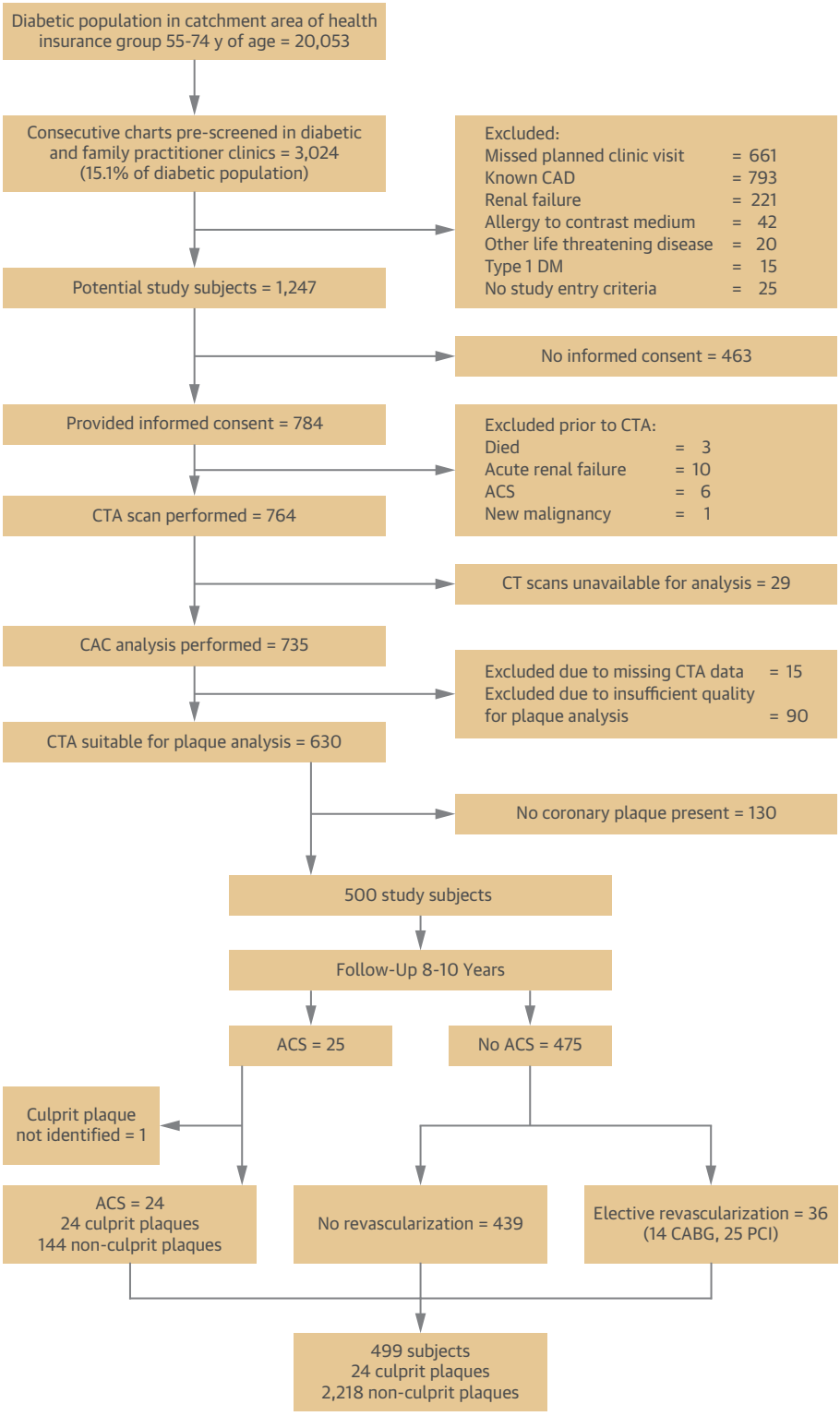
STUDY POPULATION. The study cohort of 630 subjects was derived as detailed in Figure 1. Eligible subjects had type 2 DM, age 55 to 74 years of age, no history of CAD, and at least 1 additional cardiovascular risk factor: DM diagnosed ≥5 years previously; systemic hypertension; current smoking; age >60 years; family history of CAD in a first-degree relative <55 years of age; peripheral, cerebral, or carotid vascular disease; diabetic retinopathy; neuropathy; or albuminuria. Ethics approval was obtained from the Ethics Committee of the Lady Davis Carmel Medical Center and all patients provided written informed consent before study inclusion. Exclusion criteria were serum creatinine >1.4 mg/100 ml, allergy to contrast media, and chronic atrial fibrillation. Baseline clinical risk was assessed using the UKPDS (United Kingdom Prospective Diabetes Study) coronary heart disease risk score. Treating physicians and study participants received an assessment of risk (below average, average, or above average) based on the CAC score. If high-grade stenosis of the left main or very proximal left anterior descending arteries was diagnosed, the subject was referred to an independent cardiologist who assessed the subjects by standard means (generally exercise and or nuclear stress testing) without specific knowledge of the CTA findings.

CARDIAC SCANNING PARAMETERS. CTA was performed between October 2006 and October 2008 with a 64-slice scanner (Brilliance CT, Philips Healthcare, Cleveland, Ohio) using a spiral, retrospective, electrocardiograph-gated protocol. Beta blockers and sublingual nitrates were used routinely. Details of the scanning procedure have previously been described (11). Two slightly different concentrations of intravenous contrast agent were used (370 mg iodine/ml in 54% subjects; 350 mg iodine/ml in 46% subjects). The dose-length product was 779 ± 201 mGy/cm equivalent to 13.2 ± 3.4 mSv.

CORONARY ARTERY AND PLAQUE ANALYSIS. All scans were examined in axial, multiplanar reformat and short-axis cross-sectional views by 1 viewer. A second viewer examined a sample of 100 plaques in 30 subjects. Window settings were adjusted by the operator to obtain the best differentiation between plaque, surrounding tissue, and vessel lumen and to differentiate between intraplaque densities. Plaque was defined as any extraluminal density that could be clearly assigned to the coronary arterial wall. Plaque position and length were defined along the arterial centerline. Dedicated cardiac analysis software with a plaque analysis application (Cardiac Viewer and Comprehensive Cardiac Analysis, Extended Brilliance Workspace V4.0.2, Philips Healthcare) was used for plaque definition and analysis with manual adjustment as required. Only studies with good or adequate delineation of arterial borders were used for analysis.

Plaque and artery volumes were calculated for each plaque individually. Plaque burden was calculated for each plaque as the volume of plaque divided by the total volume of the same section of coronary artery containing the plaque. Area remodeling was measured as maximal cross-sectional artery area at plaque/plaque-free cross-sectional area, sited proximally whenever possible. Bifurcations were assessed by the Medina classification (12). We analyzed bifurcations in which plaque involved all aspects of the bifurcation in relation to all other plaques. Coronary stenosis was assessed visually on a 5-point scale (0 = no plaque, 1 = plaque with <25% narrowing, 2 = 25% to 49%, 3 = 50% to 74%, 4 = 75% to 99%, 5 = 100%). Calcification was assessed visually on a 6-point scale (0 = none, 1 = minimal, 2 = greater than minimal but <50%, 3 = 50% to 70%, 4 = 71% to 94%, 5 = 95% to 100%). A graphic representation of the frequency distribution of the volume and CT density of each constituent plaque was presented by the software and stored numerically in a data file. To exclude artifact at arterial borders CT densities below -40 Hounsfield units (HU) were considered to be fatty tissue outside the arterial wall and were excluded from analysis (13). Both intrapericardial fat, possibly related to adipose tissue inflammation, and mechanical factors related to endothelial shear stress, which varies with changing blood flow and stress patterns related to the position of plaque and the bending pattern of the artery, have been shown to predict outcome events (14,15). We therefore also examined if plaques facing the pericardium, which are most likely

FIGURE 1 **Derivation of the Study Population**



ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; CAC = coronary artery calcium; CAD = coronary artery disease; CT = computed tomography; CTA = computed tomography angiography; DM = diabetes mellitus; PCI = percutaneous coronary intervention.

TABLE 1 Individual Patient Data for Patients With ACS During Follow-Up

Patient #	ACS Type	Time From CTA to ACS (yrs)	Segment Involved	Stenosis Grade on Baseline CTA*	No. of High-Risk Plaque Features†
1	STEMI	0.6	Proximal RCA	3	2
2	NSTEMI	9.7	Proximal LAD	2	1
3	STEMI	3.8	Proximal LAD	4	1
4	STEMI	8.3	Mid-LAD	4	1
5	STEMI	7.8	First diagonal	3	2
6	STEMI	1.0	Mid-LAD	3	3
7	UAP	0.9	Proximal LAD	1	3
8	UAP	6.1	Mid-LAD	2	1
9	NSTEMI	3.8	Mid-RCA	2	0
10	NSTEMI	4.3	LM	2	2
11	STEMI	1.9	Proximal LAD	2	2
12	UAP	0.5	Proximal RCA	3	3
13	UAP	4.4	Mid-RCA	2	3
14	NSTEMI	2.4	Proximal Cx	1	1
15	NSTEMI	0.6	Mid-LAD	3	2
16	NSTEMI	8.5	Proximal LAD	2	2
17	STEMI	7.5	PDA	3	1
18	STEMI	4.8	Proximal LAD	4	3
19	NSTEMI	7.6	Proximal Cx	1	0
20	NSTEMI	2.5	Mid-Cx	3	2
21	STEMI	4.8	Mid-RCA	2	3
22	NSTEMI	3.7	Mid-LAD	3	1
23	NSTEMI	6.6	Mid-Cx	1	0
24	STEMI	1.8	Mid-LAD	2	0

*Grade 1 = 0%–24% luminal narrowing on visual assessment; grade 2 = 25%–49%; grade 3 = 50%–69%; grade 4 =70%–99%; grade 5 = 100%. †Features considered: upper quartile for plaque volume or percent low-density plaque (<50 HU) or presence of mild calcification (<50% calcified).

ACS = acute coronary syndrome; CTA = computed tomography angiography; Cx = left circumflex coronary artery; LAD = left anterior descending coronary artery; LM = left main coronary artery; PDA = posterior descending branch of the right coronary artery; RCA = right coronary artery; NSTEMI = non–ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; UAP = unstable angina pectoris.

to be in immediate proximity to overlying fat or plaques on the inner or outer curvatures of the artery, were more likely to be related to events. Interobserver variation was examined in 100 individual coronary plaques in 30 patients following resegmentation, and moderate correlation was previously reported (11).

FOLLOW-UP. All acute coronary syndrome (ACS) events were identified using an electronic database encompassing all national hospitalizations and laboratory investigations for the health maintenance organization to which all study subjects belonged. All events were adjudicated according to pre-defined criteria by an independent adjudication committee presented with all current clinical and laboratory data while blinded to baseline CAC and CTA data. Deaths were identified from a national registry of deaths. Patients with ACS underwent invasive angiography at the presenting hospital; the angiographic film was obtained by the study center. The culprit plaque was identified on the angiographic film with the aid of clinical data as necessary and on the baseline CTA with the aid of anatomic landmarks. Plaques undergoing elective percutaneous intervention (PCI) and all plaques after coronary artery bypass surgery (CABG) were censored at this time.

STATISTICAL ANALYSIS. Statistical Analysis Software, version 9.4 (SAS Institute, Cary, North Carolina), was used for most statistical analyses. Categorical variables are presented as numbers and percentages and continuous variables as mean ± SD or median (interquartile range [IQR]). Time to a culprit plaque event was estimated by the cumulative incidence function and elective revascularization and death before an event were considered as competing events. Cumulative incidence function curves were compared by the method of Fine and Gray (16). The association between study variables and time to a culprit plaque event was evaluated with the use of cause-specific hazard ratios (HR) and 95% confidence intervals (CI), estimated by the Cox proportional hazards model with adjusted standard errors to account for correlations induced by clustering of plaques within patients (SAS PHREG procedure, sandwich formula). A nested, matched, case-control sensitivity analysis was conducted in ACS patients (24 culprit, 144 nonculprit plaques) in which each nonculprit plaque served as a "control" for a culprit plaque. Conditional logistic regression was used to assess association between study variables and culprit plaque events (IBM SPSS, version 24). All p values are 2-tailed and level of significance was 0.05.

RESULTS

In 130 of 630 subjects (20.6%), no coronary plaque was present; these were excluded from the current analysis (**Figure 1**). These subjects suffered no ACS events throughout the follow-up period. The median plaque follow-up was 9.2 years (IQR: 8.4 to 9.8 years) and ACS events were identified following event adjudication in 25 patients. A single culprit plaque was identified on coronary angiography in 24 patients, whereas in 1 patient with severe multivessel disease a culprit plaque could not be identified. In addition to 24 culprit plaques, these ACS patients had 144 nonculprit plaques on the baseline CTA. In the total cohort of 499 subjects, 2,242 plaques were identified on the baseline CTA. In 36 patients without ACS, an elective revascularization procedure was performed (14 CABG, 25 PCI) at a mean of 4.1 ± 2.9 years after CTA (**Figure 1**). The type of ACS event, its timing in relation to the baseline CTA, stenosis grade on baseline CTA, and the number of high-risk plaque characteristics are tabulated in **Table 1**. Clinical characteristics and laboratory data of subjects at study

entry and at the time of ACS are listed in Table 2. Findings were mostly similar in the ACS and non-ACS cohorts, but no subject in the ACS cohort had a baseline low density lipoprotein cholesterol (LDL-C) level <70 mg/dl in contrast to 66 (13.9%) in the non-ACS cohort (p = 0.050). In contrast to this, we found a clear relationship between a low-density plaque volume >10% of total plaque (density <50 HU) and plasma lipid levels (LDL-C: 99.7 ± 31.1 vs. 96.5 ± 27.3, p = 0.012; high-density lipoprotein cholesterol: 44.8 ± 10.4 vs. 48.1 ± 11.1, p < 0.0001; non-high-density lipoprotein cholesterol: 135.1 ± 39.0 vs. 129.6 ± 35.5, p = 0.001).

Plaque variables examined for prediction of ACS culprit plaque are shown in Table 3. Data are provided separately for the entire plaque and for the maximal plaque cross-section. The most prominent predictors of ACS culprit plaque were larger plaque volume, percent low density plaque content (Figure 2), and mild calcification on visual assessment (Figure 3). Mild plaque calcification was associated with more culprit plaques, whereas heavy plaque calcification was a stabilizing factor. High-risk plaque (HRP) was designated as plaque with any 2 of the previously mentioned 3 high-risk characteristics. A culprit plaque ACS event occurred in 13 of 376 (3.5%) HRPs and in 11 of 1,866 (0.6%) non-HRPs (p < 0.0001). The cumulative incidence of events increased with the number of high-risk characteristics (Figure 2). Luminal stenosis was also a predictor of a plaque event, with the latter occurring in 11 of 341 (3.2%) of stenoses (≥50%) and in 13 of 1,901 (0.7%) without stenosis (p < 0.0001). In the presence of HRP and stenosis (N = 131) culprit plaque events occurred in 7 (5.3%) (p < 0.0001 vs. all other plaques) (Figure 2). In addition, visual assessment demonstrated that plaques involving bifurcations, involving that portion of the artery facing the pericardium, or causing luminal stenosis were more likely to develop into culprits (Table 3). The prevalence, HRs, and test characteristics for combinations of predictors of culprit plaque are shown in Figure 4. Despite the high HR of various plaque characteristics for an ACS culprit plaque event, the positive predictive value of any individual or combination of characteristics remained low because of the very large number of stable plaques and small number of culprits.

MAXIMAL PLAQUE CROSS-SECTION. Findings for maximal cross-section of plaque were qualitatively similar to those for the total plaque. In addition, circumferential plaque extent and plaque eccentricity at this site predicted culprit plaque outcomes (Table 3). The remodeling index was numerically higher in culprit than nonculprit plaques but not significantly different.

TABLE 2 Clinical and Laboratory Characteristics of Patients With and Without Subsequent ACS

	ACS (N = 24)	No ACS (N = 475)	p Value
Age, yrs	63.2 ± 5.5	64.0 ± 5.3	0.45
Male	17 (70.8)	252 (53.3)	0.092
BMI, kg/m^2	28.6 ± 3.9	29.0 ± 4.7	0.66
Duration DM, yrs	12.4 ± 9.4	10.4 ± 7.6	0.23
Hypertension	16 (66.7)	322 (67.8)	0.91
Smoking, pack-yrs	13.3 ± 19.0	15.8 (24.6)	0.63
UKPDS risk score	20.5 ± 10.3	19.0 ± 11.5	0.54
HbA_{1c} (%) at baseline	8.0 ± 1.8	7.4 ± 1.5	0.105
HbA_{1c} (%) at ACS or follow-up	7.4 ± 1.5	7.5 ± 1.4	0.615
Creatinine clearance, ml/min/1.73 m^2	85.5 ± 19.5	86.9 ± 19.0	0.75
Hypoglycemic and lipid-lowering therapy			
Insulin treated	6 (25.0)	100 (21.1)	0.65
Insulin treated before ACS	9 (37.5)	902 (40.7)	0.75
Number of hypoglycemic drugs at study entry			
0	1 (4.2)	52 (10.9)	
1	11 (45.8)	179 (37.7)	
2	9 (37.5)	168 (35.4)	
3	3 (12.5)	73 (15.4)	
4	0 (0)	3 (0.6)	0.951
Metformin at baseline	20 (83.3)	368 (77.4)	0.500
Statin treated at baseline	18 (75)	349 (73.5)	0.816
Statin treated at follow-up	18 (78.3)*	379 (84.2)	0.45
Plasma lipids			
Cholesterol at baseline	186.7 ± 43.9	178.9 ± 36.0	0.307
Cholesterol at ACS or follow-up	154.5 ± 46.8	153.7 ± 37.9	0.923
HDL-C at baseline	46.6 ± 10.9	47.0 ± 11	0.843
HDL-C at ACS or follow-up	41.0 ± 11.9	46.7 ± 17.5	0.107
TG at baseline	192.3 ± 189.9	173.0 ± 124.7	0.623
TG at ACS or follow-up	181.7 ± 193.8	146.7 ± 82.1	0.387
LDL-C at baseline†	105.4 ± 28.9	97.5 ± 28.6	0.207
LDL-C <70 mg/dl at baseline	0	66 (13.9)	0.050
LDL-C at ACS or follow-up	79.8 ± 30.6	79.2 ± 34.5	0.930
Non-HDL-C at baseline	140 ± 40	131 ± 36	0.24
Non-HDL at ACS or follow-up	113.5 ± 44.0	106.9 ± 37.1	0.382

Values are mean ± SD or n (%). *Some missing data. †Not calculated in 3 ACS and 71 non-ACS subjects at baseline and in 2 ACS and 30 non-ACS subjects at follow-up or ACS because of TG >400 mg/dl.

ACS = acute coronary syndrome; BMI = body mass index; DM = diabetes mellitus; HbA_{1c} = hemoglobin A_{1c}; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; UKPDS = United Kingdom Prospective Diabetes Study.

ADJUSTMENT FOR RISK FACTORS. An adjustment for patient risk factors was made in a model including the UKPDS risk score in addition to plaque volume, percent low density plaque, and mild plaque calcification. The latter 3 variables were independent predictors of a culprit plaque outcome (plaque volume: p = 0.0007 [HR: 1.03; 95% CI: 1.01 to 1.04)/10 mm^3]; percent low-density content <50 HU: p = 0.003 [HR: 1.4; 95% CI: 1.1 to 1.7)/10%]; mild plaque calcification: p = 0.022 [HR: 2.6; 95% CI: 1.1 to 5.8]).

TABLE 3 Predictors of Culprit Plaque

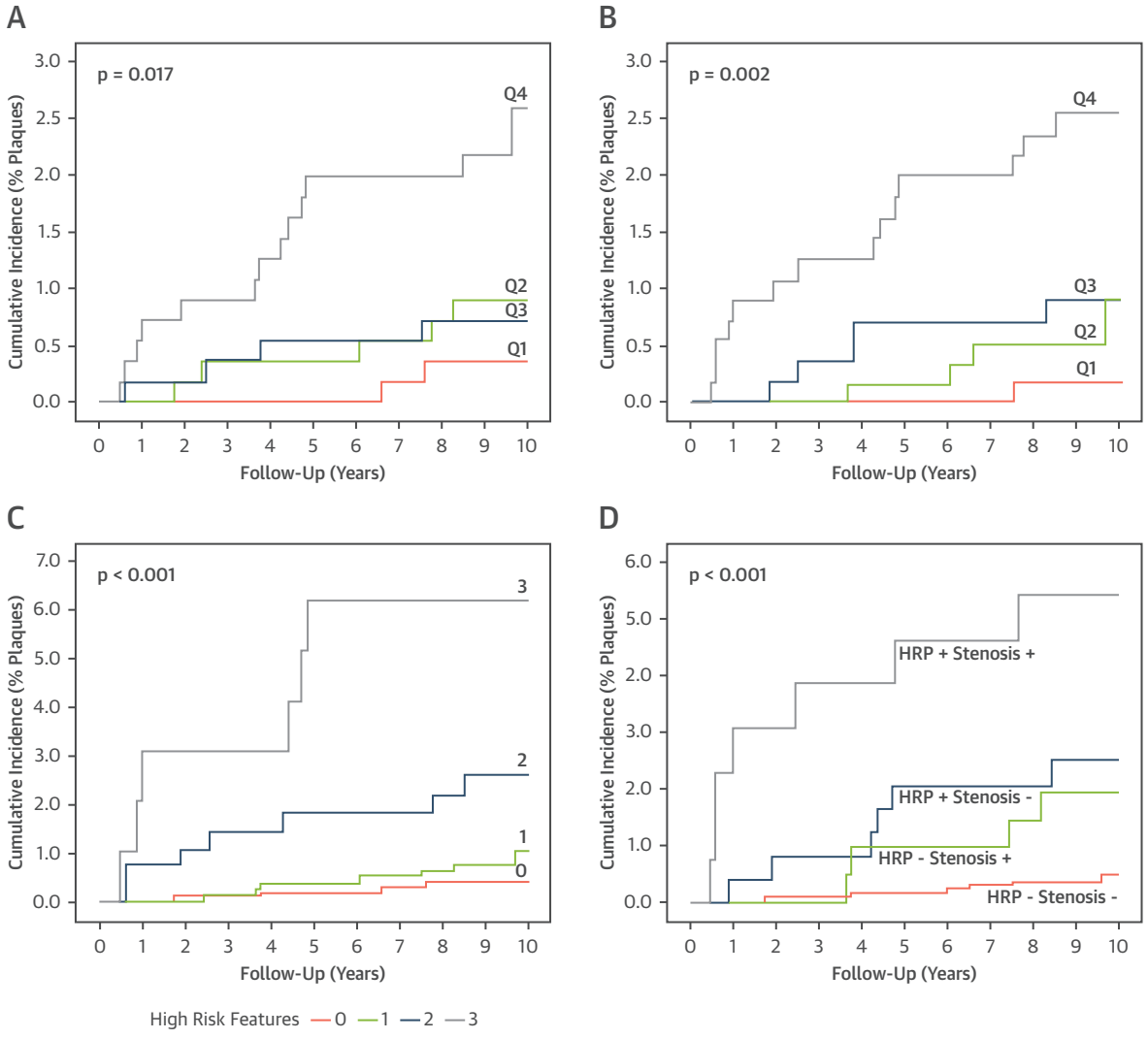
	Culprit (n = 24, 24 Plaques)	Nonculprit (n = 475, 2,218 Plaques)	HR for Plaque Event*	
			HR*	p Value*
Entire plaque				
Plaque length, mm	18.1 (9.5-31.2)	8.3 (4.8-15.4)	7.6 (1.7-33.4)	0.007
Plaque volume, mm^3	108.5 (42.6-194.2)	44.6 (23.2-94.3)	6.9 (1.6-30.8)	0.011
Plaque burden, %†	57.3 (47.1-64.3)	48.7 (37.2-60.7)	3.4 (0.91-12.4)	0.068
Min lumen area, mm^2	1.8 (1.4-3.0)	2.9 (1.5-5.3)	0.24 (0.05-1.2)	0.079
Distance from aorta, mm‡	23.6 (13.5-46.5)	26.6 (13.3-46.8)	0.27 (0.08-0.95)	0.042
Mean plaque density, HU	184.7 (134.5-313.1)	289 (206-371)	0.31 (0.10-0.94)	0.037
Plaque <30 HU, mm^3	11.2 (3.4-23.5)	2.0 (0.66-5.7)	7.3 (1.7-32.3)	0.009
Plaque <30 HU, %	9.0 (4.1-17.5)	4.4 (2.1-8.1)	14.3 (1.9-109)	0.010
Plaque <50 HU, mm^3	16.0 (4.8-35.7)	3.2 (1.2-8.9)	7.3 (1.7-32.2)	0.010
Plaque <50 HU, %	13.6 (8.3-25.7)	6.9 (3.7-12.5)	14.2 (1.9-108)	0.010
Low density plaque, ≤50 HU ≥10% of total plaque	15 (62.5)	735 (33.1)	3.4 (1.5-7.7)	0.004
Low density plaque, ≤50 HU ≥20% of total plaque	8 (33.3)	258 (11.6)	3.9 (1.6-9.0)	0.002
Plaque <150 HU, mm^3	47.5 (21.3-102.6)	13.2 (5.7-30.4)	7.9 (1.8-34.8)	0.006
Plaque <150 HU, %	50.4 (29.1-63.3)	28.2 (18.6-43.4)	14.2 (1.9-107)	0.010
Mild plaque calcification <50%§	12 (50.0)	514 (23.2)	3.3 (1.5-7.2)	0.003
Plaque-artery relations				
Stenosis ≥50%§	11 (45.8)	330 (14.9)	5.3 (2.4-11.7)	<0.0001
Plaque facing myocardium‖	18 (75.0)	930 (41.9)	2.2 (0.89-5.7)	.090
Plaque facing pericardium‖	18 (75.0)	1137 (51.3)	2.9 (1.2-7.5)	0.023
Plaque facing myocardium and pericardium	12 (50)	583 (26.3)	3.0 (1.3-6.7)	0.008
Plaque includes inner curve of artery¶	22 (91.7)	1645 (75.4)	3.5 (0.83-15.1)	0.088
Plaque includes outer curve of artery¶	14 (58.3)	1197 (54.8)	1.2 (0.55-2.8)	0.606
plaque includes both inner and outer curves¶	12 (50)	721 (33.0)	2.2 (0.96-4.8)	0.063
True bifurcation (vs. all other plaques)#	12 (50)	473 (21.3)	3.8 (1.7-8.5)	0.001
Maximal plaque X-section				
Plaque area, mm^2	9.7 (6.2-15.5)	8.1 (5.7-11.8)	1.8 (0.52-6.1)	0.363
Plaque burden, %†	73.4 (60.3-83.0)	65.8 (50.8-79.4)	9.2 (1.2-72.9)	0.035
Lumen area at maximal plaque, mm^2	3.0 (2.2-5.2)	3.8 (2.1-6.4)	0.18 (0.02-1.5)	0.113
Distance from aorta, mm	29.8 (25.9-49.6)	32.6 (19.3-51.6)	0.56 (0.07-2.3)	0.401
Mean plaque density, HU	219 (132-387)	330 (213-433)	0.42 (0.15-1.2)	0.098
Plaque <30 HU, mm^3**	0.35 (0.07-0.89)	0.13, (0.04-0.32)	3.0 (0.98-9.5)	0.055
Plaque <30 HU, %	10.5 (1.9-19.7)	3.9 (1.4-9.0)	2.2 (0.82-5.7)	0.119
Plaque <50 HU, mm^3	0.51 (0.10-1.3)	0.21 (0.08-0.50)	4.1 (1.2-14.4)	0.028
Plaque <50 HU, %	15.4 (3.9-28.7)	6.3 (2.6-13.3)	3.3 (1.1-10.0)	0.038
Plaque <150, mm^3	1.4 (0.58-3.3)	0.80 (0.43-1.6)	3.4 (0.94-12.5)	0.062
Plaque <150 HU, %	43.1 (14.8-64.1)	24.2 (14.5-41.0)	2.0 (0.75-5.3)	0.162
Plaque circumferential extent	300 (30-360)	210 (180-300)	8.1 (1.1-61.0)	0.043
Plaque eccentricity††	0.87 (0.73-0.91)	0.90 (0.86-0.93)	0.26 (0.07-0.93)	0.038
Arterial remodeling‖‖	1.7 (1.3-2.2)	1.5 (1.2-1.8)	2.6 (0.82-8.5)	0.104

Values are median (IQR) or n (%). *For continuous variables, HRs and p values are for upper versus lower quartiles. †Calculated as percentage plaque volume/total arterial volume along length of plaque. ‡Measured to proximal border of plaque. §Visual analysis. ‖At least part of plaque facing myocardium or pericardium, respectively. ¶Not assessed for 6 nonculprit plaques in straight portion of artery. Percentages are of plaques assessed. #Medina type 3 (plaque proximal, directly opposite, and distal to side branch) versus all others. **The cross section has a patient-specific slice thickness providing a volume rather than cross-sectional area of plaque. ††Calculated as 1 – (minimal plaque thickness/maximal plaque thickness). ‖‖Cross-sectional area of artery at maximal plaque area/proximal arterial reference area.

HR = hazard ratio; HU = Hounsfield units.

ADDITIONAL FINDINGS. Two different iodine concentrations of contrast agents were used for the baseline CTA (350 and 370 mg iodine/ml). Mean enhancement of the left main and proximal 25 cross sections of the left anterior descending coronary arteries in subjects without coronary plaque was 359 ± 62 HU versus 371 ± 68 HU, respectively; p = 0.081. The volume and percentage content of low-density plaque <30 HU and <50 HU were on average 16% less with the lower iodine concentration (p = 0.002 and 0.004, respectively); however, the iodine concentration of the contrast agent was not a predictor of culprit plaque on univariate analysis (p = 0.33).

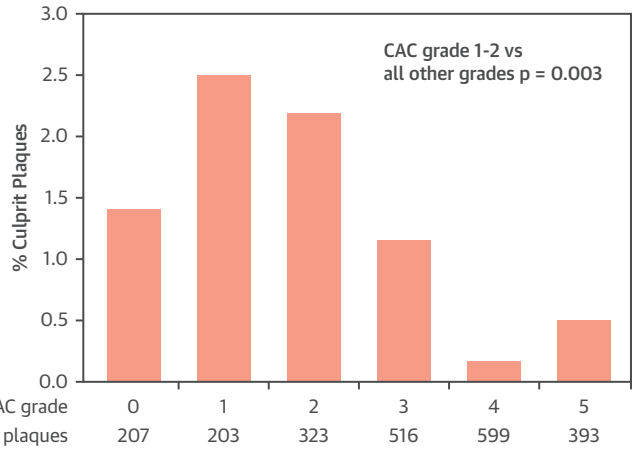
FIGURE 2 **ACS Culprit Plaque Events**



Cumulative incidence of events in relation to **(A)** quartiles of plaque volume. **(B)** Quartiles of percentage low-density plaque content <50 Hounsfield units. **(C)** Number of high-risk plaque characteristics present (none, plaque volume, percentage low-density content, mild calcification). **(D)** Combinations of HRP (≥2 HRP characteristics) and luminal stenosis. ACS = acute coronary syndrome; HRP = high-risk plaque; Q1-Q4 = first to fourth quartiles.

We performed a sensitivity analysis by exclusion of small-volume, heavily calcified plaques. Plaques ≥70% calcified by visual analysis (grade 3 to 4) (Figure 4) and plaques in the lowest quartile of volume were both sequentially excluded. Excluding small volume plaques, plaque volume ($p = 0.001$), percent content <30 HU ($p < 0.0001$), and percent content <50 HU ($p < 0.0001$) remained significant predictors of plaque outcome. Excluding heavily calcified plaques, plaque volume ($p < 0.001$), percent content <30 HU, and <50 HU ($p = 0.006$ for both) remained significant predictors and excluding both small volume and heavily calcified plaques, plaque volume ($p = 0.005$), percent content <30 HU ($p = 0.006$) and percent content <50 HU ($p = 0.005$) remained significant predictors of culprit plaque. In addition, we examined predictors of culprit plaque in the 24 ACS patients with 168 plaques that acted as their own controls for patient-related variables and found similar plaque-related outcome predictors (Table 4).

FIGURE 3 Culprit Plaque in Relation to Baseline Calcium Grade



The proportion of plaques at each baseline CTA calcium grade that became late culprit plaques is shown. Plaques with mild calcification were most likely to become culprit plaques, whereas plaques at high calcium grades were likely to remain stable. Abbreviation as in Figure 1. For definition of calcium grades, see the Methods section in text. CAC = coronary artery calcium; CTA = computed tomography angiography.

DISCUSSION

This study showed that in this initially asymptomatic diabetic patient cohort, most plaques leading to late clinical events had at least 1 HRP characteristic on baseline CTA and in 54% of cases 2 HRP characteristics were present. Nearly one-half of the culprit plaques were associated with a ≥50% luminal stenosis on the baseline CTA (Table 2). The time to a plaque event was often prolonged (median 4.0; range 0.5 to 9.7 years), attesting to the chronicity of atherosclerotic CAD with a low individual plaque event rate in this asymptomatic population (Figure 2).

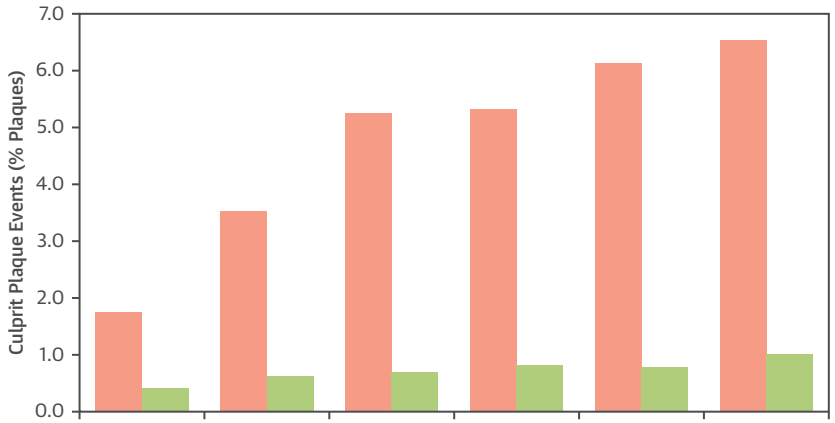
Although multivessel coronary arterial plaque was common, totally plaque-free arteries were found on baseline CTA in an important 20% subgroup of patients, attesting to the heterogeneity of coronary arterial findings in patients with type 2 diabetes. Subjects without coronary plaque were excluded from the present analysis. Quantitative analysis showed that larger volume plaques, particularly those with a greater low-density content and mild calcification, were the most likely to become culprit ACS plaques over the following 8 to 10 years; however, the vast majority of coronary plaques were not involved in an acute clinical event over the follow-up period. Thus despite a high HR of the designated HRP for plaque events, the positive predictive value of a specified HRP remained low (around 5% over 8 to 10 years) (Figure 4), highlighting the improbability that individual plaque interventions based on CTA criteria would be of prophylactic benefit. Studies in patients without diabetes have demonstrated similar plaque characteristics acutely and at mid-term outcomes (7-10,17). A recent study examining combined patient outcomes in asymptomatic patients with diabetes reported two-thirds of patient events among those with CTA defined obstructive disease (2).

Clinical data, particularly control of diabetes and plasma lipids, were previously correlated both with plaque characteristics and outcome events (11,18). In view of the limited number of events in the current study, we could only show a correlation of ACS of borderline significance with baseline LDL-C levels (Table 2); however, we have reported a clear correlation between baseline plasma lipids and extent of low-density plaque.

In the current study, identification of plaque events was based on patient presentation with ACS. Silent plaque events may occur without clinical consequences because of dissolution of non-obstructive plaque-associated thrombus or intraplaque hemorrhage with plaque healing. The latter may lead to increase in plaque size and additional luminal stenosis (19). The determinants of progression to a clinically recognizable event may depend not only on plaque characteristics, but also the extent of the prothrombotic milieu, arterial tone or spasm, plaque and arterial geometry, and flow characteristics at the time of a localized plaque event as well as the presence of a recruitable collateral circulation (20,21). We found that plaque facing the pericardium, and therefore more likely to be in intimate contact with intrapericardial lipid, was more likely to become an ACS plaque. The relation of intrapericardial lipid volume and inflammation with outcomes has been reported (14). We found only a tendency to more ACS from plaques on the inner surface of arterial bends where lower endothelial shear stress is expected (15).

Low-density plaque on CTA represents lipid-rich plaque (17). We elected to use a primary cutoff value <50 HU in our low density definition. Since others have used various values (9,22) we have also provided additional data with a cutoff <30 HU. The volume of low-density plaque identified varies with scanning protocols, the cutoff level used to define low-density plaque and the iodine content of the contrast medium, but the significance of the findings was unchanged whichever cutoff was chosen and for both contrast agent concentrations.

FIGURE 4 Test Characteristics for Combinations of Plaque Event Predictors



	1 HRA	2 HRA	Q4 Volume + Low Density	2 HRA + Stenosis	All 3 HRA	All 3 HRA + Stenosis
Hazard ratio	4.6 (1.6-13.5)	6.1 (2.7-13.6)	8.3 (3.7-18.7)	7.7 (3.2-18.6)	8.1 (3.2-20.5)	8.7 (2.6-29.3)
Prevalence (%)	52.1	16.8	8.6	5.8	4.4	2.1
Sensitivity	83.3	54.2	41.7	29.2	25.0	12.5
Specificity	48.2	83.6	91.7	94.4	95.9	98.1
PPV	1.7	3.5	5.2	5.3	6.1	6.5
NPV	99.6	99.4	99.3	99.3	99.2	99.0
PA	48.6	83.3	91.2	93.7	95.1	97.1
P-value	0.005	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0005

HRA = high-risk attribute; NPV = negative predictive value; PA = predictive accuracy; PPV = positive predictive value.

Plaques in close approximation to pericardial fat may be more susceptible to localized pro-inflammatory influences (13), and we found that plaque on the pericardial side of the artery, in proximity to intrapericardial lipid, was more likely to become culprit. Plaques at sites of coronary bifurcations were also more likely to become culprit lesions. Hemodynamic, geometric, and compositional factors are related to the increased plaque prevalence, larger volume, and more rapid progression at these sites (23,24). Whereas a higher Agatston CAC score is a predictor of coronary events, this appears to be based on the volume component of the score, whereas more dense calcium is a protective factor (25). At the level of the individual plaque, mild or spotty calcification is a predictor of adverse outcome, whereas heavy calcification is protective (25,26).

We prospectively selected maximal plaque cross-sections for special analysis and found them to be less predictive than data obtained from the plaque as a whole. This is in keeping with recent studies that have shown that the site of plaque rupture at ACS most frequently occurred proximal to the minimal luminal area and was related to plaque longitudinal asymmetry and regional distribution of hemodynamic stress (21). In distinction to other studies (9), we did not find positive remodeling to be a significant outcome predictor. This may be a real finding in this diabetic population several years before the acute event or alternatively greater positive remodeling in the culprit plaques may have been obscured by other factors. A proximal reference site only was used in the data presented, but re-examination of the data using a mean of proximal and distal references did not alter the findings (data not shown). Plaque calcification is particularly prominent in patients with diabetes, and nonculprit lesions were more heavily calcified, which may lead to greater blooming of the image at the site of the plaque in nonculprit lesions, thus tending to mask differences in arterial remodeling between stable and culprit plaque sites.

STUDY LIMITATIONS. The number of plaque events within the context of ACS was small (attesting to the long-term stability of most plaques with current medical therapy). The findings were robust because they remained significant for different cutoff definitions of low-density plaque, when plaques in the

TABLE 4 Predictors of ACS Culprit Plaque (ACS Patient Cohort)

	Culprit (N = 24)	Nonculprit (N = 144)	HR for Plaque Event*	
			HR*	p Value*
Entire plaque				
Plaque length, mm	18.1 (9.5–31.2)	9.0 (5.2–16.8)	9.2 (1.4–62.1)	0.022
Plaque volume, mm^3	108.5 (42.6–194.2)	51.1 (24.1–109.5)	6.1 (1.2–31.0)	0.027
Plaque burden, %†	57.3 (47.1–64.3)	54.4 (39.7–64.1)	2.4 (0.52–10.9)	0.267
Min lumen area, mm^2	1.8 (1.4–3.0)	2.4 (1.1–5.0)	0.43 (0.08–2.4)	0.433
Distance from aorta, mm‡	23.6 (13.5–46.5)	31.4 (14.2–65.6)	0.12 (0.03–0.50)	0.004
Mean plaque density, HU	184.7 (134.5–313.1)	287.5 (189.7–384.7)	0.22 (0.04–1.0)	0.057
Plaque <30 HU, mm^3	11.2 (3.4–23.5)	2.2 (0.85–6.3)	9.3 (1.5–59.4)	0.019
Plaque <30 HU, %	9.0 (4.1–17.5)	5.0 (2.8–8.0)	32.0 (2.3–441)	0.010
Plaque <50 HU, mm^3	16.0 (4.8–35.7)	3.6 (1.4–9.4)	9.3 (1.5–58.5)	0.017
Plaque <50 HU, %	13.6 (8.3–25.7)	8.1 (4.6–13.0)	45 (2.2–917)	0.013
Low density plaque, ≤50 HU ≥10% of total plaque	15 (62.5)	49 (34.0)	4.8 (1.6–14.3)	0.005
Low density plaque, ≤50 HU ≥20% of total plaque	8 (33.3)	17 (11.8)	4.6 (1.5–13.8)	0.007
Plaque volume <150 HU, mm^3	47.5 (21.3–102.6)	14.8 (6.1–41.1)	10.8 (1.3–91.7)	0.030
Plaque <150 HU, %	50.4 (29.1–63.3)	30.0 (20.7–46.9)	49.8 (2.8–886)	0.008
Mild plaque calcification (<50%)§	12 (50.0)	35 (24.3)	3.0 (1.1–8.1)	0.029
Plaque-artery relations				
Stenosis ≥50%§	11 (45.8)	32 (22.2)	3.8 (1.4–10.4)	0.010
Plaque facing myocardium‖	18 (75.0)	94 (65.3)	1.3 (0.50–3.6)	0.554
Plaque facing pericardium‖	18 (75.0)	69 (47.9)	2.8 (1.1–7.6)	0.038
Plaque facing myocardium and pericardium	12 (50)	41 (28.5)	2.3 (0.88–5.8)	0.090
Plaque includes inner curve of artery¶	22 (91.7)	106 (76.8)	3.3 (0.73–15.1)	0.121
Plaque includes outer curve of artery¶	14 (58.3)	78 (56.5)	1.0 (0.41–2.6)	0.947
plaque includes both inner and outer curves¶	12 (50)	49 (34.0)	2.0 (0.76–5.0)	0.163
True bifurcation, vs. all others#	12 (50)	26 (18.1)	4.2 (1.7–10.6)	0.002
Maximal plaque X-section				
Plaque area, mm^2	9.7 (6.2–15.5)	8.4 (5.7–13.0)	2.5 (0.58–10.8)	0.216
Plaque burden, %†	73.4 (60.3–83.0)	73.5 (57.9–84.1)	5.1 (0.54–48.7)	0.156
Lumen area at maximal plaque, mm^2	3.0 (2.2–5.2)	3.2 (1.6–5.8)	0.42 (0.04–4.1)	0.456
Distance from aorta, mm	29.8 (25.9–49.6)	37.8 (19.4–70.2)	1.3 (0.28–6.2)	0.731
Mean Plaque density, HU	219 (132–387)	332 (195–449)	0.33 (0.08–1.4)	0.138
Plaque <30 HU, mm^3**	0.35 (0.07–0.89)	0.16 (0.04–0.36)	4.0 (0.86–18.7)	0.077
Plaque <30 HU, %	10.5 (1.9–19.7)	4.1 (1.5–9.1)	2.4 (0.62–9.4)	0.207
Plaque <50 HU, mm^3	0.51 (0.10–1.3)	0.26 (0.08–0.59)	14.6 (1.4–153.8)	0.026
Plaque <50 HU, %	15.4 (3.9–28.7)	6.4 (2.5–13.6)	6.1 (1.1–32.9)	0.036
Plaque <150, mm^3	1.4 (0.58–3.3)	0.91 (0.41–1.9)	10.2 (1.0–99.8)	0.046
Plaque <150 HU, %	43.1 (14.8–64.1)	24.2 (15.3–42.5)	2.7 (0.56–13.3)	0.213
Plaque eccentricity††	0.87 (0.73–0.91)	0.90 (0.86–0.92)	0.35 (0.09–1.4)	0.140
Arterial remodeling area‡‡	1.7 (1.3–2.2)	1.5 (1.2–1.9)	1.3 (0.38–4.6)	0.670

Values are median (IQR) or n (%). *For continuous variables, hazard ratios and p values are for upper versus lower quartiles unless stated otherwise. †Calculated as percentage plaque volume/total arterial volume along length of plaque. ‡Measured to proximal border of plaque. §Visual analysis. Mild calcification = grades 1–2 of 0–5 grades. ‖At least part of plaque facing myocardium or pericardium, respectively. ¶Not assessed for 6 nonculprit plaques in straight portion of artery. Percentages are of plaques assessed. #Medina type 3 (plaque proximal, directly opposite and distal to side branch) versus all others. **The cross-section has a patient-specific slice thickness providing a volume rather than cross-sectional area of plaque. ††Calculated as 1 - (minimal plaque thickness/maximal plaque thickness). ‡‡Cross-sectional area of artery at maximal plaque area/proximal arterial reference area.

Abbreviations as in Tables 1 and 3.

lower quartile for plaque volume and plaques ≥70% calcified were excluded from the analysis, and also in the presence of differing concentrations of contrast medium, the latter suggesting wide applicability of the findings under varying scanning conditions.

We necessarily censored plaques after elective revascularization, which was analyzed as a competing event. Plaques in electively revascularized patients may have had a higher rate of events if revascularization had not been performed than in those not undergoing elective revascularization. However, prediction of outcomes should be examined within the framework of usual clinical practice as was the case in this study. Only 36 subjects underwent an elective revascularization procedure, limiting its effect on outcomes.

CONCLUSIONS

This plaque level analysis in asymptomatic patients with type 2 diabetes identified CTA-based plaque characteristics that predicted late ACS culprit plaque several years later. Also of note was the low incidence of clinical events in the current era of intense primary and secondary prevention despite the high HR for events in plaques with these features.

ADDRESS FOR CORRESPONDENCE: Prof. David A. Halon, Cardiovascular Clinical Research Institute, Lady Davis Carmel Medical Center, 7 Michal Street, Haifa 3436212, Israel. E-mail: halondav@technion.ac.il.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A heterogeneity of plaque findings exists in patients with type 2 diabetes. Individual plaque characteristics increase the risk of a plaque-related ACS but the large majority of plaques remained stable over 9 years in this asymptomatic diabetic population receiving guideline-based medical therapy; ACS was uncommon.

TRANSLATIONAL OUTLOOK: It is likely that identification of asymptomatic diabetic patients who will benefit from individualized preventive therapy will require approaches based on several different lines of investigation in addition to CTA plaque analysis.

REFERENCES

1. Fox CS, Golden SH, Anderson C, et al. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation 2015;132:691–718.

2. Kang SH, Park G-M, Lee S-W, et al. Long-term prognostic value of coronary CT angiography in asymptomatic type 2 diabetes mellitus. J Am Coll Cardiol Img 2016;9:1292–300.

3. Raggi P, Cooil B, Ratti C, Callister TQ, Budoff M. Progression of coronary artery calcium and occurrence of myocardial infarction in patients with and without diabetes mellitus. Hypertension 2005;46:238–43.

4. Anand DV, Lim E, Hopkins D, et al. Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. Eur Heart J 2006;27:713–21.

5. Malik S, Zhao Y, Budoff M, et al. Coronary artery calcium score for long-term risk classification in individuals with type 2 diabetes and metabolic syndrome from the Multi-Ethnic Study of Atherosclerosis. JAMA Cardiol 2017;2:1332–40.

6. Burke AP, Kolodgie FD, Zieske A, et al. Morphologic findings of coronary atherosclerotic plaques in diabetics: a postmortem study. Arterioscler Thromb Vasc Biol 2004;24:1266–71.

7. Park HB, Heo R, Ó Hartaigh B, et al. Atherosclerotic plaque characteristics by CT angiography identify coronary lesions that cause ischemia: a direct comparison to fractional flow reserve. J Am Coll Cardiol Img 2015;8:1–10.

8. Dey D, Achenbach S, Schuhbaeck A, et al. Comparison of quantitative atherosclerotic plaque burden from coronary CT angiography in patients with first acute coronary syndrome and stable coronary artery disease. J Cardiovasc Comput Tomogr 2014;8:368–74.

9. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. J Am Coll Cardiol 2015;66:337–46.

10. Puchner SB, Liu T, Mayrhofer T, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. J Am Coll Cardiol 2014;64:684–92.

11. Halon DA, Azencot M, Rubinshtein R, Zafrir B, Flugelman MY, Lewis BS. Coronary computed tomography (CT) angiography as a predictor of cardiac and noncardiac vascular events in asymptomatic type 2 diabetics: a 7-year population-based cohort study. J Am Heart Assoc 2016;5:e003226.

12. Louvard Y, Thomas M, Dzavik V, et al. Classification of coronary artery bifurcation lesions and treatments: time for a consensus! Catheter Cardiovasc Interv 2008;71:175–83.

13. Gorter PM, van Lindert ASR, de Vos AM, et al. Quantification of epicardial and peri-coronary fat using cardiac computed tomography; reproducibility and relation with obesity and metabolic syndrome in patients suspected of coronary artery disease. Atherosclerosis 2008;197:896–903.

14. Cheng VY, Dey D, Tamarappoo B, et al. Pericardial fat burden on electrocardiogram-gated noncontrast CT in asymptomatic patients who subsequently experience adverse cardiovascular events. J Am Coll Cardiol Img 2010;3:352–60.

15. Stone PH, Saito S, Takahashi S, et al. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION study. Circulation 2012;126:172–81.

16. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation 2016;133:601–9.

17. Marwan M, Taher MA, El Meniawy K, et al. In vivo CT detection of lipid-rich coronary artery atherosclerotic plaques using quantitative histogram analysis: a head to head comparison with IVUS. Atherosclerosis 2011;215:110–5.

18. Shin S, Park H-B, Chang H-J, et al. Impact of intensive LDL cholesterol lowering on coronary artery atherosclerosis progression. J Am Coll Cardiol Img 2017;10:437–46.

19. Burke AP, Kolodgie FD, Farb A, et al. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. Circulation 2001;103:934–40.

20. Choi G, Lee JM, Kim HJ, et al. Coronary artery axial plaque stress and its relationship with lesion geometry. Application of computational fluid dynamics to coronary CT angiography. J Am Coll Cardiol Img 2015;8:1156–66.

21. Lee JM, Choi G, Hwang D, et al. Impact of longitudinal lesion geometry on location of plaque rupture and clinical presentations. J Am Coll Cardiol Img 2017;10:677–88.

22. Feuchtner G, Kerber J, Burghard P, et al. The high-risk criteria low-attenuation plaque <60 HU and the napkin-ring sign are the most powerful predictors of MACE: a long-term follow-up study. Eur Heart J Cardiovasc Imaging 2017;18:772–9.

23. García-García H, Gomez-Lara J, Gonzalo N, et al. A comparison of the distribution of necrotic core in bifurcation and non-bifurcation coronary lesions: an in vivo assessment using intravascular ultrasound radiofrequency data analysis. EuroIntervention 2010;6:321–7.

24. Morbiducci U, Kok AM, Kwak BR, Stone PH, Steinman DA, Wentzel JJ. Atherosclerosis at arterial bifurcations: evidence for the role of haemodynamics and geometry. Thromb Haemost 2016;115:484–92.

25. Criqui MH, Knox JB, Denenberg JO, et al. Coronary artery calcium volume and density: potential interactions and overall predictive value: the Multi-Ethnic Study of Atherosclerosis. J Am Coll Cardiol Img 2017;10:845–54.

26. Shaw LJ, Narula J, Chandrashekhar Y. The never-ending story on coronary calcium: is it predictive, punitive, or protective? J Am Coll Cardiol 2015;65:1283–5.

KEY WORDS acute coronary syndrome, coronary plaque, CT angiography, diabetes mellitus, primary prevention