Association of High-Density Calcified 1K Plaque With Risk of Acute Coronary Syndrome

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IMPORTANCE Plaque morphologic measures on coronary computed tomography angiography (CCTA) have been associated with future acute coronary syndrome (ACS). However, the evolution of calcified coronary plaques by noninvasive imaging is not known.

OBJECTIVE To ascertain whether the increasing density in calcified coronary plaque is associated with risk for ACS.

DESIGN, SETTING, AND PARTICIPANTS This multicenter case-control cohort study included individuals enrolled in ICONIC (Incident Coronary Syndromes Identified by Computed Tomography), a nested case-control study of patients drawn from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry, which included 13 study sites in 8 countries. Patients who experienced core laboratory–verified ACS after baseline CCTA (n = 189) and control individuals who did not experience ACS after baseline CCTA (n = 189) were included. Patients and controls were matched 1:1 by propensity scores for age; male sex; presence of hypertension, hyperlipidemia, and diabetes; family history of premature coronary artery disease (CAD); current smoking status; and CAD severity. Data were analyzed from November 2018 to March 2019.

EXPOSURES Whole-heart atherosclerotic plaque volume was quantitated from all coronary vessels and their branches. For patients who underwent invasive angiography at the time of ACS, culprit lesions were coregistered to baseline CCTA lesions by a blinded independent reader. Low-density plaque was defined as having less than 130 Hounsfield units (HU); calcified plaque, as having more than 350 HU and subcategorized on a voxel-level basis into 3 strata: 351 to 700 HU, 701 to 1000 HU, and more than 1000 HU (termed *1K plaque*).

MAIN OUTCOMES AND MEASURES Association between calcium density and future ACS risk.

RESULTS A total of 189 patients and 189 matched controls (mean [SD] age of 59.9 [9.8] years; 247 [65.3%] were male) were included in the analysis and were monitored during a mean (SD) follow-up period of 3.9 (2.5) years. The overall mean (SD) calcified plaque volume (>350 HU) was similar between patients and controls (76.4 [101.6] mm^3 vs 99.0 [156.1] mm^3; *P* = .32), but patients who experienced ACS exhibited less 1K plaque (>1000 HU) compared with controls (3.9 [8.3] mm^3 vs 9.4 [23.2] mm^3; *P* = .02). Individuals within the highest quartile of 1K plaque exhibited less low-density plaque, as a percentage of total plaque, when compared with patients within the lower 3 quartiles (12.6% [10.4%] vs 24.9% [20.6%]; *P* < .001). For 93 culprit precursor lesions detected by CCTA, the volume of 1K plaque was lower compared with the maximally stenotic lesion in controls (2.6 [7.2] mm^3 vs 7.6 [20.3] mm^3; *P* = .01). The per-patient and per-lesion results were similar between the 2 groups when restricted to myocardial infarction cases.

CONCLUSIONS AND RELEVANCE Results of this study suggest that, on a per-patient and per-lesion basis, 1K plaque was associated with a lower risk for future ACS and that measurement of 1K plaque may improve risk stratification beyond plaque burden.

+ Supplemental content

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Coronary computed tomography angiography (CCTA) allows for quantification of coronary atherosclerotic plaque. Overall plaque burden is a determinant of future major cardiovascular events. In addition, based on pathologic analysis and imaging results, lesions associated with acute coronary syndrome (ACS) or sudden coronary death exhibit necrotic lipid-laden cores, positive remodeling, spotty calcification, high cross-sectional plaque burden, high stenosis severity, and thin-cap fibroatheroma.[1,2] Evolution of fibroatheromas, the development of sheets of calcification and reduction in necrotic core size, is considered plaque stabilizing.[3]

The evolution of calcified coronary plaques by noninvasive imaging is not known; however, it has been posited that increasing Hounsfield unit (HU) density (ie, brightness) on CCTA may reflect a stabilizing process. This hypothesis is consistent with the results from the Multi-Ethnic Study of Atherosclerosis (MESA), which used noncontrast computed tomographic (CT) imaging for coronary artery calcium scoring in which higher overall calcium density score was associated with lower risk for major cardiovascular events after adjusting for overall calcium volume.[4]

The present case-control cohort study analyzes the Incident Coronary Syndromes Identified by Computed Tomography (ICONIC), a study with, to our knowledge, the largest cohort of patients who experienced core laboratory-verified ACS after baseline CCTA. Individuals with ACS (referred to as *cases* or *patients*) were matched with those without ACS (referred to as *control individuals*) on the basis of cardiovascular risk factors and angiographic coronary artery disease (CAD) severity, with the total plaque volume not differing between the 2 groups. The aim of the present study was to ascertain the association between increasing density of calcified plaque and risk of future ACS.

Methods

Study Design

ICONIC was a nested case-control study that comprised patients with no known CAD drawn from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry, which included 13 sites in 8 countries (United States, Canada, Italy, Germany, South Korea, Austria, Portugal, and the Netherlands).[2] Each participating site obtained local institutional review board or ethics board approval. Written or oral patient informed consent or a waiver of consent was obtained according to site-specific regulations.

The specific methods for inclusion and exclusion of patients and the construction of the ICONIC cohort have been previously described.[2] Briefly, the CONFIRM registry prospectively collected baseline demographic and clinical data of patients who underwent clinically indicated CCTA for suspected CAD and monitored them for the occurrence of major adverse cardiovascular events.[5] Patients who experienced site-adjudicated ACS were matched 1:1 to within-site control individuals who did not experience ACS during the mean (SD) follow-up period of 3.9 (2.5) years. Hence, the results of the

Key Points

Question Is the density of coronary calcified plaque associated with future development of acute coronary syndrome?

Findings In this case-control study of 189 patients who experienced vs 189 control individuals who did not experience an acute coronary syndrome after baseline coronary computed tomography angiography imaging, the volume of plaque with more than 1000 Hounsfield unit (termed *1K plaque*) was associated with lower risk for acute coronary syndrome. The specific acute coronary syndrome precursor culprit lesion had less 1K plaque compared with the most stenotic lesion in control individuals.

Meaning This study's findings suggest that 1K plaque detected by coronary computed tomography angiography is associated with lower risk of future occurrence of acute coronary syndrome.

present study were prospective but observational. Sites submitted clinical, electrocardiographic, imaging, and laboratory data that supported ACS to the Clinical and Data Coordinating Center (Dalio Institute of Cardiovascular Imaging, New York, New York) for uniform adjudication of ACS while masked to CCTA evaluation findings. In addition, DICOM (Digital Imaging and Communications in Medicine) files were sent to the CCTA core laboratory (Severance Cardiovascular Hospital, Seoul, South Korea), which performed quantitative, whole-heart, 18-segment coronary tree analysis and was blinded to case status.

After exclusion of site-reported ACS cases with insufficient adjudication data, ACS cases in revascularized coronary segments, and CCTA scans with insufficient image quality for quantitative analysis, the final ICONIC cohort consisted of 234 cases of ACS and 234 propensity score-matched control individuals. The propensity score was based on age; male sex; the presence of hypertension, hyperlipidemia, and diabetes; family history of premature CAD; current smoking status; and CAD severity by CCTA (defined as nonobstructive CAD or as 1-vessel, 2-vessel, or 3-vessel or left main obstructive CAD [≥50% stenosis]).[2]

Patients or control individuals older than 75 years were excluded (along with their counterparts) from the present study because current guidelines do not recommend routine risk assessment above this age threshold and to avoid excessive calcification.[6] Data for patient or matched control individuals older than 75 years are presented in eTable 2 in the Supplement.

ACS Event Adjudication

A detailed description of event adjudication has been published previously.[2] The Clinical and Data Coordinating Center reviewed symptoms of ischemia, cardiac laboratory biomarker data, electrocardiogram results, and invasive coronary angiograms for site-reported ACS cases and adjudicated cases according to the World Health Organization definition and the third universal definition of myocardial infarction[7,8] or unstable angina. Myocardial infarction cases consisted of ST-segment elevation myocardial infarction (STEMI), non–

STEMI, or unclassified myocardial infarction (abnormal cardiac enzyme level [>99% of the upper limit of normal], presence of other supporting information, and ambiguous electrocardiogram unsuitable for STEMI or non-STEMI classification). Six physicians (F.Y.L., L.B., I.C., D.H., J.-H.L., and A.R.) who were blinded to CCTA results adjudicated ACS cases, and 2 additional physicians (F.Y.L., D.H.) adjudicated ambiguous cases. Acute coronary syndrome cases related to previous percutaneous coronary intervention, stent thrombosis, or coronary artery bypass graft were excluded because these events could not be related to baseline CCTA plaques.

In addition, 1 culprit lesion per patient was adjudicated for patients who underwent invasive angiography at the time of ACS.[2] In patients with 1 single significant stenosis, this lesion was considered the culprit lesion. In cases with 2 or more lesions, the culprit lesion was defined on the basis of luminal narrowing, the complexity of the lesion's morphologic structure, and the electrocardiogram for the distribution of ischemia. In cases with multiple candidate culprits, consensus reading with a second cardiologist was performed. Subsequently, the invasive angiography-defined culprit lesion was coregistered to baseline CCTA lesions by coronary segment coding, distance from ostia, and vessel branch points as landmarks. Unblinded comparison of invasive coronary angiography with CCTA was allowed for coregistration of ambiguous cases.

CCTA Evaluation

Coronary computed tomography angiography scans were acquired with at least 64-slice scanners in accordance with the Society of Cardiovascular Computed Tomography guidelines, and sites visually interpreted images for coronary plaque presence, stenosis severity, location, and composition from an 18-segment coronary tree model.[9,10] The DICOM files were sent to the CCTA core laboratory, where independent level III-experienced readers performed quantitative plaque analysis using semiautomated software (QAngioCT Research Edition, version 2.1.9.1; Medis Medical Imaging Systems).

The methods, including routine interreproducibility and intrareproducibility checks, are described elsewhere.[2] Briefly, lumen, vessel, and plaque volumes were measured in each coronary segment from the coronary tree 2 mm or more in diameter on every 1-mm cross-section; data were summed to per-segment and per-patient levels. Plaque composition was defined as necrotic core, fibro-fatty, fibrous, and calcified, using the following HU strata: 30 or less, 31 to 130, 131 to 350, and more than 350.[11,12] The present study focused on calcified plaque, and additional calcification subgroups were created by calculating plaque strata starting from 351 HU: 351 to 700, 701 to 1000, and more than 1000 HU which, was referred to as *1K plaque* and resembled very dense calcification. These thresholds differed from categories of HU densities for calculation of Agatston score because all measurements were performed on contrast-enhanced CCTA, which is known to increase the attenuation (ie, HU) of all vascular structures. Besides segmental analysis, measurements of length, volume, composition, stenosis, and maximal cross-sectional plaque burden were performed for each coronary lesion.[13] The same plaque composition HU strata as in a per-segment level

were calculated on a per-lesion level analysis. Plaque data were provided by absolute volume. Primary analysis was performed between ACS cases and control individuals, and secondary analysis included comparisons between cases of myocardial infarction and control individuals.

Statistical Analysis

Continuous data were described as mean (SD) regardless of distribution, for uniformity of presentation. The 2-tailed, unpaired *t* test or Mann-Whitney test was used for comparisons of unpaired continuous data; the paired *t* test or Wilcoxon rank sum test was used for paired data. Categorical data were compared with the McNemar test. First, at the per-patient level, the calcified plaque strata were compared between patients and control individuals. Second, patients and control individuals in the top quartile of 1K plaque were compared with the remaining 3 quartiles of individuals for relative amounts of calcified, fibrous, fibro-fatty, and necrotic core plaques (calculated by dividing by the total plaque volume and multiplying by 100%). Third, calcified plaque strata of culprit precursor lesions were compared with the lesion with the highest diameter stenosis in the matched control individual.

Two-sided *P* < .05 was considered statistically significant. All analyses were performed with SAS, version 9.4 (SAS Institute Inc), and R, version 3.3.0 (R Foundation for Statistical Computing). Data analyses were performed from November 2018 to March 2019.

Results

Patients

The study population included 189 patients experiencing core laboratory-verified ACS and 189 propensity score-matched control individuals. The mean (SD) age of the population was 59.9 (9.8) years, and 247 (65.3%) were male. Patients and control individuals were well matched on their mean (SD) propensity scores (0.07 [0.04] vs 0.07 [0.04]; *P* = .76). Of the individual score components, the presence of diabetes was lower in patients with ACS compared with control individuals (37 [19.6%] vs 57 [30.2%]; *P* = .006), whereas CAD severity tended to be more severe in the control individuals compared with cases (**Table 1**). Patients more frequently underwent interval coronary revascularization (92 patients [48.7%] vs 42 [22.2%]; *P* < .001) of nonculprit lesions. Patients, compared with control individuals, displayed higher mean (SD) maximal stenosis severity (42.5% [25.9%] vs 31.9% [21.1%]; *P* < .001). The total mean (SD) plaque volume was similar in both groups (258.9 [271.0] mm³ vs 252.9 [286.9] mm³; *P* = .38) (**Table 2**).

Patient-Level Calcified Plaque in Patients vs Controls

Total mean (SD) calcified plaque volume (>350 HU) was not different between patients and control individuals (76.4 [101.6] mm³ vs 99.0 [156.1] mm³; *P* = .32) (Table 2). With each increasing calcium density stratum, calcification volume was lower in patients than in control individuals with increasing levels of significance. The mean (SD) volume of 1K plaque (>1000 HU) was 3.9 (8.3) mm³ in patients and 9.4 (23.2) mm³ in control in-

Table 1. Propensity Score and Clinical Characteristics

	Frequency, No. (%)		
Variable	ACS Group (n = 189)	Control Group (n = 189)	P Value
Included in propensity score			
Age, mean (SD), y	59.6 (10.3)	60.3 (9.3)	.33
Male sex	126 (66.7)	121 (64.0)	.33
Diabetes	37 (19.6)	57 (30.2)	.006
Hypertension	116 (62.0)	106 (56.1)	.21
Hyperlipidemia	105 (55.6)	102 (54.0)	.82
Familial history of CAD	80 (43.5)	78 (41.3)	.44
Current smoker	56 (29.6)	43 (22.8)	.09
CAD severity			
None	13 (7.3)	25 (13.2)	
Nonobstructive	69 (38.8)	75 (39.7)	
1-Vessel obstructive	26 (14.6)	38 (20.1)	.06
2-Vessel obstructive	31 (17.4)	21 (11.1)	
3-Vessel/left main obstructive	39 (21.9)	30 (15.9)	
Angina type			
Asymptomatic	25 (14.0)	64 (35.0)	
Noncardiac	20 (11.2)	23 (12.6)	
Atypical	8 (47.8)	69 (37.7)	.001
Typical	48 (27.0)	27 (14.8)	
Race/ethnicity			
White	85 (62.0)	89 (62.2)	
East Asian	43 (31.4)	42 (29.4)	.59
Other	9 (6.6)	12 (8.4)	
Lipid profile, mean (SD), mg/dL			
Cholesterol			
Total	190.0 (48.2)	186.7 (40.7)	.67
Low-density lipoprotein	116.6 (42.6)	119.2 (32.1)	.78
High-density lipoprotein	43.5 (10.9)	47.8 (13.2)	.09
Medications			
Statins	75 (58.1)	64 (49.2)	.24
Aspirin	73 (52.5)	66 (47.5)	.78
ACEI/ARB	51 (37.0)	52 (37.4)	>.99
β-Blocker	49 (35.5)	49 (35.3)	.79
Interval coronary revascularization	92 (48.7)	42 (22.2)	<.001
ACS type			
Myocardial infarction			
ST-segment elevation	33 (17.5)	NA	NA
Non-ST-segment elevation	90 (47.6)	NA	NA
Unclassified	3 (1.6)	NA	NA
Unstable angina	63 (33.0)	NA	NA

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CAD, coronary artery disease; NA, not applicable.

SI conversion factor: To convert cholesterol levels to millimoles per liter, multiply by 0.0259.

dividuals (*P* = .02) (**Figure 1**). An example of a coronary artery with 1K plaque is shown in **Figure 2**. When restricting to patients who experienced myocardial infarction (n = 126), the results were similar (eTable 1 in the Supplement). The mean (SD) volume of 1K plaque in patients who experienced myocardial infarction was 3.6 (7.2) mm^3 compared with that in control individuals of 10.0 (23.6) mm^3 (*P* = .01) (eTable 1 in the Supplement). The 1K plaque did not differ between patients and control individuals older than 75 (eTable 2 in the Supplement).

Patients or control individuals in the top quartile of 1K plaque by volume were characterized by a higher overall mean (SD) plaque volume compared with the patients in the other 3 quartiles (539.6 [339.7] mm^3 vs 206.9 [196.6] mm^3; *P* < .001) (**Figure 3**). Individuals in the highest quartile of 1K plaque had relatively more calcified plaque (48.3% [17.3%] vs 24.9% [21.0%]; *P* < .001) and relatively less necrotic core plus fibro-fatty plaque (12.6% [10.4%] vs 24.9% [20.6%]; *P* < .001) compared with the other 3 quartiles of the population (Figure 3).

## Lesion-Level Calcified Plaque in Culprit Precursors vs Controls

In 93 patients (49.2%), a CCTA precursor lesion for future ACS culprit lesion could be identified at the time of invasive angi-

Table 2. Per-Patient Atherosclerotic Characteristics

Variable	Mean (SD)		P Value
	ACS Group (n = 189)	Control Group (n = 189)	
Atherosclerotic feature, %			
Maximal			
Diameter stenosis	42.5 (25.9)	31.9 (21.1)	<.001
Area stenosis	60.2 (27.1)	49.1 (27.9)	<.001
Cross-sectional plaque burden	64.8 (25.7)	54.4 (29.1)	<.001
Mean plaque burden	10.4 (9.5)	10.5 (10.5)	.45
Total plaque volume, mm^3	258.9 (271.0)	252.9 (286.9)	.38
Calcified (>350 HU)	76.4 (101.6)	99.0 (156.1)	.32
Fibrous (131-350 HU)	117.4 (121.6)	109.3 (121.8)	.30
Fibro-fatty (31-130 HU)	58.3 (82.9)	40.7 (62.5)	.007
Necrotic core (<30 HU)	6.8 (14.9)	4.1 (8.7)	.01
Fibro-fatty + necrotic core (<30-130 HU)	65.1 (93.1)	44.7 (68.9)	.006
Calcium density, mm^3			
Calcification (351-700 HU)	57.1 (73.6)	66.8 (99.12)	.61
Calcification (701-1000 HU)	14.8 (23.8)	23.0 (44.5)	.11
1K plaque (>1000 HU)	3.9 (8.3)	9.4 (23.2)	.02

Abbreviations: ACS, acute coronary syndrome; HU, Hounsfield units.

Figure 1. Whole-Heart Plaque Volume by Composition for Patients With Acute Coronary Syndrome (ACS) and Control Individuals
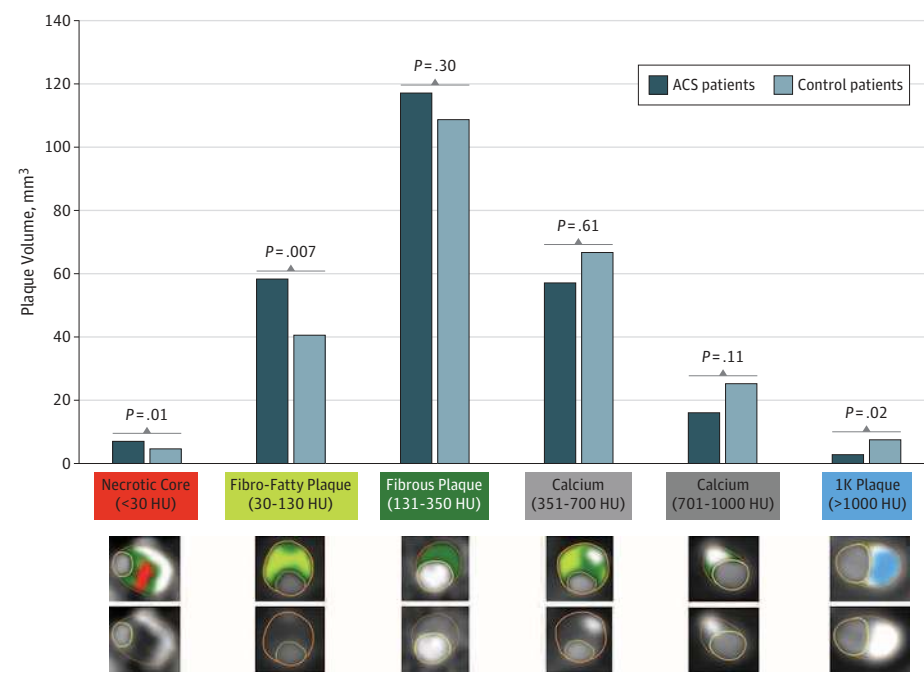
Per-patient volumes of necrotic core (<30 Hounsfield units [HU]), fibro-fatty (30-130 HU), fibrous (131-350 HU), calcified (351-700 HU), calcified (701-1000 HU), and 1K (>1000 HU) plaques are reported. Patients with ACS reported significantly more necrotic core and fibro-fatty plaques and less 1K plaque compared with control individuals. Cross-sectional examples of the different plaque composition types are displayed by different colors. 1K plaque is shown in blue.

ography. Compared with the lesion associated with the greatest stenosis in control individuals, the culprit precursor lesion had a lower mean (SD) volume of 1K plaque (2.6 [7.2] mm^3 vs 7.6 [20.3] mm^3; P = .01) (eTable 3 in the Supplement). When restricted to myocardial infarction cases, the results were similar; the mean (SD) volume of 1K plaque in myocardial infarction culprit precursors was 2.0 [4.7] mm^3 compared with that in control lesions of 9.2 [20.7] mm^3 (P = .02) (eTable 4 in the Supplement).

Discussion

ICONIC was a study of patients who experienced ACS after baseline CCTA and control individuals who did not have the same experience, and these 2 groups were propensity matched on overall plaque burden and cardiovascular risk factors. We observed that the per-patient volume of 1K plaque was lower in patients than in control individuals (3.9 [8.3] mm^3 vs 9.4 [23.2]

Figure 2. Example of a Vessel With 1K Plaque

A No noncalcified plaque and high 1K plaque burden

B High noncalcified plaque burden and no 1K plaque

■ Fibrous: 131-350 HU   □ Calcium: 351-1000 HU   ■ 1K plaque: >1000 HU
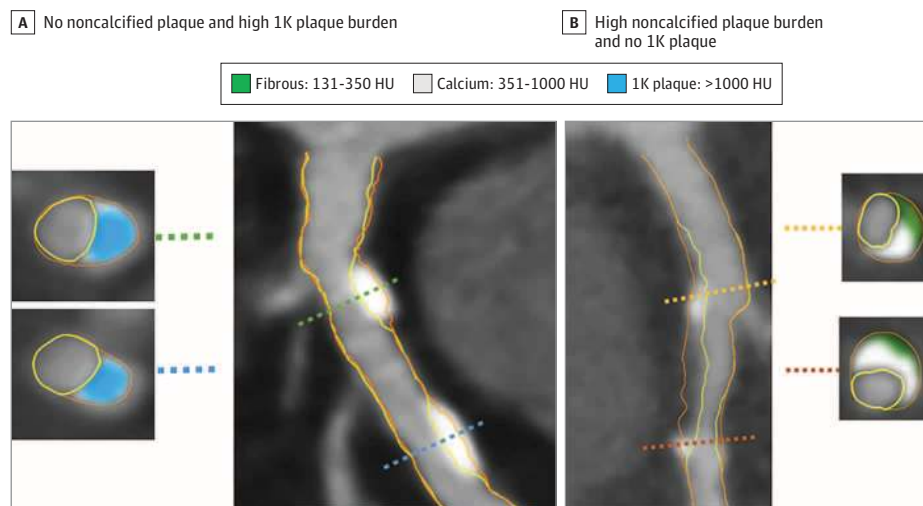
The artery segment in the left panel (A) shows 2 lesions composed of 1K plaque (ie, plaque with a volume >1000 Hounsfield units [HU]), without noncalcified plaque. Cross-sectional examples are shown with 1K plaque (blue). The artery segment in the right panel (B) shows calcifications between 351 and 1000 HU (gray) intermingled in noncalcified plaque. Two cross-sections show 351- to 1000-HU calcium plaque together with 130- to 350-HU fibrous plaque tissue (green).

mm^3; P = .02). Furthermore, the precursor lesion at baseline CCTA associated with development of future ACS demonstrated a smaller volume of 1K plaque compared with the most severely stenotic lesion in control individuals (2.6 [7.2] mm^3 vs 7.6 [20.3] mm^3; P = .01). We believe these results support the identification of varied atherosclerotic plaque features associated with low risk to high risk prognostic results. For 1K plaque, these results support the hypothesis that higher-density plaque signifies stability and a reduced occurrence of ACS.

Calcified Component of Plaque and Risk for ACS

Studies have demonstrated that patients who underwent imaging at the time of ACS compared with patients who presented with stable CAD were more likely to have a larger proportion of noncalcified plaque.[14-18] Leber et al[16] observed that, among 21 patients who presented with acute myocardial infarction and 19 patients with stable angina who underwent CCTA, the proportion of plaque being noncalcified was higher in patients with myocardial infarction.

These observations are well supported by histopathologic findings that ruptured coronary plaques are characterized by fibroatheromas with large necrotic cores and thin, inflamed fibrous caps.[19] Fibroatheromas (which consist mainly of lipid-rich plaque and necrotic core) may evolve into fibrocalcific plaques or healed ruptures, which are associated with an increase in calcification and a decrease of necrotic core. This process is considered a factor in the stabilization of coronary plaque and is supported by data from intravascular ultrasonography and CCTA, which show that statins are associated with increased calcification burden on follow-up imaging and reduced necrotic core volume.[20,21]

However, the detection of calcification on imaging is not, per se, a reassuring sign. In CT, the calcified plaque represents histopathologic sheets of calcium that only develop later

Figure 3. Plaque Composition in Individuals With a Large 1K Plaque Volume
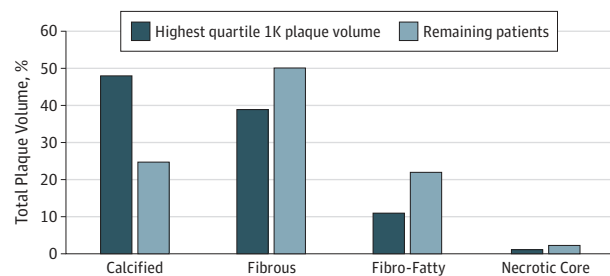
Individuals with the highest quartile of 1K plaque (ie, plaque with a volume >1000 Hounsfield units [HU]) had relatively more calcified plaque but less fibrous, fibro-fatty, and necrotic core plaques compared with the other 3 quartiles of patients. Absolute volumes and comparisons are provided in eTable 5 in the Supplement.

in the atherosclerotic disease process and therefore represent more advanced plaque formation. On a noncontrast-enhanced CT examination, a high coronary artery calcium score has been associated with a large coronary plaque burden and elevated cardiovascular event rates, whereas the absence of calcium excluded advanced plaque and portended excellent cardiovascular outcomes.[22,23] An increasing burden of calcification is equal to an increasing amount of coronary atherosclerosis, thus explaining the strong prognostic value of coronary calcium scoring.

Hence, calcified plaque represents advanced atherosclerosis but has a more stable histopathological appearance, either owing to the stabilizing property of calcification sheets or the lower burden of necrotic core. These observations suggest that the relative burden of calcium is important and may be associated with the risk for future cardiovascular events. The

answer to this question requires a baseline plaque evaluation with follow-up and is therefore not possible with histopathologic analysis.

The MESA study investigated whether an increase in calcium density on noncontrast calcium scans was prognostically important among 3398 individuals who experienced 175 coronary heart disease events during the 7½ years of follow-up.[4] In a noncontrast CT study, coronary artery calcium density is scored from 1 to 4, representing HU densities from more than 130 to more than 400. In the MESA report, the mean per-patient calcium density score was derived by dividing the Agatston score by the calcium volume and adjusted for slice thickness. In Cox proportional hazards regression models that adjusted for the overall volume of coronary artery calcium, the increasing density (specifically, the highest density category) was associated with lower risk for myocardial infarction, resuscitated cardiac arrest, or coronary heart disease death.[4] This finding from the MESA study was supportive of the present findings that higher plaque density was associated with a reduced event risk.

The strongest association was observed for 1K plaque, whereas calcium between 351 and 1000 HU was not statistically significantly lower in patients compared with control individuals. This higher attenuation threshold corresponds with previous reports that histopathologically defined calcification has CT attenuation of 715 HU[24] or 966 HU.[25] Absence of the prognostic effect for calcification with lower than 1000 HU may be associated with the partial volume effect, whereby small calcifications are associated with blooming artifacts compared with more lipid-rich plaque, which results in CCTA calcification with Hounsfield units between 351 and 1000 (Figure 2). In addition to the per-patient analysis, we analyzed 1K plaque in the specific precursor lesion associated with future occurrence of ACS. Similarly, culprit precursor lesions had less 1K plaque than the most severe lesion in control individuals, supporting the concept of plaque stability on per-patient and per-lesion levels. Furthermore, we observed that patients with a large amount of 1K plaque showed relatively less noncalcified plaque, which was associated with reduced risk for ACS.[2] This finding may suggest that higher-density atherosclerosis in the coronary tree presents a plaque phenotype with lower adverse event risk. However, the findings of this study are merely suggestive; prospective studies should confirm our observations. Clinically, the findings of lower risk for a per-lesion and per-patient volume of 1K plaque can help refine risk stratification beyond the coronary plaque burden. In addition, the burden of 1K plaque may serve as a surrogate marker of risk for clinical outcomes in serial CCTA studies.

Limitations

This study has some limitations. Patients and control individuals were drawn from a large observational registry, which had inherent limitations such as selection bias and unmeasured confounders. For adjudication of ACS, patients who died without enough evidence of ACS were excluded. In the small subset of patients older than 75 years, the 1K plaque density was not lower in patients with ACS. The higher prevalence of total plaque and calcified plaque with age may be explanatory for the diminished relationship of 1K plaque in patients with ACS. Coronary lesions with 100% stenosis could not be evaluated with quantitative CCTA. Although the propensity scores were similar between the 2 groups, some imbalance between the individual propensity score components may be observed. No information was available on post-CCTA medication use patterns. The HU of different plaque composition types is dependent on the luminal contrast attenuation and provided kilovolt during acquisition, which was not standardized for all included patients.

Conclusions

Identifying the type of atherosclerotic plaque that serves as a determinant of both higher and lower risk status is an ever-unfolding story. Previous research has indicated that lower plaque density in calcified plaque was associated with a higher risk of major coronary events.[4] In the present analysis of the ICONIC study, higher-density calcified plaque, referred to as 1K plaque, was associated with a reduced risk for future ACS on per-patient and per-lesion bases. We believe these results support the plaque stabilization hypothesis with coronary calcium and help in understanding the varying risk signatures that can be detected in atherosclerotic plaque.

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REFERENCES

1. 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(4):337-346. doi:10.1016/j.jacc.2015.05.069

2. Chang HJ, Lin FY, Lee SE, et al. Coronary atherosclerotic precursors of acute coronary syndromes. *J Am Coll Cardiol*. 2018;71(22):2511-2522. doi:10.1016/j.jacc.2018.02.079

3. Mori H, Torii S, Kutyna M, Sakamoto A, Finn AV, Virmani R. Coronary artery calcification and its progression: what does it really mean? *JACC Cardiovasc Imaging*. 2018;11(1):127-142. doi:10.1016/j.jcmg.2017.10.012

4. Criqui MH, Denenberg JO, Ix JH, et al. Calcium density of coronary artery plaque and risk of incident cardiovascular events. *JAMA*. 2014;311(3):271-278. doi:10.1001/jama.2013.282535

5. Min JK, Dunning A, Lin FY, et al. Rationale and design of the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) Registry. *J Cardiovasc Comput Tomogr*. 2011;5(2):84-92. doi:10.1016/j.jcct.2011.01.007

6. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2935-2959. doi:10.1016/j.jacc.2013.11.005

7. Thygesen K, Alpert JS, Jaffe AS, et al; Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction; ESC Committee for Practice Guidelines (CPG). Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33(20):2551-2567. doi:10.1093/eurheartj/ehs184

8. Mendis S, Thygesen K, Kuulasmaa K, et al; Writing group on behalf of the participating experts of the WHO consultation for revision of WHO definition of myocardial infarction. World Health Organization definition of myocardial infarction: 2008-09 revision. *Int J Epidemiol*. 2011;40(1):139-146. doi:10.1093/ije/dyq165

9. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol*. 2007;50(12):1161-1170. doi:10.1016/j.jacc.2007.03.067

10. Abbara S, Blanke P, Maroules CD, 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(6):435-449. doi:10.1016/j.jcct.2016.10.002

11. Park HB, Lee BK, Shin S, 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(10):3073-3083. doi:10.1007/s00330-015-3698-z

12. Brodoefel H, Reimann A, Heuschmid M, et al. Characterization of coronary atherosclerosis by dual-source computed tomography and HU-based color mapping: a pilot study. *Eur Radiol*. 2008;18(11):2466-2474. doi:10.1007/s00330-008-1019-5

13. Cury RC, Abbara S, Achenbach S, et al. Coronary Artery Disease - Reporting and Data System (CAD-RADS): an expert consensus document of SCCT, ACR and NASCI: endorsed by the ACC. *JACC Cardiovasc Imaging*. 2016;9(9):1099-1113. doi:10.1016/j.jcmg.2016.05.005

14. Schoenhagen P, Ziada KM, Kapadia SR, Crowe TD, Nissen SE, Tuzcu EM. Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: an intravascular ultrasound study. *Circulation*. 2000;101(6):598-603. doi:10.1161/01.CIR.101.6.598

15. van Velzen JE, de Graaf FR, Jukema JW, et al. Comparison of the relation between the calcium score and plaque characteristics in patients with acute coronary syndrome versus patients with

stable coronary artery disease, assessed by computed tomography angiography and virtual histology intravascular ultrasound. *Am J Cardiol*. 2011;108(5):658-664. doi:10.1016/j.amjcard.2011.04.009

16. Leber AW, Knez A, White CW, et al. Composition of coronary atherosclerotic plaques in patients with acute myocardial infarction and stable angina pectoris determined by contrast-enhanced multislice computed tomography. *Am J Cardiol*. 2003;91(6):714-718. doi:10.1016/S0002-9149(02)03411-2

17. Shemesh J, Apter S, Itzchak Y, Motro M. Coronary calcification compared in patients with acute versus in those with chronic coronary events by using dual-sector spiral CT. *Radiology*. 2003;226 (2):483-488. doi:10.1148/radiol.2262011903

18. Ehara S, Kobayashi Y, Yoshiyama M, et al. Spotty calcification typifies the culprit plaque in patients with acute myocardial infarction: an intravascular ultrasound study. *Circulation*. 2004;110(22):3424-3429. doi:10.1161/01.CIR.0000148131.41425.E9

19. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*. 2000;20(5):1262-1275. doi:10.1161/01.ATV.20.5.1262

20. Lee SE, Chang HJ, Sung JM, et al. Effects of statins on coronary atherosclerotic plaques: the PARADIGM study. *JACC Cardiovasc Imaging*. 2018;11 (10):1475-1484. doi:10.1016/j.jcmg.2018.04.015

21. Puri R, Nicholls SJ, Shao M, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. *J Am Coll Cardiol*. 2015;65(13):1273-1282. doi:10.1016/j.jacc.2015.01.036

22. Budoff MJ, Young R, Burke G, et al. Ten-year Association of Coronary Artery Calcium With Atherosclerotic Cardiovascular Disease (ASCVD) events: the Multi-Ethnic Study of Atherosclerosis (MESA). *Eur Heart J*. 2018;39(25):2401-2408. doi:10.1093/eurheartj/ehy217

23. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. *Circulation*. 1995; 92(8):2157-2162. doi:10.1161/01.CIR.92.8.2157

24. Schroeder S, Kuettner A, Leitritz M, et al. Reliability of differentiating human coronary plaque morphology using contrast-enhanced multislice spiral computed tomography: a comparison with histology. *J Comput Assist Tomogr*. 2004;28(4): 449-454. doi:10.1097/00004728-200407000-00003

25. Chopard R, Boussel L, Motreff P, et al. How reliable are 40 MHz IVUS and 64-slice MDCT in characterizing coronary plaque composition? An ex vivo study with histopathological comparison. *Int J Cardiovasc Imaging*. 2010;26(4):373-383. doi:10.1007/s10554-009-9562-y

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Invited Commentary

The Importance of Coronary Artery Calcium Density

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In this issue of *JAMA Cardiology*,[1] an international research group reports results from the Incident Coronary Events Identified by Computed Tomography (ICONIC) Study, a prospective nested case-control study. Patients underwent coronary computed tomography angiography (CCTA) for suspected coronary artery disease (CAD). After a mean follow-up of 3.9 years, 189 patients were identified with acute coronary syndrome (ACS) and propensity-matched to 189 controls who remained ACS free. Importantly, the propensity matching included the qualitative coronary atherosclerotic extent based on CCTA. Overall, cases had less calcified coronary plaque and more fatty, fibrous, and necrotic core plaques. The most striking result was the greater number of high-attenuation plaques in controls, plaques with more than 1000 Hounsfield units that the authors termed *1K plaque*.

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Higher coronary artery calcium (CAC) density has previously been shown to be associated with a reduced risk of coronary events in a large multiethnic cohort free of CAD at baseline.[2] This protective association became evident only after adjustment for CAC volume, underscoring the elevated risk of the presence and extent of calcified atherosclerosis in the coronary arteries and the partial mitigation of risk marked by highly dense calcium. With additional follow-up, this association was shown to be consistent across subgroups defined by age, sex, race/ethnicity, diabetes, estimated glomerular filtration rate, and atherosclerotic cardiovascular disease (ASCVD) risk score.[3] This study[1] extends this observation of the protective association of densely calcified plaque to persons with image-documented CAD at baseline.

Considering all CAD risk factors and all subclinical CAD measures, extensive population-based research has shown CAC to be the strongest single marker of CAD risk[4] The combined measures of CAC volume and CAC density have shown to account for more risk area under the receiver operator characteristic curve than the combination of the risk factors in the standard ASCVD risk equation (ie, total cholesterol levels, high-density lipoprotein cholesterol levels, systolic blood pressure, hypertension medication use, diabetes, and current smoking[3]). Thus, prevention guidelines routinely suggest considering CAC as a "tie-breaker" in persons with borderline ASCVD risk for whom the decision to initiate certain preventive treatment strategies is ambiguous.[5] The Agatston score is widely used to quantify CAC in risk prediction, but the score is upwardly weighted for a higher density, which is "backward" because CAC density appears to be protective. Nonetheless, the Agatston score works well because of its high association with CAC volume, which works even better. The best prediction comes from considering the independent associations of CAC volume (positive) and CAC density (inverse) separately.[2,3]

With optimal CAC density imaging, the predictive strength in terms of the hazard ratio (HR) per standard deviation increment of CAC density (inverse) is only modestly less than that of CAC volume (positive).[2,3] In the scanners used in the Multi-Ethnic Study of Atherosclerosis (MESA) at baseline 2 decades ago, CAC density and CAC volume were associated with better prediction when electron beam computed tomography (EBCT) scanners were used compared with multidetector computed tomography (MDCT) scanners. However, production of EBCT scanners was halted in 2006 and EBCT scanners are rarely used today. The older MDCT scanners have been mostly replaced with newer updated MDCT scanners that use more slices. To our knowledge, no population data are currently available for the predictive value of either CAC volume or CAC