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Coronary Atherosclerotic Precursors of Acute Coronary Syndromes

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BACKGROUND The association of atherosclerotic features with first acute coronary syndromes (ACS) has not accounted for plaque burden.

OBJECTIVES The purpose of this study was to identify atherosclerotic features associated with precursors of ACS.

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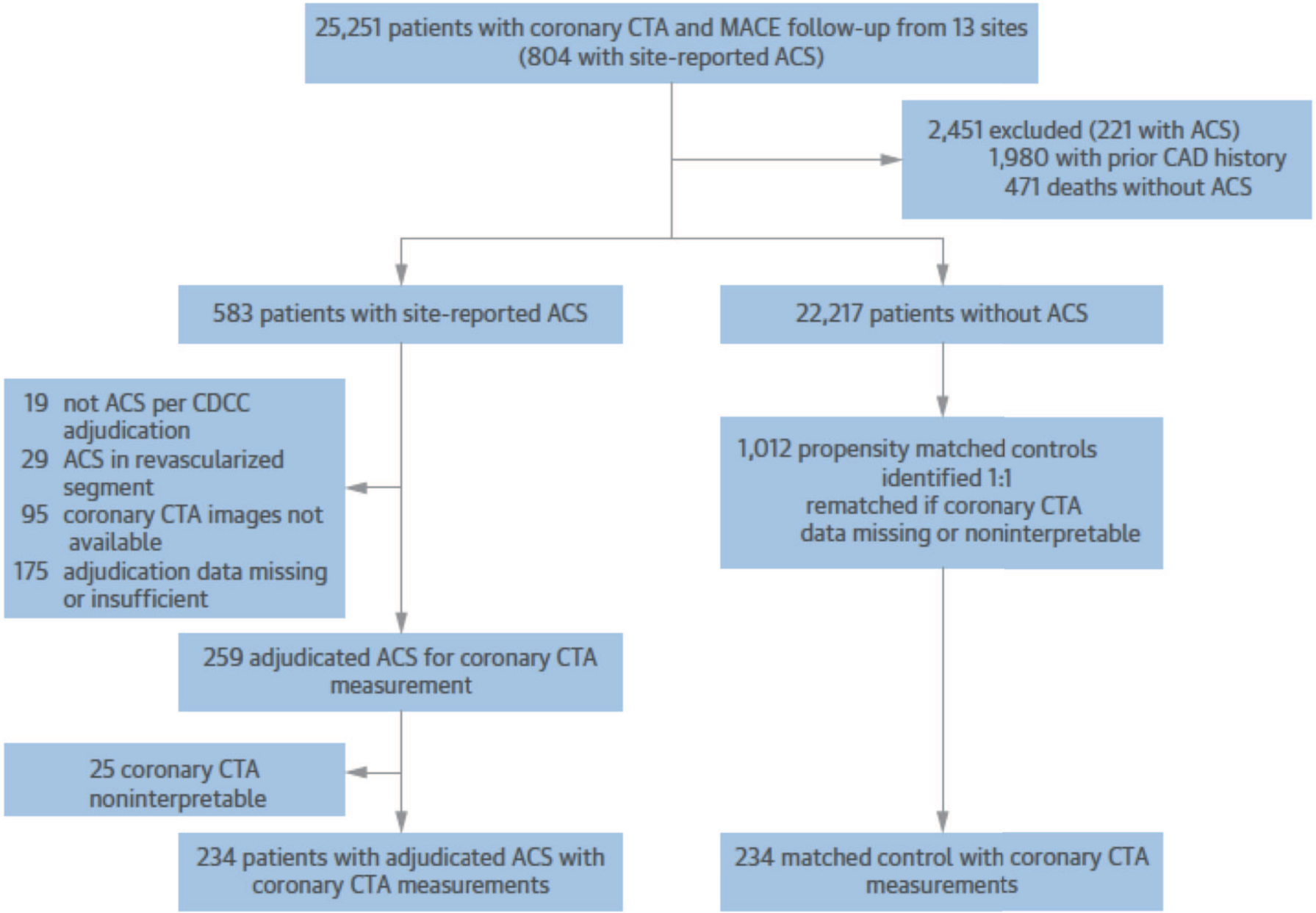
METHODS We performed a nested case-control study within a cohort of 25,251 patients undergoing coronary computed tomographic angiography (CTA) with follow-up over 3.4 ± 2.1 years. Patients with ACS and nonevent patients with no prior coronary artery disease (CAD) were propensity matched 1:1 for risk factors and coronary CTA–evaluated obstructive (≥50%) CAD. Separate core laboratories performed blinded adjudication of ACS and culprit lesions and quantification of baseline coronary CTA for percent diameter stenosis (%DS), percent cross-sectional plaque burden (PB), plaque volumes (PVs) by composition (calcified, fibrous, fibrofatty, and necrotic core), and presence of high-risk plaques (HRPs).

RESULTS We identified 234 ACS and control pairs (age 62 years, 63% male). More than 65% of patients with ACS had nonobstructive CAD at baseline, and 52% had HRP. The %DS, cross-sectional PB, fibrofatty and necrotic core volume, and HRP increased the adjusted hazard ratio (HR) of ACS (1.010 per %DS, 95% confidence interval [CI]: 1.005 to 1.015; 1.008 per percent cross-sectional PB, 95% CI: 1.003 to 1.013; 1.002 per mm^3 fibrofatty plaque, 95% CI: 1.000 to 1.003; 1.593 per mm^3 necrotic core, 95% CI: 1.219 to 2.082; all $p < 0.05$). Of the 129 culprit lesion precursors identified by coronary CTA, three-fourths exhibited <50% stenosis and 31.0% exhibited HRP.

FIGURE 1 CONSORT Diagram for the ICONIC study



ACS = acute coronary syndrome; CAD = coronary artery disease; CDCC = The Clinical and Data Coordinating Center; CTA = computed tomography angiography; ICONIC = Incident COroNary Syndromes Identified by Computed Tomography; MACE = major adverse cardiac event.

TABLE 1 Coronary CTA Findings in Patient-Level Analysis

Atherosclerotic Feature	ACS (n = 234)	Control (n = 234)	p Value
Number of total lesions	3.9 (2.5)	3.7 (2.7)	0.400
%DS	44.2 ± 26.4	33.7 ± 22.0	<0.001
%DS ≥50%	81 (34.6)	45 (19.2)	<0.001
%DS ≥70%	30 (12.8)	12 (5.1)	0.007
Area stenosis, %	61.9 ± 27.2	51.2 ± 27.9	<0.001
Minimum luminal area, mm^2	2.3 ± 2.1	2.6 ± 1.9	0.014
Minimum luminal diameter, mm	1.3 ± 0.7	1.5 ± 0.6	0.004
CAD severity by number of vessels			0.020
None	15 (6.4)	34 (14.5)	
Nonobstructive (≤50% DS)	104 (44.4)	91 (38.9)	
1-vessel disease	69 (29.5)	59 (25.2)	
2-vessel disease	25 (10.7)	21 (9.0)	
3-vessel/left main disease	21 (9.0)	29 (12.4)	
Total plaque volume, mm^3	289.7 ± 308.4	267.2 ± 285.7	0.321
Calcified, mm^3	97.7 ± 136.1	109.3 ± 164.0	0.389
Fibrous, mm^3	126.8 ± 131.6	112.3 ± 119.3	0.137
FF, mm^3	58.7 ± 85.8	41.4 ± 62.2	0.009
NC, mm^3	6.5 ± 14.0	4.2 ± 8.8	0.026
FF + NC, mm^3	65.2 ± 95.4	45.6 ± 68.8	0.008
Noncalcified, mm^3	192.0 ± 207.8	157.9 ± 173.6	0.030

Composition by % vessel volume			
% Calcified	4.1 ± 5.9	4.5 ± 6.2	0.709
% Fibrous	5.2 ± 4.6	4.5 ± 6.2	0.067
% FF	2.3 ± 3.0	1.7 ± 2.5	0.011
% NC	0.3 ± 0.7	0.2 ± 0.4	0.039
% FF + NC	2.6 ± 3.5	1.9 ± 2.7	0.012
% Noncalcified volume	7.8 ± 7.2	6.5 ± 6.7	0.020
Mean plaque burden, %	11.9 ± 10.9	11.0 ± 10.7	0.152
Max cross-sectional plaque burden, %	66.1 ± 25.8	56.5 ± 28.7	<0.001
Diffuseness, %	25.8 ± 19.4	22.3 ± 19.2	0.030
Adverse plaque characteristics			
Bifurcation, no. of lesions	2.3 ± 1.6	2.1 ± 1.7	0.218
Tortuous vessels, no. of lesions	0.08 ± 0.34	0.05 ± 0.28	0.477
High-risk plaque present	122 (52.1)	78 (33.3)	0.003
Low-attenuation plaque present	101 (43.2)	64 (27.4)	<0.001
Positive remodeling present	205 (87.6)	187 (79.9)	0.026
Spotty calcification present	72 (30.8)	47 (20.1)	0.013

Values are n (%) or mean ± SD.

ACS = acute coronary syndrome; CAD = coronary artery disease; CTA = computed tomography angiography; DS = diameter stenosis; FF = fibrofatty; NC = necrotic core.

TABLE 2 Per-Patient Multivariate Marginal Cox Model Predicting Acute Coronary Syndrome

Atherosclerotic Feature	HR (95% CI)*	p Value
Highest % diameter stenosis severity, per %	1.010 (1.005–1.015)	0.002
Presence of ≥50% diameter stenosis	1.437 (0.948–2.179)	0.088
Presence of ≥70% diameter stenosis	1.536 (1.141–2.067)	0.005
Plaque volume, per mm^3	1.000 (0.999–1.000)	0.792
Calcified	0.999 (0.998–1.000)	0.092
Fibrous	1.000 (0.999–1.001)	0.941
FF	1.002 (1.000–1.004)	0.048
NC	1.013 (1.003–1.022)	0.009
FF and NC	1.002 (1.000–1.003)	0.037
Noncalcified	1.000 (1.000–1.001)	0.352
Mean plaque burden, %	1.005 (0.997–1.013)	0.209
Max cross-sectional plaque burden, %	1.008 (1.003–1.013)	0.003
Diffuseness, per %	1.146 (0.622–2.111)	0.662
High-risk plaque present	1.593 (1.219–2.082)	0.001
Low-attenuation plaque present	1.378 (1.051–1.805)	0.020
Positive remodeling present	1.401 (0.955–2.056)	0.085
Spotty calcification present	1.543 (1.169–2.037)	0.002

*Adjusted for angina severity and interval revascularization.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

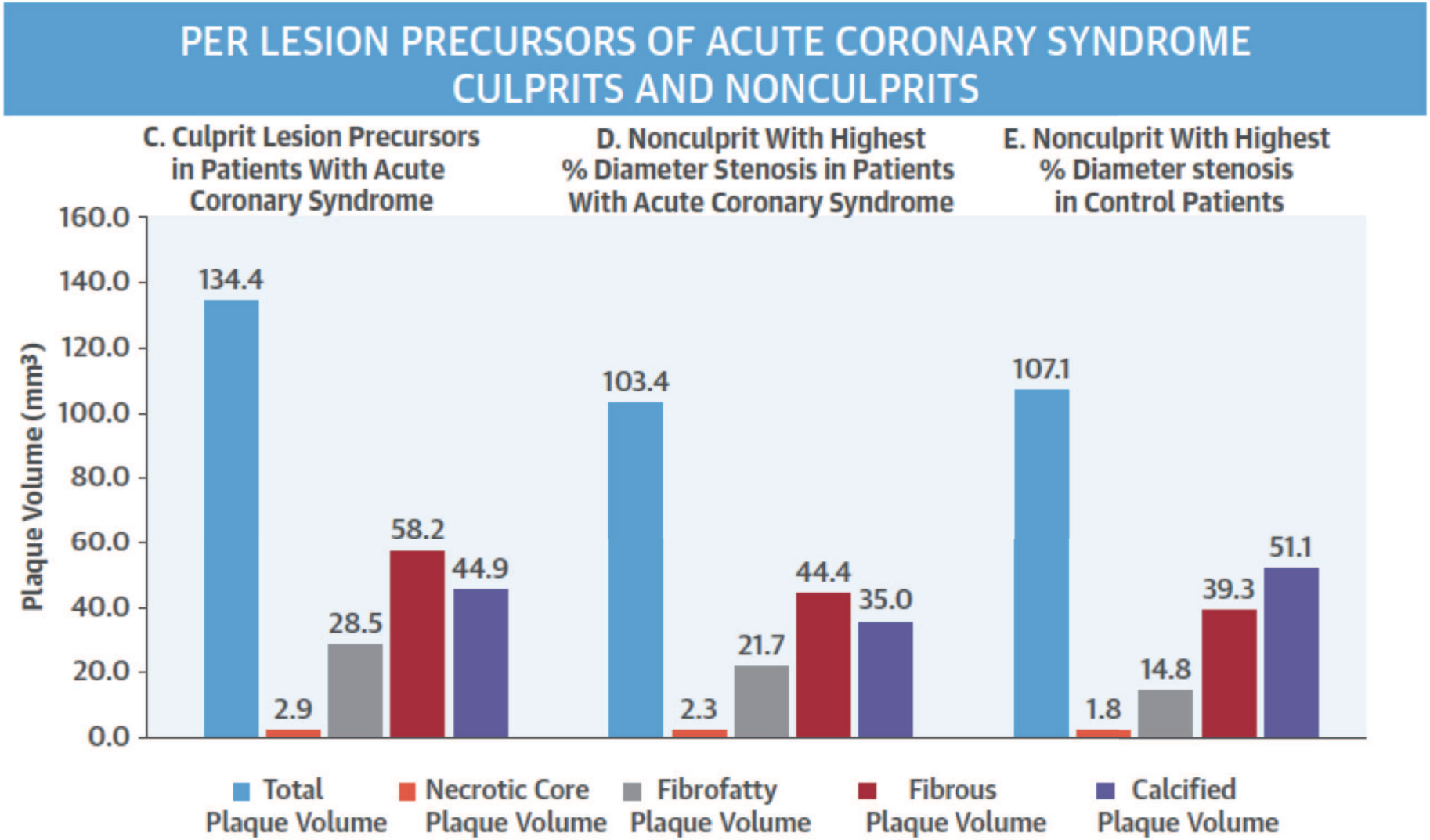
TABLE 3 Lesion-Level Analysis for Identification of Culprit Lesion Precursors

	Culprit Lesion Precursor (n = 129)	Within-Patient All Nonculprits in Patients With ACS (n = 479)			Within-Patient Nonculprit With Highest %DS in Patients With ACS (n = 118)*			Between-Patient Lesion With Highest %DS in Control Patients (n = 129)		
			HR† (95% CI)	p Value		HR† (95% CI)	p Value		HR† (95% CI)	p Value
%DS	38.27 ± 20.97	26.23 ± 18.02	1.023 (1.015–1.031)	<0.001	42.64 ± 22.23	1.002 (0.994–1.011)	0.612	37.04 ± 20.63	1.001 (0.992–1.010)	0.898
%DS ≥50%	32 (24.81)	41 (6.68)	2.813 (1.736–4.558)	<0.001	31 (26.27)	1.256 (0.796–1.982)	0.328	27 (20.93)	1.086 (0.682–1.729)	0.727
%DS ≥70%	6 (4.65)	11 (1.25)	1.717 (0.678–4.350)	0.254	11 (9.32)	0.607 (0.227–1.622)	0.319	8 (6.20)	0.684 (0.268–1.746)	0.427
Lesion length, mm	35.90 ± 21.66	23.71 ± 15.90	1.021 (1.013–1.029)	<0.001	30.55 ± 17.63	1.010 (1.001–1.018)	0.029	29.36 ± 21.71	1.004 (0.997–1.011)	0.225
Plaque volume, mm^3	134.4 ± 141.50	61.75 ± 113.07	1.002 (1.001–1.003)	<0.001	103.44 ± 160.55	1.001 (1.000–1.002)	0.030	107.11 ± 125.80	1.000 (0.999–1.002)	0.590
Calcified	44.88 ± 60.29	21.18 ± 45.78	1.004 (1.001–1.006)	0.002	35.0 ± 56.89	1.002 (1.000–1.004)	0.077	51.07 ± 83.89	0.998 (0.996–1.001)	0.137
Fibrous	58.22 ± 62.39	27.49 ± 46.47	1.005 (1.002–1.007)	<0.001	44.38 ± 60.78	1.002 (0.999–1.005)	0.108	39.31 ± 47.11	1.002 (0.999–1.005)	0.154
FF	28.47 ± 50.18	11.99 ± 34.08	1.007 (1.003–1.010)	<0.001	21.71 ± 55.67	1.003 (0.999–1.007)	0.124	14.80 ± 26.29	1.006 (1.002–1.010)	0.006
NC	2.85 ± 9.27	1.09 ± 4.20	1.029 (1.018–1.040)	<0.001	2.28 ± 6.86	1.014 (1.001–1.027)	0.042	1.75 ± 4.71	1.012 (1.002–1.022)	0.021
FF and NC	31.32 ± 55.5	13.08 ± 37.28	1.006 (1.003–1.009)	<0.001	23.99 ± 60.5	1.003 (0.999–1.007)	0.119	16.55 ± 29.96	1.005 (1.001–1.008)	0.006
Noncalcified	89.51 ± 107.36	40.55 ± 77.27	1.003 (1.002–1.005)	<0.001	68.34 ± 114.82	1.002 (1.000–1.003)	0.066	55.85 ± 67.15	1.002 (1.000–1.004)	0.042
Mean plaque burden, %	27.12 ± 13.40	19.67 ± 11.5	1.045 (1.032–1.059)	<0.001	24.52 ± 11.36	1.028 (1.011–1.045)	0.001	25.42 ± 14.75	1.003 (0.989–1.017)	0.680
Max plaque burden, %	62.54 ± 22.38	50.70 ± 20.38	1.027 (1.018–1.035)	<0.001	63.24 ± 21.31	1.008 (1.000–1.016)	0.050	57.84 ± 27.83	1.003 (0.996–1.010)	0.415
High-risk plaque	40 (31.01)	95 (19.83)	1.954 (1.317–2.899)	0.001	36 (30.51)	1.239 (0.841–1.827)	0.279	23 (17.83)	1.542 (1.105–2.153)	0.011
Low-attenuation plaque	31 (24.03)	68 (14.20)	1.805 (1.198–2.721)	0.005	28 (23.73)	1.085 (0.696–1.693)	0.718	22 (17.05)	1.223 (0.840–1.780)	0.294
Positive remodeling	99 (76.74)	379 (79.12)	1.048 (0.675–1.628)	0.835	87 (73.73)	1.202 (0.743–1.946)	0.453	73 (56.59)	2.031 (1.306–3.160)	0.002
Spotty calcification	23 (17.83)	62 (12.94)	1.702 (1.064–2.722)	0.026	18 (15.25)	1.506 (0.955–2.375)	0.078	13 (10.08)	1.763 (1.241–2.503)	0.002

Values are mean ± SD or n (%), unless otherwise indicated. *Eleven patients had measurements only for the culprit lesion and lacked a within-patient comparator. †Adjusted for angina severity and interval revascularization.

Abbreviations as in Tables 1 and 2.

CENTRAL ILLUSTRATION **Precursors of Acute Coronary Syndrome and Control Subjects as Identified by Coronary CTA**



(A) Adjudicated first ACS cases with coronary CTA measurements (n = 234) of a nested case-control cohort of 25,251 patients undergoing coronary CTA exhibit elevated fibrofatty and necrotic core volumes (65.2 ± 95.4 mm^3); 34.6% exhibit diameter stenosis ≥50%, and 52.1% exhibit high-risk plaque. **(B)** Nonevent control subjects propensity matched by demographics, risk factors, and number of obstructive vessels by coronary CTA exhibit lesser fibrofatty and necrotic core volumes (45.6 ± 68.8, multivariate adjusted p = 0.008) with no difference in calcified or total plaque volumes (p = NS for all); %DS and HRP are significantly decreased in control patients (p <0.05 for all). **(C)** Culprit lesion precursors exhibit elevated fibrofatty and necrotic core volumes (31.32 ± 55.5 mm^3). **(D)** Within-patient controls, using the nonculprit with the highest baseline %DS, exhibit lesser total plaque and necrotic core volumes (p <0.05 for both). **(E)** Between-patient controls, using the lesion with the highest % DS in the control patient, exhibit lesser non-calcified plaque components (p = 0.04), but no decrease in calcified plaque volume (p = NS). ACS = acute coronary syndrome; coronary CTA = coronary computed tomographic angiography; %DS = percent diameter stenosis; HRP = high-risk plaque; NS = nonsignificant.

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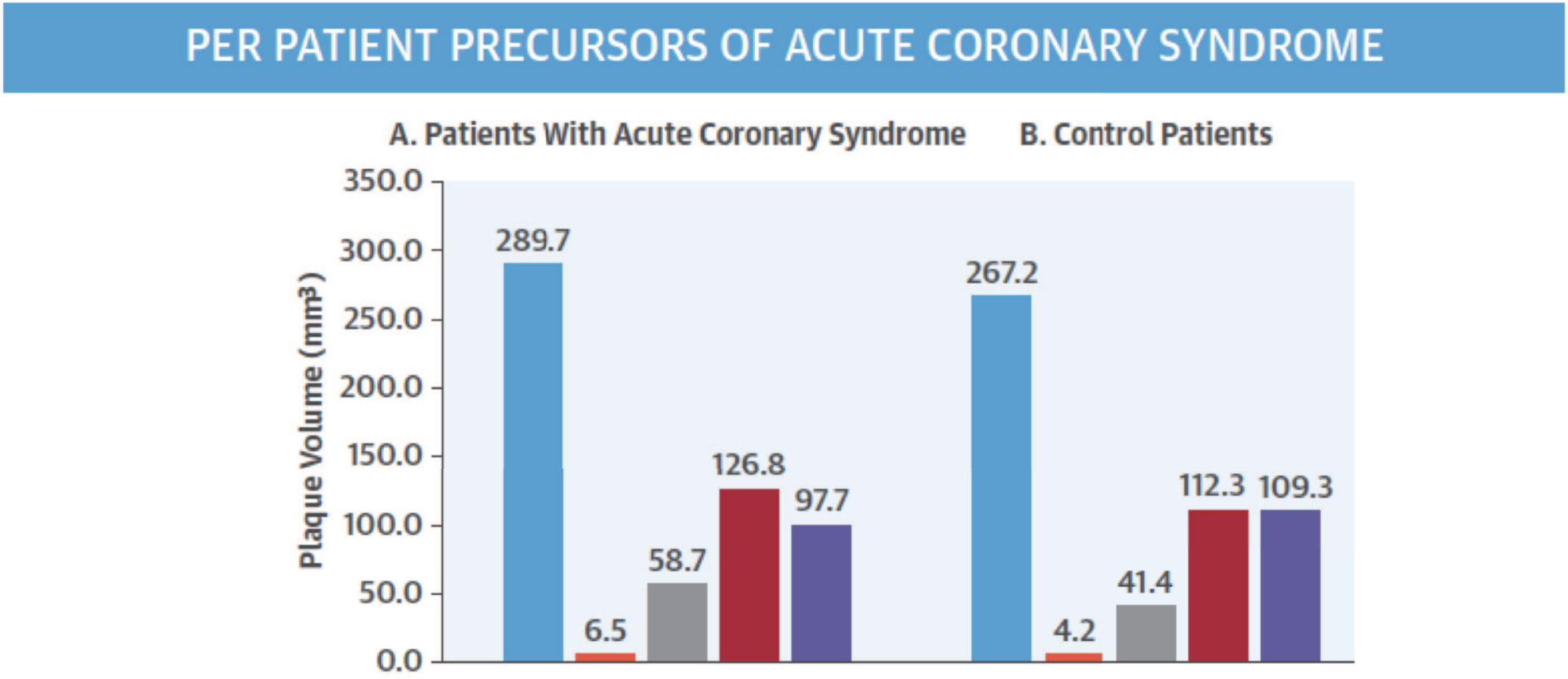

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CONCLUSIONS Although ACS increases with %DS, most precursors of ACS cases and culprit lesions are nonobstructive. Plaque evaluation, including HRP, PB, and plaque composition, identifies high-risk patients above and beyond stenosis severity and aggregate plaque burden. (J Am Coll Cardiol 2018;71:2511–22) Published by Elsevier on behalf of the American College of Cardiology Foundation.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Although ACS are typically associated with stenotic coronary lesions, precursors of culprit lesions are commonly nonobstructive. HRP characteristics, plaque composition, and cross-sectional PB as assessed by coronary CTA can predict the development of ACS independently of stenosis severity and aggregate PB.

TRANSLATIONAL OUTLOOK: These characteristics of nonstenotic but high-risk coronary artery lesions should be investigated further in cohort studies and in prospective heart attack prevention trials.