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Research paper

Age related compositional plaque burden by CT in patients with future ACS

Alexander R. van Rosendael [a,b], Inge J. van den Hoogen [a,b], Fay Y. Lin [a], Umberto Gianni [a,c], Yao Lu [d], Daniele Andreini [e], Mouaz H. Al-Mallah [f], Filippo Cademartiri [g], Kavitha Chinnaiyan [h], Benjamin J.W. Chow [i], Edoardo Conte [e], Ricardo C. Cury [j], Gudrun Feuchtner [k], Pedro de Araújo Gonçalves [l], Martin Hadamitzky [m], Yong-Jin Kim [n], Jonathon A. Leipsic [o], Erica Maffei [p], Hugo Marques [l], Fabian Plank [q], Gianluca Pontone [e], Gilbert L. Raff [h], Todd C. Villines [r], Sang-Eun Lee [s,t], Subhi J. Al'Aref [a], Lohendran Baskaran [a,u], Iksung Cho [a,s,v], Ibrahim Danad [w], Heidi Gransar [x], Matthew J. Budoff [y], Habib Samady [z], Renu Virmani [aa], James K. Min [ab], Jagat Narula [ac], Daniel S. Berman [ad], Hyuk-Jae Chang [s], Leslee J. Shaw [ac], Jeroen J. Bax [b,*]

[a] *Department of Radiology, New York-Presbyterian Hospital and Weill Cornell Medicine, New York, NY, USA*
[b] *Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands*
[c] *Department of Molecular Medicine, Section of Cardiology, University of Pavia, Pavia, Italy*
[d] *Department of Healthcare Policy and Research, New York-Presbyterian Hospital and the Weill Cornell Medical College, New York, NY, USA*
[e] *Centro Cardiologico Monzino, IRCCS Milan, Italy*
[f] *Houston Methodist DeBakey Heart & Vascular Center, Houston Methodist Hospital, Houston, TX, USA*
[g] *Department of Radiology, Fondazione Monasterio (FTGM)-CNR, Pisa, Italy*
[h] *Department of Cardiology, William Beaumont Hospital, Royal Oak, MI, USA*
[i] *Department of Medicine and Radiology, University of Ottawa, ON, Canada*
[j] *Department of Radiology, Miami Cardiac and Vascular Institute, Miami, FL, USA*
[k] *Department of Radiology, Medical University of Innsbruck, Innsbruck, Austria*
[l] *UNICA, Unit of Cardiovascular Imaging, Hospital da Luz, Lisboa, Portugal*
[m] *Department of Radiology and Nuclear Medicine, German Heart Center Munich, Munich, Germany*
[n] *Department of Internal Medicine, Seoul National University College of Medicine, Cardiovascular Center, Seoul National University Hospital, Seoul, South Korea*
[o] *Department of Medicine and Radiology, University of British Columbia, Vancouver, BC, Canada*
[p] *Department of Radiology, Area Vasta 1/ASUR Marche, Urbino, Italy*
[q] *Department of Cardiology, Innsbruck Medical University, Innsbruck, Austria*
[r] *Department of Medicine, University of Virginia Health System, Charlottesville, VA, USA*
[s] *Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Yonsei University Health System, Seoul South Korea*
[t] *Yonsei-Cedars-Sinai Integrative Cardiovascular Imaging Research Center, Yonsei University College of Medicine, Yonsei University Health System, South Korea*
[u] *Department of Cardiovascular Medicine, National Heart Centre, Singapore*
[v] *Chung-Ang University Hospital, Seoul, South Korea*
[w] *VU University Medical Center, Amsterdam, the Netherlands*
[x] *Department of Imaging, Cedars Sinai Medical Center, Los Angeles, CA, USA*
[y] *Department of Medicine, Los Angeles Biomedical Research Institute, Torrance CA, USA*
[z] *Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA*
[aa] *Department of Pathology, CVPath Institute, Gaithersburg, MD, USA*
[ab] *Cleerly, Inc, New York, NY, USA*
[ac] *Icahn School of Medicine at Mount Sinai, Mount Sinai Heart, Zena and Michael A. Wiener Cardiovascular Institute, And Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, New York, NY, USA*
[ad] *Department of Imaging and Medicine, Cedars Sinai Medical Center, Los Angeles, CA, USA*

Abbreviations: ACS, acute coronary syndrome; CACS, coronary artery calcium score; MI, myocardial infarction; CCTA, coronary computed tomography angiography; CAD, coronary artery disease; LAD, left anterior descending coronary artery; HRP, high-risk plaque.

* Corresponding author. Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands, 2300 RC.
E-mail address: j.j.bax@lumc.nl (J.J. Bax).

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ABSTRACT

Background: We examined age differences in whole-heart volumes of non-calcified and calcified atherosclerosis by coronary computed tomography angiography (CCTA) of patients with future ACS.
Methods: A total of 234 patients with core-lab adjudicated ACS after baseline CCTA were enrolled. Atherosclerotic plaque was quantified and characterized from the main epicardial vessels and side branches on a 0.5 mm cross-sectional basis. Calcified plaque and non-calcified plaque were defined by above or below 350 Hounsfield units. Patients were categorized according to their age by deciles. Also, coronary artery calcium scores (CACS) were evaluated when available.
Results: Patients were on average 62.2 ± 11.5 years old. On the pre-ACS CCTA, patients showed diffuse, multi-site, predominantly non-obstructive atherosclerosis across all age categories, with plaque being detected in 93.5% of all ACS cases. The proportion calcified plaque from the total plaque burden increased significantly with older presentation (10% calcification in those <50 years, and 50% calcification in those >80 years old). Patients with ACS <50 years had remarkably lower atherosclerotic burden compared with older patients, but a high proportion of high risk markers such as low-attenuation plaque. CACS was >0 in 85% of the patients older than 50 years, and in 57% of patients younger than 50 years.
Conclusion: The proportion of calcified plaque varied depending on patient age at the time of ACS. Only a small proportion of plaque was calcified when ACS occurred at <50 years old, while this increased gradually with older age. Purely non-calcified atherosclerotic plaque was not uncommon in patients <50 years.

1. Introduction

Traditional markers of heightened cardiovascular risk such as the presence of cardiovascular risk factors have suboptimal precision in estimation of future cardiovascular event risk.[1] Multiple studies have observed strong concordance between risk and atherosclerotic plaque burden, detected with either invasive coronary angiography, intravascular coronary ultrasound, or coronary computed tomographic angiography (CCTA).[2–6] Importantly, absence of atherosclerosis, even in the presence of risk factors, portends very favorable long term outcomes.[7,8]

In the formation of atheroma, non-calcified plaque develops by the inflammatory process following entrapment of low-density lipoprotein cholesterol in the sub endothelium. Later, calcium crystals (micro-calcifications) are formed within the necrotic cores which may become fragments and sheets of calcium.[9]

Despite the potential to miss non-calcified plaque, a CACS of zero has been shown to be a reliable marker of very low risk. While higher Agatston scores have a stepwise association with more events.[7] The importance of non-calcified plaque is understudied, especially in younger individuals with lower likelihood of calcification.[10]

Prior work from our group has examined specific atherosclerotic plaque precursors for ACS.[11,12] However, our prior findings did not specify the role of age as determining the baseline plaque burden and variable precursor findings for incident ACS. The ICONIC (Incident COroNary Syndromes Identified by Computed Tomography) study includes patients with core-lab verified ACS after baseline CCTA with detailed plaque quantification from the entire coronary tree.[11] This design allows to describe the atherosclerotic profile before the occurrence of ACS. This study aimed to assess the atherosclerotic burden – divided into calcified and non-calcified - from patients with future ACS, stratified by their age at ACS.

2. Methods

2.1. Patients

The ICONIC is a nested case control study of patients derived from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry.[11] CONFIRM is a longitudinal observational cohort of patients undergoing clinically indicated CCTA from 13 sites and 8 countries (Canada, United States, The Netherlands, Germany, Austria, Italy, Portugal, and South Korea).[13] Physicians or nurses from each participating site prospectively collected demographic, laboratory, and clinical patient data at the time of the baseline CCTA and 95.4% of patients were followed 3.4 ± 2.1 years for major adverse cardiac events. For ICONIC, sites submitted clinical and CCTA imaging data of patients with site adjudicated ACS to the Clinical and Data Coordinating Center for uniform ACS adjudication blinded to CCTA. Further, CCTA DICOM files were submitted to a separate CCTA core-laboratory for comprehensive whole-heart quantitative coronary plaque characterization. Among 25,251 patients with follow-up for major adverse cardiac event, cases with prior CAD (prior revascularization of MI, N = 221), insufficient clinical data (N = 181), ACS with the culprit lesion in a revascularized coronary segment (N = 29), adjudication by core-laboratory not meeting ACS criteria (N = 19), unavailable CCTA data to submit to the core lab (N = 95), or CCTA that was of insufficient quality for core lab quantitative plaque measurements (N = 25) were excluded. The ICONIC cohort included 234 core-lab adjudicated ACS cases.

2.2. ACS event adjudication

The Clinical and Data Coordinating Center evaluated cardiac biomarker measurement, ECG, and invasive coronary angiogram data blinded to coronary CTA and adjudicated ACS according to the World Health Organization and Universal Definition of Myocardial Infarction.[14,15] A full description of event adjudication has been previously reported.[11] In short, six physicians categorized cases into ST-segment elevation myocardial infarction (STEMI), non-STEMI, or unstable angina. Patients with culprit lesions in previously revascularized segments were excluded. Unstable angina was defined as new or worsening ischemia symptoms and ischemic ECG changes with normal cardiac biomarkers.[15] Additionally, cases were categorized as unclassified MI in case of an ambiguous adjudication ECG, other supportive information supportive for ACS, and elevated cardiac biomarkers (>99% local upper limit of normal). Cases other than ACS (i.e., myocarditis, congestive heart failure) were excluded.

2.3. CCTA image analysis

Baseline CCTAs were acquired using ≥64-slice scanners in accordance with the Society of Cardiovascular Computed Tomography (SCCT) Guidelines.[16] Independent level III-experienced readers at the CCTA core-laboratory performed qualitative evaluation and standardized quantitative evaluation using semi-automated plaque analysis software (QAngioCT Research Edition version 2.1.9.1, Medis Medical Imaging Systems, Leiden, the Netherlands) with manual correction where needed. Readers were blinded to clinical data. Briefly, each segment from the 18-segment coronary tree larger than 2 mm in diameter was annotated for vessel wall and lumen on a 0.5 mm cross-sectional basis. Segmental data were summed to patient level. Plaque was categorized as calcified and non-calcified by the

fixed threshold of 350 Hounsfield Units (HU). In addition, low-density plaque was defined by ≤ 130 HU.[17,18] Systematic intra- and interobserver repeatability measurements were performed showing excellent intraclass correlation coefficients (>0.95), as previously described.[11] Percent atheroma volume (PAV) was defined as plaque volume divided by vessel volume * 100%. Diffuseness was defined as the length of all lesions together divided by the length of the coronary arteries * 100%. The segment involvement score is equal to the number of coronary segments with atherosclerosis; the segment stenosis score multiplies diseased segments by a stenosis weight factor (1 = 1–49% stenosis, 2 = 50–69% stenosis, 3 ≥ 70% stenosis).[2] In addition to quantitative segmental evaluation, each coronary lesion was evaluated for luminal narrowing compared to a proximal non-diseased reference site. For patients with available calcium scan, the coronary artery calcium score (CACS) was calculated using the Agatston method.[19]

2.4. Statistical analysis

Continuous data was reported as mean (standard deviation) if normally distributed and median (interquartile range) for non-gaussian distribution. Categorical data was presented as counts (percentage). Clinical and baseline CCTA information is presented stratified by age at time of ACS and categorized as <50, 50–59,60-69, 70–79, and ≥80 years. The analysis of variance (ANOVA) and Kruskal-Wallis test were used to compare continuous data across multiple groups, as appropriate. The Wilcoxon Signed Rank test was used for paired comparisons of continuous data. The Chi-square test was used to compare categorical data. A two-sided *P*-value <0.05 is considered statistically significant. Results restricting to myocardial infarction (MI) cases only are described in appendix.

3. Results

3.1. Baseline characteristics stratified by age at ACS

The age at baseline CCTA was 62.2 ± 11.5 years and the time to ACS was <2 weeks, 2 weeks to 2 years, and more than 2 years in 33.3%, 46.2%, and 20.5%, respectively (Table 1). Those who experienced ACS before the age of 50 underwent CT imaging at age 41.5 ± 5.4 and were characterized by male sex (72.4%), elevated BMI (28.5 ± 5.3 kg/m^2), frequent smoking (51.7%) and family history positive for CAD (74.1%). The majority of the population was Caucasian and had chest pain at baseline CCTA (84.2%).

3.2. Atherosclerotic plaque characterization stratified by age at ACS

Non-calcified plaque volume was significantly larger than calcified plaque volume for patients younger than 80 (P < 0.001), Table 2, Fig. 1. A gradual increase in calcified plaque volume was observed with increasing age at ACS: from 4.6 mm^3 (IQR 0.0–23.7) for patients younger than 50–140.0 mm^3 (IQR 28.3–301.2) for patients older than 80, P < 0.001, Table 2. Non-calcified plaque volume for patients younger than 50 was 47.9 mm^3 (IQR 22.4–234.2), and magnitudes observed in those older than 50 were comparable: ranging between 115.9 and 157.6 mm^3, P = 0.156. The calcified proportion of plaque increased gradually from 10.0% (IQR 0.1–28.7) to 50.9% (IQR 23.8–60.1) for patients younger than 50 to older than 80 years of age. The proportion of low-density plaque was the highest in the youngest age categories: 29.3% (IQR 8.6–47.9) for age below 50, and 21.8% (IQR 9.5–42.7) for age 50–59. 93.5% of the patients had detectable atherosclerosis at baseline CCTA. Atherosclerotic extent increased with older age when defined by PAV, the segment involvement score, segment stenosis score, or diffuseness of plaque (Table 2).

Table 1
Baseline characteristics stratified by age at ACS.

	Age at ACS					
	Age <50 (N = 29)	Age 50–59 (N = 52)	Age 60–69 (N = 78)	Age 70–79 (N = 59)	Age ≥80 (N = 16)	p-value
Baseline characteristics at CT scan acquisition						
Age, year	41.5 ± 5.4	54.2 ± 3.5	63.6 ± 3.3	72.3 ± 2.9	81.5 ± 4.3	<0.001
Male, n	21 (72.4)	38 (73.1)	51 (65.4)	33 (55.9)	6 (37.5)	0.054
Body mass index, kg/m^2	28.5 ± 5.3	29.3 ± 4.4	28.0 ± 6.1	25.9 ± 3.4	24.2 ± 3.3	0.001
Cardiovascular risk factors						
Hypertension, n	11 (39.3)	35 (68.6)	42 (53.8)	49 (83.1)	11 (68.8)	<0.001
Diabetes, n	1 (3.4)	15 (28.8)	20 (25.6)	8 (13.6)	2 (12.5)	0.024
Dyslipidemia, n	11 (39.3)	32 (61.5)	47 (60.3)	29 (50.0)	10 (62.5)	0.240
Current smoking, n	15 (51.7)	21 (40.4)	20 (25.6)	15 (25.9)	1 (6.3)	0.006
Family history of CAD, n	20 (74.1)	26 (53.1)	28 (35.9)	19 (32.8)	1 (6.3)	<0.001
Ethnicity						0.584
White, n	13 (65.0)	23 (65.7)	36 (61.0)	30 (61.2)	10 (71.4)	
East Asian, n	3 (15.0)	11 (31.4)	18 (30.5)	17 (34.7)	4 (28.6)	
Others, n	4 (20.0)	1 (2.9)	5 (8.5)	2 (4.0)	0	
Chest pain						0.550
Asymptomatic, n	4 (14.8)	9 (18.4)	13 (17.6)	6 (10.7)	5 (31.3)	
Non-cardiac, n	3 (11.1)	9 (18.4)	5 (6.8)	9 (16.1)	2 (12.5)	
Atypical, n	12 (44.4)	21 (42.9)	35 (47.3)	21 (37.5)	5 (31.3)	
Typical, n	8 (29.6)	10 (20.4)	21 (28.4)	20 (35.7)	4 (25.0)	
Lipid profile						
Total cholesterol, mg/dl	198.7 ± 63.7	195.5 ± 44.8	190.7 ± 54.3	192.2 ± 46.9	192.5 ± 22.7	0.816
LDL-cholesterol, mg/dl	113.9 ± 48.5	121.4 ± 39.8	117.0 ± 43.4	112.5 ± 44.8	126.9 ± 30.9	0.296
HDL-cholesterol, mg/dl	45.0 ± 18.9	46.1 ± 11.7	43.6 ± 11.0	53.9 ± 14.5	51.6 ± 13.4	0.111
Time to ACS, days						0.021
< 2 weeks, n	18 (62.1)	15 (28.8)	22 (28.2)	19 (32.2)	4 (25.0)	
2 weeks to 2 years, n	5 (17.2)	30 (57.7)	40 (51.3)	25 (42.4)	8 (50.0)	
>2 years, n	6 (20.7)	7 (13.5)	16 (20.5)	15 (25.4)	4 (25.0)	
ACS type						0.536
STEMI, n	4 (13.8)	10 (19.2)	15 (19.2)	9 (15.3)	2 (12.5)	
NSTEMI, n	14 (48.3)	23 (44.2)	38 (48.7)	30 (50.8)	9 (56.3)	
MI, non-specified, n	1 (3.4)	2 (3.8)	1 (1.3)	0	2 (12.5)	
Unstable angina, n	10 (34.5)	17 (32.7)	24 (30.8)	20 (33.9)	4 (18.8)	

ACS, acute coronary syndrome; CAD, coronary artery disease; CT, computed tomography; HDL, high-density lipoprotein; LDL, low-density lipoprotein; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction.

Table 2
Per-patient atherosclerotic plaque stratified by age at ACS.

	Age at ACS					
	Age <50 (N = 29)	Age 50–59 (N=52)	Age 60–69 (N=78)	Age 70–79 (N=59)	Age ≥80 (N=16)	p-value
Baseline characteristics at CT scan acquisition						
Plaque volume						
Calcified plaque, m	4.6 (0.0, 23.7)	27.6 (6.9, 126.5)	47.9 (4.9, 113.3)	85.2 (24.9, 163.9)	140.0 (28.3, 301.2)	<0.001
Non-calcified plaque, mm^3	47.9 (22.4, 234.2)	142.2 (64.5, 316.4)	115.9 (41.9, 254.8)	152.7 (67.0, 289.8)	157.6 (70.8, 208.65)	0.156
Low-density plaque, mm^3	13.3 (0.7, 81.5)	45.8 (14.4, 120.4)	26.4 (4.2, 74.7)	30.9 (7.7, 76.8)	21.9 (3.0, 36.3)	0.243
Plaque composition						
Calcified plaque proportion, %[a]	10.0 (0.1, 28.7)	24.7 (6.5, 38.4)	31.8 (7.0, 45.5)	38.8 (23.3, 49.8)	50.9 (23.8, 60.1)	<0.001
Low-attenuation plaque proportion, %[a]	29.3 (8.6, 47.9)	21.8 (9.5, 42.7)	16.8 (6.1, 33.8)	13.9 (5.8, 21.6)	5.6 (1.6, 15.0)	0.002
Maximal lumen diameter stenosis						
Maximal diameter stenosis, %	34.4 (17.6, 59.3)	41.2 (28.1, 58.1)	43.1 (26.3, 53.8)	44.6 (32.5, 53.5)	55.4 (27.5, 64.8)	0.388
≥50% stenosis, n	9 (31.0)	17 (32.7)	23 (29.5)	22 (37.3)	10 (62.5)	0.145
≥70% stenosis, n	4 (13.8)	6 (11.5)	11 (14.1)	6 (10.2)	3 (18.8)	0.896
Plaque extent						
PAV, %	3.6 (1.1, 11.6)	9.0 (2.9, 16.2)	7.6 (3.0, 16.2)	11.4 (4.7, 18.5)	15.7 (5.2, 26.4)	0.020
Number of plaques	2 (1, 3)	4 (2, 5)	4 (2, 6)	4 (3, 6)	4 (2, 7)	0.119
Segment involvement score	3 (1, 6)	5 (3, 8)	5 (3, 8)	6 (4, 8)	6 (4, 8)	0.019
Segment stenosis score	4 (2, 8)	8 (4, 14)	8 (4, 14)	11 (6, 14)	13 (5, 20)	0.032
Diffuseness[b], %	9.0 (5.0, 23.2)	21.6 (10.3, 38.8)	22.5 (10.7, 37.3)	24.7 (12.3, 44.2)	28.0 (13.3, 64.2)	0.011
High risk plaque						
High risk plaque present, n	14 (48.3)	28 (53.8)	41 (52.6)	33 (55.9)	6 (37.5)	0.744
Number high risk plaques	0.72 ± 0.96	0.92 ± 1.12	0.86 ± 1.07	0.86 ± 0.97	0.68 ± 1.08	0.816
Number of low-attenuation plaques	0.62 ± 0.94	0.75 ± 0.93	0.68 ± 1.1	0.64 ± 0.80	0.4 ± 0.89	0.560
Number of positive remodeled plaques	2.3 ± 2.4	3.1 ± 2.2	2.9 ± 2.3	3.3 ± 2.1	3.3 ± 1.9	0.082
Number of plaques with spotty calcification	0.52 ± 0.69	0.46 ± 0.85	0.50 ± 0.91	0.53 ± 1.1	0.63 ± 1.1	0.897

PAV, percent atheroma volume. Other abbreviations as in Table 1.
[a] Restricted to patients with plaque volume >0 mm^3.
[b] Length of all coronary lesions divided by length of the coronary arteries * 100%.

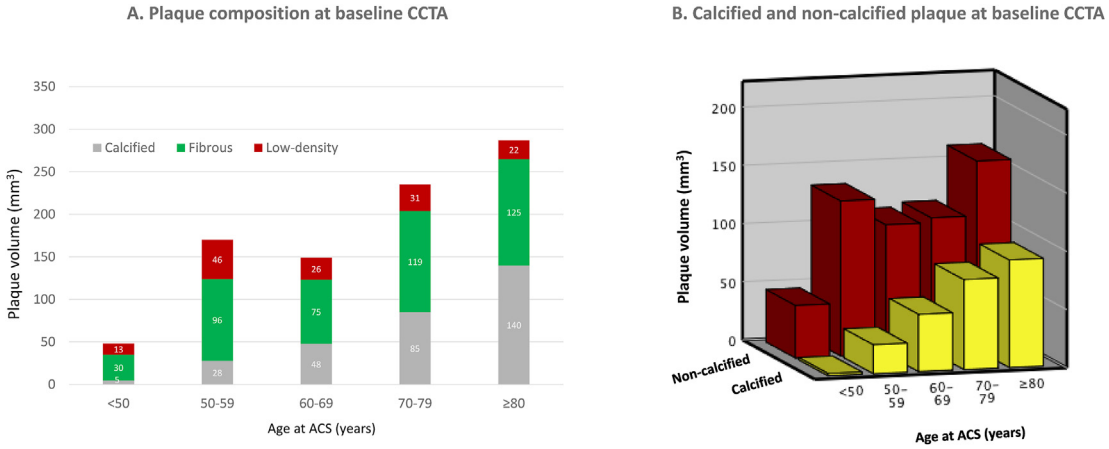

Fig. 1. Atherosclerosis by CCTA in 234 patients with future ACS. Panel A shows the median plaque volume of calcified (>350 HU), fibrous (130–350 HU), and low-density plaque (<130 HU) according to age category. Most of coronary atherosclerosis is non-calcified and calcified plaque increased proportionally with age. Panel B shows median volumes of calcified and non-calcified plaque according to age category. Below the age of 80, non-calcified plaque was significantly larger. Actual values can be derived from Table 2.

Severe stenosis (≥70%) was present in less than 20% of the patients, regardless of age category. The results when restricted to MI cases only were comparable (appendix Table 1).

Sensitivity analyses were performed when patients <50 years old were excluded. Calcified plaque proportion was still higher with older age (P < 0.001), however, PAV, number of plaques, segment involvement score, segment stenosis score, and diffuseness, were not significantly different with older age (P = 0.224, 0.570, 0.580, 0.346, 0.267, respectively).

3.3. Baseline CACS stratified by age at ACS

Of the 148 ACS patients with available CACS, median values were 1 (IQR 0–69), 123 (IQR 16–348), 222 (IQR 4–574), 267 (IQR 72–915), and 430 (IQR 76–819) for age at ACS <50, 50–59, 60–69, 70–79, and ≥80.

CACS was 0, <10, and <100 in 19.6%, 26.4%, and 43.9% of the population. In patients younger than 50 years of age, CACS was 0, <10, and <100 in 43.5%, 61.5%%, and 79.3% (Fig. 2). In patients equal to and older than 50, CACS was 0, <10, and <100 in 15.2%, 20.8%, and 36.8%. Results when restricted to MI cases only were similar (Appendix Table 2.)

4. Discussion

The current study shows that patients with future ACS had extensive, predominantly non-obstructive but diffuse multi-segment coronary atherosclerosis. The proportion of calcified plaque depended significantly on the age at presentation, with higher proportions at older age. Patients under 50 years of age had a lower plaque burden which was largely non-calcified with prevalent high risk markers including low-

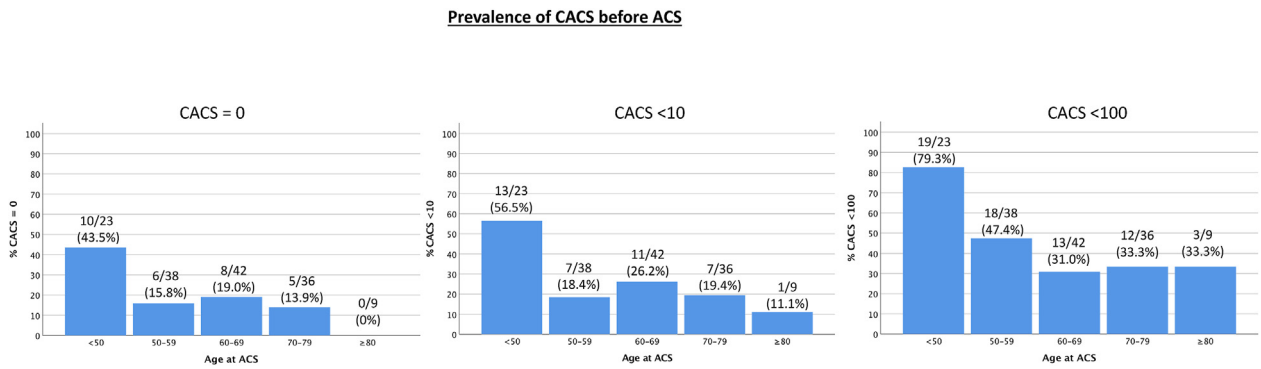

Fig. 2. Prevalence of CACS before occurrence of future ACS. The prevalence of coronary artery calcium score (CACS) of 0, <10, and <100 is shown according to age category of ACS. Absence of CACS is observed especially in patients experiencing ACS before the age of 50.

attenuation plaque. In this cohort of symptomatic patients, CACS was overall sensitive to incident ACS, but among patients <50 years old, ACS largely occurred with a CACS of zero.

4.1. Atherosclerotic plaque burden and ACS

The occurrence of coronary events typically requires destabilization of atherosclerotic plaque (erosion or rupture) and thrombosis leading to artery occlusion.[20] Histopathological evaluation of patients with sudden cardiac death have demonstrated that culprit coronary plaques that eroded or ruptured are voluminous, large in lipid pool and covered by a thin inflamed fibrous cap.[21] When more atherosclerotic plaque is prevalent, the higher the likelihood of plaque destabilization leading to acute rupture or erosion with an occlusive or nonocclusive thrombotic, clinically apparent, event.

A major advantage of employing CCTA is that it allows for non-invasive whole heart characterization of plaque and is therefore well-suited for quantification of total plaque burden. All CCTAs in ICONIC have been quantitatively analyzed on 0.5 mm cross-sectional basis, which enhances the precision of disease measurement as well as reproducibility as compared to a qualitative interpretation where atherosclerotic extent is restricted to counts of diseased coronary plaques or segments.

The current study revealed that atherosclerotic burden on CCTA is dominated by non-calcified plaque, with significant covariation by age. In patients with ACS younger than 50, only 10% of plaque was calcified, while this increased to 50% among those older than 80 years of age. This indicates that a similar calcium burden corresponds with a larger total plaque burden in young than old patients, indicating that even small amount of calcium is reflective of advanced atherosclerosis and confers high risk in young individuals. This is supported by a substudy from the CARDIA (Coronary Artery Risk Development in Young Adults) which followed 3043 individuals with an average age of 40 years for 12.5 years, and observed a 5 fold increase in coronary heart disease events for the presence of any calcium, after statistical adjustment.[22]

The current study also included a subgroup of special interest were the patients experiencing ACS before the age of 50 (undergoing CT imaging at 42 years of age) had a remarkably lower atherosclerotic burden than the older patients. However, these patients still showed a relatively high plaque burden compared with 'average' patients undergoing clinically indicated CCTA of a similar age. Among 13,735 patients from the CONFIRM registry, patients aged 40–49 years had a mean segment involvement score of approximately 1, compared to 4 in the current study.[23] Similarly, 1345 patients from the PARADIGM (Progression of AtheRoscelerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) registry who underwent CCTA at age 60 on average, demonstrated a whole-heart PAV of 2.0% compared to 3.4% of the patients with ACS <50 years in the current study.[24] These findings support the concept that also young patients with ACS have accelerated atherosclerosis development in the coronary tree, which likely corresponds with higher risk for plaque destabilization and subsequent thrombotic coronary events. In addition, patients below 50 had the highest proportion of low-density plaque (29% of all plaque) which reflects more 'vulnerable' milieu for atherosclerotic plaque.[25]

4.2. Coronary artery calcium score (CACS)

Prior studies have evaluated the sensitivity of CACS to identify ACS. In the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) study, 17% of MI and cardiovascular death cases and 13% of ACS and cardiovascular death occurred in patients with CACS = 0.[26] In MESA (Multi-Ethnic Study of Atherosclerosis), 22% of the hard cardiovascular events, and in the Heinz Nixdorff Recall study, 12% of the MI and coronary death events occurred in patients without CACS.[7,27] These numbers are comparable to the 19.6% in the current study. Patients younger than 50 years of age in the current study had a CACS of 0 in 43.5%, a proportion similar to the previously mentioned CARDIA study that included young patients (47% of CHD events).[22] In addition, data from the Western Denmark Heart Registry showed that in patients with obstructive CAD the prevalence of CACS-0 ranged from 58% among patients younger than 40 years, 34% among those aged 40–49 years, 18% among those aged 50–59 years, 9% among those aged 60–69 years.[28] Together with our data this suggests that in patients younger than 50, a CACS of zero is less reassuring.

Nevertheless, the absolute event risk in young individuals without CACS is still very low. In the population-based CARDIA registry, 10 year coronary heart disease rates were <1% when CAC was absent.

4.3.1. Limitations

Patients were included from an observational cohort study and potential referral or selection bias may have been introduced. However ICONIC represents the largest currently existing cohort of ACS occurrence after baseline CT imaging with detailed plaque characterization. Patients underwent baseline CT imaging for a clinical indication (predominantly because of symptoms), which may limit generalizability of the findings to 'all' ACS events, and especially to asymptomatic individuals. Chronic total occlusion on baseline CCTA could not be quantified for plaque volume which may have impacted plaque burden measures. Plaque composition was defined by fixed thresholds of HU, which may be influenced by lumen contrast attenuation. Atherosclerotic characterization was only performed at a single time point, thus information regarding plaque progression in patients with ACS remains unknown. A proportion of patients experienced the events within 2 weeks after CCTA evaluation, which may represent more 'unstable' symptoms, thereby limiting generalizability to the stable chest pain population. The study provides age related differences in plaque burden in patients with future ACS, but does not provide evidence for differences in plaque compared with control patients or the general population. Finally, CACS

was only available in a subset of patients and measured by local sites instead of core lab.

5. Conclusion

Patients with future ACS had extensive, predominantly non-obstructive and diffuse multi-segment coronary atherosclerosis. The proportion of calcified plaque depended significantly on the age at presentation, with higher proportions at older age. Patients under 50 years of age had a lower plaque burden with high risk features, but this burden was high when compared with stable patient cohorts within the literature.[24] In the ICONIC cohort, CACS was sensitive to identify ACS, but in ACS cases <50 years old, a preceding CACS of zero was often present.

6. Perspectives

6.1. Clinical competencies

Patients with future ACS had extensive, predominantly non-obstructive and diffuse multi-segment coronary atherosclerosis. The plaque composition was dependent on age, with increasing proportion of calcified plaque with older age. Patients under 50 years of age had a remarkable lower plaque burden, which was commonly completely non-calcified.

6.2. Translational outlook

The value of quantitative plaque evaluation for the prediction of future acute coronary syndromes should be further studied.

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Declaration of competing interest

Dr. Chinnaiyan is a non-compensated medical advisory board member of Heartflow Inc. Dr. Chow holds the Saul and Edna Goldfarb Chair in Cardiac Imaging Research, receives support from CV Diagnostix and Ausculsciences, receives educational support from TeraRecon Inc., and has equity interest in General Electric. Dr. Min is an employee of Cleerly, Inc. Dr. Samady serves on the scientific advisory board of Philips, has equity interest in Covanos Inc., and has a research grant from Medtronic, Abbott Vascular, and Philips. Dr. Shaw is on the scientific advisory board for Covanos, Inc. The remaining authors have no relevant conflicts to disclose.

Appendix

Table 1
Per-patient atherosclerotic plaque stratified by age at MI

	Age at MI					
	Age <50 (N = 19)	Age 50–59 (N=35)	Age 60–69 (N=54)	Age 70–79 (N=39)	Age ≥80 (N=13)	p-value
Baseline characteristics at CT scan acquisition						
Plaque volume						
Calcified plaque, mm^3	0.4 (0, 12.3)	28.5 (13.5, 127.7)	53.8 (3.9, 117.2)	71.0 (16.4, 189.1)	131.0 (18.2, 290.6)	0.004
Non-calcified plaque, mm^3	47.7 (25.5, 283.7)	205.6 (64.3, 326.2)	118.5 (39.2, 247.4)	149.3 (55.5, 366.0)	147.9 (71.0, 207.6)	0.187
Low-attenuation plaque, mm^3	12.6 (0.4, 57.5)	56.8 (14.3, 119.3)	26.4 (3.6, 69.2)	25.0 (6.0, 76.8)	20.7 (3.3, 34.9)	0.152
Plaque composition						
Calcified plaque proportion, %	6.0 (0.1, 33.8)	25.5 (7.0, 37.9)	30.4 (7.0, 45.8)	39.1 (18.5, 51.0)	42.0 (23.9, 66.6)	0.001
Low-density plaque proportion, %	30.9 (8.2, 45.3)	18.9 (9.7, 42.4)	17.4 (7.4, 30.4)	13.8 (4.7, 21.0)	5.0 (1.6, 13.7)	0.014
Maximal lumen diameter stenosis						
≥50% stenosis, n	5 (26.3)	13 (37.3)	15 (27.8)	13 (33.3)	8 (61.5)	0.652
≥70% stenosis, n	3 (15.8)	5 (14.3)	9 (16.7)	5 (12.8)	3 (23.1)	0.885
Plaque extent						
PAV, %	3.4 (1.0, 11.9)	9.5 (2.5, 17.2)	8.7 (2.7, 16.9)	13.4 (4.7, 21.7)	13.6 (5.4, 23.8)	0.181
Number of plaques	2 (1, 4)	4 (2, 5)	4 (2, 6)	4 (2, 6)	4 (3, 7)	0.321
Segment involvement score	3 (1, 7)	6 (3, 8)	5 (2, 8)	6 (3, 8)	6 (4, 8)	0.193
Segment stenosis score	3 (1, 8)	10 (6, 15)	10 (3, 14)	10 (5, 16)	12 (5, 17)	0.151
Diffuseness, %	7.5 (4.6, 26.2)	23.2 (12.9, 38.3)	21.6 (8.0, 37.3)	25.0 (10.0, 47.5)	27.9 (13.8, 63.7)	0.065
High risk plaque						
High risk plaque present, n	9 (47.4)	20 (57.1)	25 (46.3)	24 (61.5)	5 (38.5)	0.783
Number high risk plaques	0.74 ± 0.99	0.89 ± 0.93	0.68 ± 0.92	0.97 ± 1.01	0.69 ± 1.1	0.455
Number of low-attenuation plaques	0.68 ± 0.95	0.66 ± 0.80	0.61 ± 0.96	0.67 ± 0.81	0.38 ± 0.87	0.636
Number of positive remodeled plaques	2.4 ± 2.7	3.3 ± 2.1	2.6 ± 2.2	3.3 ± 2.6	3.4 ± 2.0	0.110
Number of plaques with spotty calcification	0.53 ± 0.70	0.40 ± 0.74	0.39 ± 0.71	0.51 ± 1.2	0.62 ± 1.2	0.822

MI, myocardial infarction; PAV, percent atheroma volume.

Table 2
Prevalence of calcium by calcium scoring before MI

	Age at MI					
	Age <50 (N = 16)	Age 50–59 (N = 26)	Age 60–69 (N = 35)	Age 70–79 (N = 26)	Age ≥80 (N = 8)	All patients (N = 111)
CACS						
0	8 (50.0)	3 (11.5)	8 (22.9)	5 (19.2)	0 (0)	24 (21.6)
<10	10 (62.5)	4 (15.4)	10 (28.6)	6 (23.1)	1 (12.5)	31 (27.9)
<100	13 (81.3)	11 (42.3)	12 (34.3)	9 (34.6)	3 (37.5)	48 (43.2)

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