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Age- and sex-related features of atherosclerosis from coronary computed tomography angiography in patients prior to acute coronary syndrome: results from the ICONIC study

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Aims Although there is increasing evidence supporting coronary atherosclerosis evaluation by coronary computed tomography angiography (CCTA), no data are available on age and sex differences for quantitative plaque features. The aim of this study was to investigate sex and age differences in both qualitative and quantitative atherosclerotic features from CCTA prior to acute coronary syndrome (ACS).

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Methods and results Within the ICONIC study, in which 234 patients with subsequent ACS were propensity matched 1:1 with 234 non-event controls, our current subanalysis included only the ACS cases. Both qualitative and quantitative advance plaque analysis by CCTA were performed by a core laboratory. In 129 cases, culprit lesions identified by invasive coronary angiography at the time of ACS were co-registered to baseline CCTA precursor lesions. The study population was then divided into subgroups according to sex and age (<65 vs. ≥ 65 years old) for analysis. Older patients had higher total plaque volume than younger patients. Within specific subtypes of plaque volume, however, only calcified plaque volume was higher in older patients (135.9 ± 163.7 vs. 63.8 ± 94.2 mm^3, $P < 0.0001$, respectively). Although no sex-related differences were recorded for calcified plaque volume, females had lower fibrous and fibrofatty plaque volume than males (Fibrofatty volume 29.6 ± 44.1 vs. 75.3 ± 98.6 mm^3, $P = 0.0001$, respectively). No sex-related differences in the prevalence of qualitative high-risk plaque features were found, even after separate analyses considering age were performed.

Conclusion Our data underline the importance of age- and sex-related differences in coronary atherosclerosis presentation, which should be considered during CCTA-based atherosclerosis quantification.

Keywords atherosclerosis • gender medicine • cardiac CT • high-risk plaque features • CCTA

Introduction

Atherosclerotic cardiovascular disease is one of the leading causes of morbidity and mortality in the world.[1] Acute cardiovascular events can be the first manifestation of atherosclerosis in asymptomatic patients that are often misclassified as being 'low risk'.[2] Evidence has demonstrated that coronary computed tomography angiography (CCTA) is an accurate diagnostic test for patients with suspected coronary artery disease (CAD).[3] When compared with other non-invasive techniques, it offers the unique opportunity to non-invasively evaluate coronary anatomy. In addition to coronary lumen stenosis quantification, CCTA also enables the identification of coronary atherosclerosis itself and advanced plaque characterization has been correlated with cardiovascular prognosis.[4,5] Both qualitative high-risk plaque characteristics, such as positive remodelling (PR), low-attenuation plaque (LAP), spotty calcification (SC), and napkin-ring sign (NRS), as well as plaque volume quantification, have been associated with future cardiovascular events beyond lumen stenosis severity at the time of CCTA.[6,7]

Recently published results from the ICONIC study, a nested case–control study within a cohort of 25 251 patients, suggested that although patients with ACS at follow-up after CCTA had higher lumen coronary stenosis, most precursors of ACS cases (culprit lesions) were non-obstructive. More importantly, it also found that plaque evaluation and plaque volume quantification by CCTA identifies high-risk patients above and beyond stenosis severity.[8]

Sex differences in plaque burden and plaque morphology leading to ACS, however, have not been deeply investigated in previous studies.[9,10] A 2016 sub-analysis of the CONFIRM registry demonstrated that women were more likely to have normal coronary arteries, but it did not identify any sex-specific patterns of atherosclerosis burden predictive of MACE.[11] A recent study by Plank *et al.*[9] provided evidence that women with high-risk plaque features have a higher relative risk for MACE and suggested that giving more weight to high-risk qualitative plaque features found in CCTA might improve prognostic stratification for female patients, whose risk could be otherwise underestimated. While some previously published studies reported sex differences in qualitative high-risk plaque features and on a per-patient level, no data have been published on age and sex differences for quantitative plaque features.[12–14] The aim of this study is to investigate sex- and age-specific differences in both qualitative and quantitative atherosclerotic features from CCTA among patients who underwent CCTA for suspected CAD and subsequently developed ACS.

Methods

Within the ICONIC study, a nested case–control study within the CONFIRM registry of 25 251 consecutive patients undergoing baseline CCTA for suspected CAD, a total of 234 patients with subsequent adjudicated ACS events were 1:1 propensity matched to non-event controls.[8] For the current sub-analysis, only the 234 cases with subsequent ACS were included, as the aim of the study was to better delineate differences in atherosclerosis expression across age and sex in patients who subsequently had ACS; moreover, a comparison between case and controls across age and sex could have been biased by the careful matching that has been performed in the original study.

Patients with prior CAD, death without antecedent ACS, insufficient data for adjudication, and elective revascularization of a culprit segment between baseline CCTA and ACS event were excluded.[8]Early-ACS was defined as occurred <1 year after CCTA.

Each site obtained local institutional review board approval and submitted study identification-coded data stripped of protected health information for central adjudication and coronary CTA measurement. The Clinical and Data Coordinating Center (CDCC) at the Dalio Institute of Cardiovascular Imaging performed uniform adjudication of ACS masked to CCTA evaluation using definitions set forth by the World Health Organization (WHO).[15]

Imaging procedure and lesion analysis

As previously described, all coronary CT evaluations were performed using single-source and dual source ≥64-detector rows scanners.[8] Different vendors were used according to availability at each institution involved in the study. The coronary CTA Core Laboratory (CL) at Yonsei University performed comprehensive and quantitative analysis of

coronary CTAs using semi-automated plaque analysis software (MEDIS QAngio CT Research Edition v2.1.9.1, Medis Medical Imaging Systems, Leiden, The Netherlands).[8,16]

Coronary plaques were defined as structures of at least 1 mm^2 area within and/or adjacent to artery lumen, clearly distinguishable from the vessel lumen, and surrounded by pericardial tissue, epicardial fat, and identified in >2 planes. For every patient, percent area stenosis, total vessel volume (VV), total plaque volume (total PV), and plaque volume by composition were quantified. Plaque composition was defined based on Hounsfield Units (HU) as follows: calcified plaque was >350 HU, fibrous plaque was 131–350 HU, fibrofatty plaque was 31–130 HU and necrotic core was ≤30 HU.[17,18] Mean plaque burden (mean PB) was defined as [(total PV/total VV) × 100] (%) and the remodelling index was calculated using comparisons of mean vessel area within 5 mm proximal and distal to the lesion.

Qualitative adverse plaque characteristics (APCs) were also evaluated as follows: PR was defined as a remodelling index ≥1.1, spotty calcification (SC) was defined by visualized observed calcification ≤3.3 mm in any direction within a plaque, low-attenuating plaque (LAP) was defined as <30 HU detected, and napkin-ring sign (NRS) was defined as a circumferential area of a non-calcified plaque that displays greater attenuation than the central portion.[8,18]High-risk plaque (HRP) lesions were defined as the presence of two or more APCs within any one plaque (NRS was not included due to low prevalence).[8] A segment involvement score (SIS) and segment stenosis score (SSS) were calculated as previously described.[19]

The study population was then divided into different subgroups according to sex and age. Older age was defined as ≥65 years old. As previously described,[8] for 129 cases, culprit lesions identified by ICA at the time of ACS were co-registered to baseline CCTA precursor lesions.

Statistical analysis

Continuous variables were presented as means with SD or as medians with interquartile range (IQR: 25°–75°) if more appropriate (non-normal distribution). Normally distributed continuous variables were compared using the Student's *t*-test for independent samples. When the variable distribution was not normal, Mann–Whitney *U* test for independent samples was used. Categorical variables were analysed using either a χ^2 analysis or Fisher's exact test, as appropriate. A multivariate logistic regression analysis was performed to unmask potential confounders. A *P*-value <0.05 was considered statistically significant. Statistical analysis and graphics were produced with MedCalc (version 11.6.1.0, Med-Calc Software; 1993–2011). All raw data are available if requested.

Results

Clinical characteristics

In the present study, we analysed 234 patients with ACS after CCTA, with a mean follow-up of 3.9 ± 2.5 years. The ACS cases included 40 ST-elevation myocardial infarctions (STEMIs), 114 non-ST elevation myocardial infarctions (non-STEMI), 6 myocardial infarctions that could not be distinguished, and 74 unstable angina cases. Early-ACS occurred in 87 (37.2%). A total of 149 (63%) males were enrolled and the mean age was 62 ± 11 years. At the time of CCTA, 124 patients were <65 years old. Female patients had lower mean body surface area (BSA) than male patients, while older patients (≥65 years) had lower mean body mass index (BMI) and BSA than younger subjects (<65 years). Moreover, among older patients, hypertension was more prevalent (71.8% vs. 55.6%, $P = 0.0151$) and the Framingham risk score was higher than in the younger patient subgroup (22.4 ± 17.3 vs. 15.4 ± 9.9, $P = 0.0002$). On the contrary, active smoking (22.7% vs. 37.9%, $P = 0.0177$) and family history of CAD (27.3% vs. 51.6%, $P = 0.0003$) were more prevalent among younger patients (<65 years old). No sex-related differences were recorded for traditional cardiovascular risk factors, apart from higher Framingham risk score in male subjects (23.1 ± 15.7 vs. 11.2 ± 6.9, $P < 0.0001$, respectively). No significant age- or sex-related differences were found between subgroups for risk factors, angina severity, or ACS type (*Tables 1* and *2*).

CCTA characteristics on a patient-based analysis

Older patients (≥65 years) had higher SIS and SSS than younger patients (*Table 3*). The older subgroup also had higher total plaque volume (242.5 ± 261.9 vs. 342.7 ± 347.2 mm^3, $P = 0.0128$) and mean plaque burden (13.9 ± 11.7% vs. 10.1 ± 9.8%, $P = 0.0074$). When subtypes of plaque volume were considered, however, only calcified plaque volume was higher in older patients (135.9 ± 163.7 vs. 63.8 ± 94.2 mm^3, $P < 0.0001$), while there were no age-related differences for necrotic core volume, fibrofatty volume, and fibrous volume (*Table 3*). The percentages of total plaque volume for necrotic core, fibrofatty, and fibrous plaque were all higher in the younger subgroup (*Table 3*). No age differences were recorded for the prevalence of high-risk plaque features prevalence except for a higher prevalence of PR among the older subgroup.

Male subjects also had a higher total plaque volume than female subjects (328.6 ± 342.1 vs. 221.4 ± 224.2 mm^3; $P = 0.0103$) (*Table 4*). Of note, no sex-related differences were recorded for calcified plaque volume and mean plaque burden, even when separate analysis for younger and older patients was performed. Females, however, did have significantly lower fibrous and fibrofatty plaque volume than males (29.6 ± 44.1 vs. 75.3 ± 98.6 mm^3, $P = 0.0001$) (*Table 4* and *Figure 1*). Although no statistically significant sex differences were found within the younger subgroup, younger males had higher fibrofatty plaque volumes than older females (67.2 ± 82.7 vs. 22.1 ± 26.5 mm^3, $P < 0.0001$) (*Table 5*). However, it should be underlined that lumen volume on a per-patient basis was lower in female vs. male patients (1904.2 ± 856 vs. 2301.9 ± 938.3, respectively, $P = 0.0015$), but no differences were found between young vs. old subjects (*Tables 3 and 4*). Moreover, a dedicated analysis adjusted for BSA, SSS, lumen volume, and Framingham risk score confirmed that calcified plaque volume was independently related to older age [OR (95% CI) 1.03 (1.02–1.05); $P < 0.001$] with no sex-dependent relationship, while both fibrous and fibrofatty volume percentage were confirmed to be lower in older subjects (*Table 6*).

No differences in the prevalence of high-risk plaque features were found between male and female subjects (*Table 4*), even at adjusted analysis for possible confounders (*Table 6*) and when a separate analysis according to age was performed (*Table 5* and *Figure 2*).

For lumen stenosis severity, no age- or sex-related differences in maximum stenosis on a patient-based analysis were demonstrated (*Table 5*) and the entire cohort had a moderate degree of stenosis (61.93 ± 2.24%). Of interest, maximal lumen stenosis, elevated fibrofatty plaque volume, and PR prevalence, but not elevated calcified plaque volume, were all associated to early-ACS occurrence (Supplementary data online, *Table S1*).

Table 1 Clinical baseline characteristics according to age

	All ACS ($n = 234$)	Age < 65 ($n = 124$)	Age ≥ 65 ($n = 110$)	*P*-value
BMI, kg/m^2	27.5 ± 5.1	28.9 ± 5.4	26.1 ± 4.2	<0.0001
BSA, m^2	1.91 ± 0.3	1.99 ± 0.33	1.84 ± 0.3	0.0004
Risk factors				
Hypertension, *n* (%)	148 (63.2)	69 (55.6)	79 (71.8)	0.0151
Hyperlipidaemia, *n* (%)	129 (55.1)	67 (54)	62 (56.4)	0.8129
Diabetes, *n* (%)	46 (19.7)	26 (20.9)	20 (18.2)	0.7233
Smoking current, *n* (%)	72 (30.7)	47 (37.9)	25 (22.7)	0.0177
Smoking past, *n* (%)	79 (33.8)	39 (31.5)	40 (36.4)	0.5141
Family history, *n* (%)	94 (40)	64 (51.6)	30 (27.3)	0.0003
Fram risk score, mean ± SD	18.7 ± 14.4	15.4 ± 9.9	22.4 ± 17.3	0.0002
Angina severity				
None, *n* (%)	37 (15.8)	24 (19.4)	13 (11.8)	0.1584
Non-cardiac, *n* (%)	28 (11.9)	15 (12.1)	13 (11.8)	0.8956
Atypical CP, *n* (%)	94 (40.2)	49 (39.5)	45 (40.9)	0.9327
Typical CP, *n* (%)	63 (26.9)	28 (22.6)	35 (31.8)	0.1510
Dyspnoea, *n* (%)	12 (5.1)	8 (6.4)	4 (3.6)	0.4996
ACS type				
STEMI, *n* (%)	40 (17.1)	24 (19.4)	16 (14.6)	0.4245
NSTEMI/MI NOS, *n* (%)	120 (51.3)	57 (45.9)	63 (57.3)	0.1073
UA, *n* (%)	74 (31.6)	37 (29.8)	37 (33.6)	0.6289

ACS, acute coronary syndrome; CP, chest pain; Fram, Framingham; NOS, not otherwise specified; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

Table 2 Clinical baseline characteristics according to sex

	All ACS ($n = 234$)	Female ($n = 85$)	Male ($n = 149$)	*P*-value
BMI, kg/m^2	27.5 ± 5.1	27.3 ± 5.8	27.7 ± 4.6	0.1829
BSA, m^2	1.91 ± 0.3	1.74 ± 0.18	2.00 ± 0.25	<0.0001
Risk factors				
Hypertension, *n* (%)	148 (63.2)	58 (68.2)	90 (60.4)	0.2941
Hyperlipidaemia, *n* (%)	129 (55.1)	43 (50.6)	86 (57.7)	0.3609
Diabetes, *n* (%)	46 (19.7)	19 (22.4)	27 (18.1)	0.5320
Smoking current, *n* (%)	72 (30.7)	19 (22.4)	53 (35.6)	0.0514
Smoking past, *n* (%)	79 (33.8)	23 (27.1)	56 (37.6)	0.1364
Family history, *n* (%)	94 (40)	31 (36.5)	63 (42.3)	0.4644
Fram risk score, mean ± SD	18.7 ± 14.4	11.2 ± 6.9	23.1 ± 15.7	<0.0001
Angina severity				
None, *n* (%)	37 (15.8)	12 (14.1)	25 (16.8)	0.7203
Non-cardiac, *n* (%)	28 (11.9)	13 (15.3)	15 (10.1)	0.3328
Atypical CP, *n* (%)	94 (40.2)	38 (44.7)	56 (37.6)	0.3540
Typical CP, *n* (%)	63 (26.9)	18 (21.1)	45 (30.2)	0.1749
Dyspnoea, *n* (%)	12 (5.1)	6 (7.1)	7 (4.7)	0.6359
ACS type				
STEMI, *n* (%)	40 (17.1)	15 (17.6)	25 (16.8)	0.9807
NSTEMI/MI NOS, *n* (%)	120 (51.3)	43 (50.6)	77 (51.7)	0.9793
UA, *n* (%)	74 (31.6)	27 (31.7)	47 (31.6)	0.8963

ACS, acute coronary syndrome; CP, chest pain; Fram, Framingham; NOS, not otherwise specified; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

Table 3 CCTA characteristics according to age

	All ACS ($n = 234$)	Age < 65 ($n = 124$)	Age ≥ 65 ($n = 110$)	*P*-value
SIS (*n*), mean ± SD	5.28 ± 3.14	4.77 ± 3.16	5.87 ± 3.03	0.0072
SSS (*n*), mean ± SD	9.92 ± 7.51	8.69 ± 7.05	11.36 ± 7.77	0.0063
Maximal lumen stenosis (%), mean ± SD	61.93 ± 2.24	58.67 ± 29.08	65.61 ± 24.64	0.0527
Lumen volume (mm^3), mean ± SD	2157.5 ± 927.5	2200.8 ± 961.8	2108.7 ± 888.9	0.4496
Total plaque volume (mm^3), mean ± SD	289.7 ± 308.4	242.5 ± 261.9	342.7 ± 347.2	0.0128
Necrotic core plaque volume (mm^3), mean ± SD	6.5 ± 13.9	5.9 ± 11.6	7.1 ± 16.3	0.5137
Fibrofatty plaque volume (mm^3), mean ± SD	58.7 ± 85.8	59.6 ± 77.7	57.6 ± 94.4	0.8591
NC + FF plaque volume (mm^3), mean ± SD	65.2 ± 95.4	65.5 ± 86.9	64.8 ± 104.7	0.9554
Fibrous plaque volume (mm^3), mean ± SD	126.8 ± 131.6	113.3 ± 123.5	142.1 ± 139.3	0.1710
Calcified plaque volume (mm^3), mean ± SD	97.7 ± 136.1	63.8 ± 94.2	135.9 ± 163.7	<0.0001
Mean plaque burden, %	11.9 ± 10.9	10.1 ± 9.8	13.9 ± 11.7	0.0074
Percent necrotic core plaque volume (%), mean ± SD	2.4 ± 4.5	2.4 ± 4.2	2.3 ± 4.9	0.8667
Percent fibrofatty plaque volume (%), mean ± SD	20.5 ± 17.1	24.9 ± 19.4	15.6 ± 14.7	0.0001
Percent NC + FF (%), mean ± SD	21.3 ± 20.6	25.1 ± 22.1	16.9 ± 17.9	0.0022
Percent fibrous plaque volume (%), mean ± SD	46.9 ± 15.3	49.8 ± 16.4	43.7 ± 13.4	0.0022
Percent calcified plaque volume (%), mean ± SD	30.3 ± 22.7	23.0 ± 20.5	38.3 ± 22.5	<0.0001
>2 HRP, *n* (%)	154 (65.8)	75 (60.5)	79 (71.8)	0.0928
>2 PR, *n* (%)	124 (52.9)	56 (45.2)	68 (61.2)	0.0206
>2 SC, *n* (%)	11 (4.7)	6 (4.8)	5 (4.5)	0.8399
>2 LAP, *n* (%)	13 (5.6)	9 (7.3)	4 (3.6)	0.3437
>2 NRS, *n* (%)	0	0	0	
PR (%), mean ± SD	77.2 ± 28.5	77.7 ± 28.3	76.6 ± 28.9	0.7692
SC (%), mean ± SD	13.1 ± 23.8	14.2 ± 24.6	11.9 ± 23.1	0.4634
LAP (%), mean ± SD	19.2 ± 27.1	21.5 ± 29.1	16.7 ± 24.7	0.1779
NRS (%), mean ± SD	1.9 ± 9.3	1.3 ± 5.6	2.7 ± 12.2	0.2518

FF, fibrofatty; HRP, high-risk plaque; LAP, low-attenuation plaque; NC, necrotic core; NRS, napkin-ring sign; PR, positive remodelling; SC, spotty calcification; SIS, segment involvement score; SSS, segment stenosis score.

CCTA characteristics on a culprit-lesion based analysis

Culprit lesion was identified by ICA in 129 cases at the time of ACS that was co-registered to a baseline CCTA precursor lesion. Lumen stenosis severity of culprit-lesion precursors was moderate, with no age- or sex-related differences (*Table 7*). For plaque volume, there was a trend for higher calcified plaque volume in older male patients, but it was not statistically significant (32.6 ± 39.1 mm^3 for younger females vs. 62.7 ± 76.8 mm^3 for older males, $P = 0.072$). Neither necrotic core nor fibrofatty plaque volume of culprit-lesion precursors was different in male vs. female or younger vs. older patients (41.1 ± 67.3 vs. 32.7 ± 55.4 mm^3, $P = 0.065$). Similarly, no sex- or age-related differences were found in the prevalence of different high-risk plaque features among culprit-lesion precursors (*Table 7*). Of interest, no differences were recorded on a per-culprit lesion analysis according to type (UA vs. NSTEMI vs. STEMI) and time (early vs. late) ACS presentation (Supplementary data online, *Table S2*).

Discussion

The present study is a sub-analysis of the nested case–control ICONIC study in which we examine patients with ACS (234 cases) who had previous CCTA for suspected stable CAD evaluation. We found that the extent of calcified plaque on a per-patient level appears to be affected by age both in female and male subjects. Females had significantly lower total plaque volume and fibrous/fibrofatty plaque volume on a per-patient level, within both the younger and older age groups. No sex- or age-related differences were demonstrated for the prevalence of qualitative high-risk plaque features and necrotic core volume. Additionally, in a per-culprit-lesion analysis, no sex- or age-related differences were found for either qualitative or quantitative high-risk plaque features.

Our findings are concordant with previous data that reported differences in atherosclerotic burden according to sex, as female subjects are thought to be protected from cardiovascular disease in premenopausal age. However, recent data suggest that women's risk of cardiovascular disease is often underestimated.[9] CCTA has recently emerged as a non-invasive technique for accurate quantification of coronary atherosclerosis.[16,18] Several previous studies underlined the prognostic role of high-risk plaque features.[4,5,7,20] More recently, Andreini *et al.*[6] demonstrated that non-calcified plaque volume but not total plaque volume may better predict future major cardiovascular events than solely traditional risk factors and coronary lumen stenosis severity. Accordingly, our data suggest that, among patients who suffered from ACS, calcified plaque volume is higher in older

Table 4 CCTA characteristics according to sex

	All ACS ($n = 234$)	Female ($n = 85$)	Male ($n = 149$)	*P*-value
SIS (*n*), mean ± SD	5.28 ± 3.14	4.8 ± 3.1	5.6 ± 3.2	0.0641
SSS (*n*), mean ± SD	9.92 ± 7.51	8.9 ± 6.9	10.5 ± 7.8	0.1173
Maximal lumen stenosis (%), mean ± SD	61.9 ± 2.24	61.2 ± 28.7	62.4 ± 26.5	0.7469
Lumen volume (mm^3), mean ± SD	2157.5 ± 927.5	1904.2 ± 856	2301.9 ± 938.3	0.0015
Total plaque volume (mm^3), mean ± SD	289.7 ± 308.4	221.4 ± 224.2	328.6 ± 342.1	0.0103
Necrotic core plaque volume (mm^3), mean ± SD	6.5 ± 13.9	4.5 ± 12.3	7.6 ± 14.3	0.0951
Fibrofatty plaque volume (mm^3), mean ± SD	58.7 ± 85.8	29.6 ± 44.1	75.3 ± 98.6	0.0001
NC + FF plaque volume (mm^3), mean ± SD	65.2 ± 95.4	34.2 ± 51.1	82.8 ± 109.5	0.0001
Fibrous plaque volume (mm^3), mean ± SD	126.8 ± 131.6	65.5 ± 97.5	146.7 ± 144.2	<0.0001
Calcified plaque volume (mm^3), mean ± SD	97.7 ± 136.1	95.2 ± 128.4	99.1 ± 140.7	0.8335
Mean plaque burden, %	11.9 ± 10.9	10.9 ± 10.5	12.4 ± 11.2	0.2755
Necrotic core (%), mean ± SD	2.4 ± 4.5	2.5 ± 5.3	2.3 ± 4.1	0.7478
Fibrofatty (%), mean ± SD	20.5 ± 17.1	16.7 ± 17.9	22.4 ± 17.6	0.0187
NC + FF (%), mean ± SD	21.3 ± 20.6	16.9 ± 20.7	23.8 ± 20.2	0.0135
Fibrous (%), mean ± SD	46.9 ± 15.3	43.8 ± 15.0	48.6 ± 15.3	0.0210
Calcified (%), mean ± SD	30.3 ± 22.7	37.0 ± 24.1	26.7 ± 21.2	0.0008
>2 HRP, *n* (%)	154 (65.8)	51 (60)	103 (69.1)	0.2048
>2 PR, *n* (%)	124 (52.9)	38 (44.7)	86 (57.8)	0.0727
>2 SC, *n* (%)	11 (4.7)	2 (2.3)	9 (6)	0.3324
>2 LAP, *n* (%)	13 (5.6)	2 (2.3)	11 (7.4)	0.1795
>2 NRS, *n* (%)	0	0	0	–
PR (%), mean ± SD	77.2 ± 28.5	75.2 ± 28.3	78.3 ± 28.7	0.4253
SC (%), mean ± SD	13.1 ± 23.8	10.3 ± 21.1	14.6 ± 25.1	0.1838
LAP (%), mean ± SD	19.2 ± 27.1	17.6 ± 26.5	20.1 ± 27.5	0.4987
NRS (%), mean ± SD	1.9 ± 9.3	1.1 ± 6.9	2.4 ± 10.4	0.3041

FF, fibrofatty; HRP, high-risk plaque; LAP: low-attenuation plaque; NC, necrotic core; NRS, napkin-ring sign; PR, positive remodelling; SC, spotty calcification; SIS, segment involvement score; SSS, segment stenosis score.

compared to younger patients. Since there was no statistically significant difference in non-calcified plaque volumes between the two age subgroups, the result suggests that the higher plaque volume reported is due to the presence of a higher calcified plaque component in older subjects (*Table 3*). Relative non-calcified plaque volume (%) was higher in younger patients when compared with older ones (*Table 3*), supporting the importance of the evaluation of plaque volume subtypes in young subjects at risk for future ACS who may have elevated percentage of non-calcified plaque even if total plaque volume is low as absolute value. Of note, these data were confirmed even at an adjusted analysis for BSA, total lumen volume, segment stenosis score, and Framingham risk score.

Mean plaque burden was affected by age but not by sex. This result could be explained by the difference in body sizes between females and males and by the lower vessel lumen on a per-patient basis (1904.2 ± 856 vs. 2301.9 ± 938.3, for female vs. male patients, respectively, $P = 0.0015$) It is plausible that smaller vessel volume that females have could contribute to the smaller plaque volumes compared to males; the lack of difference in mean plaque burden supports this hypothesis. Since all patients included in the present analysis had an ACS event, and we found no sex differences in ACS type, these findings might be considered during evaluation of atherosclerosis by CCTA. Indeed, if a low absolute burden of atherosclerosis is found in females, their cardiovascular risk might be underestimated unless sex differences in plaque volume extent are considered. Moreover, as previously suggested, lower lumen volume itself could be associated with vessel occlusion and ACS after intracoronary thrombus formation,[21] even in the presence of lower high-risk plaque volume as absolute value.

Of interest, no age and sex-related differences were identified for necrotic core plaque volume and we also did not find any significant age or sex differences in the prevalence of qualitative high-risk plaque features, maximal lumen stenosis, or plaque volume quantification from a culprit lesion-based analysis.

These data suggest that a patient-based, but not a culprit lesion-based, approach for quantifying atherosclerosis using CCTA to assess cardiovascular risk stratification appears to be affected by age and sex. The identification of high-risk plaques, even if they do not lead to obstructive lesions, should be considered an important prognostic sign, especially in younger females who may merit more aggressive cardiovascular prevention therapy and whose risk could be otherwise underestimated as recently suggested.[19] However, it must be underlined that, as previously described, only a low percentage of high-risk plaque represented future culprit-lesion precursors at

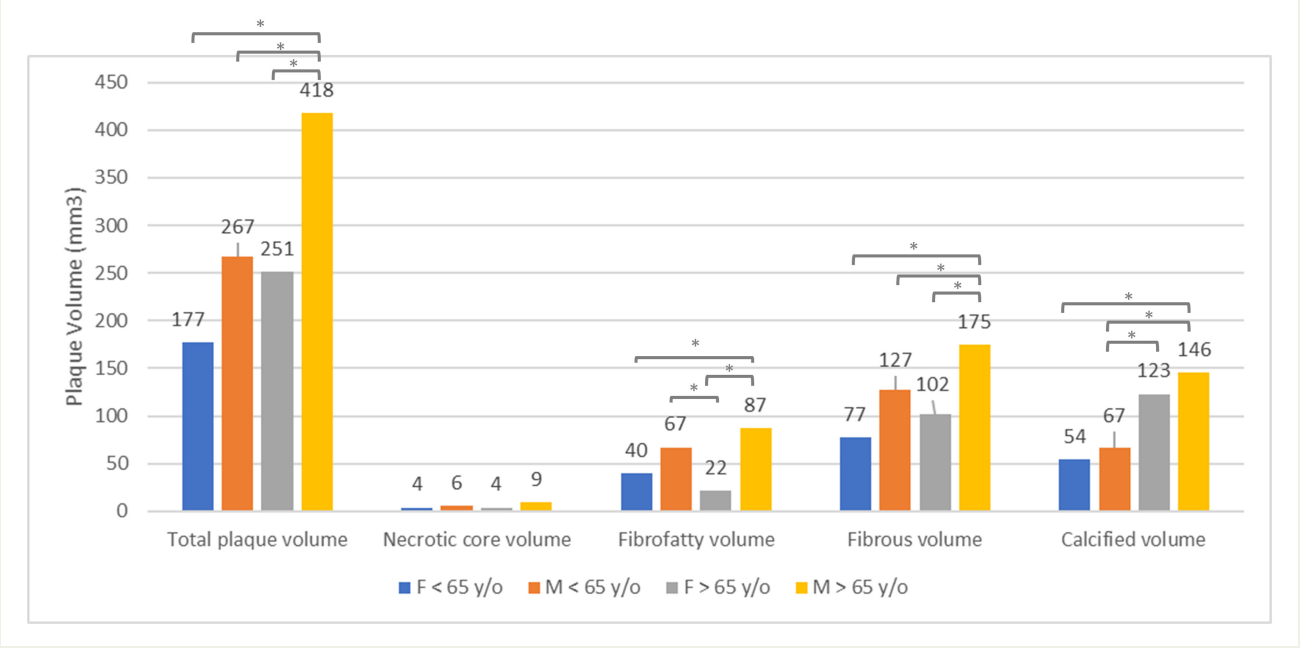

Figure 1 Total plaque volume and plaque subtypes volume quantification according to age and sex. All differences evidenced with 'a' have $P<0.005$ as outlined in *Table 5*. F, female; M, male.

Table 5 CCTA characteristics according to age and sex on a per-patient basis

	Age < 65		Age > 65		ANOVA *P*-value
	F (35)	M (89)	F (50)	M (60)	
SIS (*n*), mean ± SD	3.9 ± 3[a]	5.1 ± 3.2	5.4 ± 2.9	6.3 ± 3.0[b]	0.005
SSS (*n*), mean ± SD	7.4 ± 6.9[a]	9.2 ± 7.1[a]	9.9 ± 6.9	12.5 ± 8.3[b,c]	0.006
Maximal lumen stenosis (%), mean ± SD	56.4 ± 31.1	59.6 ± 28.3	64.5 ± 26.7	66.5 ± 22.9	0.233
Lumen volume (mm^3), mean ± SD	2048.1 ± 982.1	2260.8 ± 952.3	1803.6 ± 750.1[c]	2362.9 ± 920.8[d]	0.007
Total plaque volume (mm^3), mean ± SD	177.8 ± 224.8[a]	267.9 ± 272.1[a]	251.8 ± 220.9[a]	418.5 ± 411.6[b,c,d]	0.001
Necrotic core plaque volume (mm^3), mean ± SD	4.9 ± 11.3	6.2 ± 11.7	4.3 ± 1.9	9.5 ± 18.2	0.204
Fibrofatty plaque volume (mm^3), mean ± SD	40.4 ± 59.9[a]	67.2 ± 82.7[d]	22.1 ± 26.5[a,c]	87.2 ± 117.9[b,d]	<0.001
NC + FF plaque volume (mm^3), mean ± SD	45.3 ± 66.9[a]	73.4 ± 92.7[d]	26.4 ± 34.9[a,c]	96.8 ± 130.1[b,d]	0.001
Fibrous plaque volume (mm^3), mean ± SD	77.8 ± 116.2[a]	127.2 ± 124.1[a]	102.1 ± 81.8[a]	175.5 ± 166.7[b,c,d]	0.002
Calcified plaque volume (mm^3), mean ± SD	54.8 ± 86.9[a]	67.4 ± 97.1[d]	123.6 ± 145.0[c]	146.3 ± 178.4[b,c]	<0.001
Mean plaque burden, %	8.8 ± 10.1[a]	10.5 ± 9.8[a]	12.4 ± 10.6	15.3 ± 12.5[b,c]	0.018
Necrotic core (%), mean ± SD	2.8 ± 5.3	2.3 ± 3.8	2.3 ± 5.3	2.4 ± 4.6	0.943
Fibrofatty (%), mean ± SD	24.8 ± 22.3[d]	24.9 ± 18.5[d]	11.7 ± 12.3[a,b,c]	18.7 ± 15.8[d]	<0.001
NC + FF (%), mean ± SD	22.9 ± 25.2	26.1 ± 20.9[d]	12.8 ± 15.9[a,c]	20.4 ± 18.9[d]	0.003
Fibrous (%), mean ± SD	45.1 ± 15.8[c]	51.4 ± 16.4[a,b,d]	43.1 ± 14.7[c]	44.3 ± 12.5[c]	0.005
Calcified (%), mean ± SD	27.4 ± 24.3[d]	21.4 ± 18.9[a,d]	43.1 ± 22.2[a,b,c]	34.6 ± 22.2[c,d]	<0.001
PR (%), mean ± SD	68.7 ± 32.6	80.8 ± 26.2	79.3 ± 24.7	74.6 ± 31.9	0.199
SC (%), mean ± SD	12.3 ± 22.3	14.8 ± 25.4	8.9 ± 20.5	14.3 ± 24.8	0.574
LAP (%), mean ± SD	23.1 ± 31.2	20.9 ± 28.6	14.2 ± 22.8	18.7 ± 26.1	0.470
NRS (%), mean ± SD	0	1.7 ± 6.4	1.8 ± 8.8	3.3 ± 14.3	0.452

FF, fibrofatty; HRP, high-risk plaque; LAP, low-attenuation plaque; NC, necrotic core; NRS, napkin-ring sign; PR, positive remodelling; SC, spotty calcification; SIS, segment involvement score; SSS, segment stenosis score.
[a]$P < 0.05$ vs. male with age >65.
[b]$P < 0.05$ vs. female with age <65.
[c]$P < 0.05$ vs. male with age <65.
[d]$P < 0.05$ vs. female with age >65.

Table 6 Adjusted plaque characteristics relationship with age and sex

Plaque characteristics[a]	Older age OR (95% CI)	*P*	Male sex OR (95% CI)	*P*
Necrotic core plaque volume (%)	0.98 (0.92–1.05)	0.687	1.00 (0.97–1.03)	0.684
Fibrofatty plaque volume (%)	0.96 (0.95–0.98)	<0.001	1.02 (0.99–1.04)	0.058
NC + FF volume (%)	0.98 (0.96–0.99)	0.002	1.02 (1.01–1.04)	0.033
Fibrous plaque volume (%)	0.98 (0.96–0.99)	0.033	1.04 (1.01–1s07)	0.003
Calcified plaque volume (%)	1.03 (1.02–1.05)	<0.001	0.99 (0.99–1.00)	0.065
PR (%)	0.99 (0.98–1.01)	0.593	1.01 (0.99–1.02)	0.137
SC (%)	0.99 (0.98–1.01)	0.325	1.01 (0.99–1.03)	0.145
LAP (%)	0.98 (0.97–1.00)	0.069	1.01 (0.99–1.02)	0.208
NRS (%)	1.02 (0.98–1.05)	0.413	1.02 (0.97–1.07)	0.458

OR, Odds Ratio; NC, necrotic core; FF, fibrofatty; PR, positive remodelling; SC, spotty calcification; LAP, low-attenuation plaque; NRS, napkin-ring sign; HRP, high-risk plaque.
[a]All variables were adjusted for BSA, Framingham risk score, total lumen volume, and segment stenosis score (SSS).

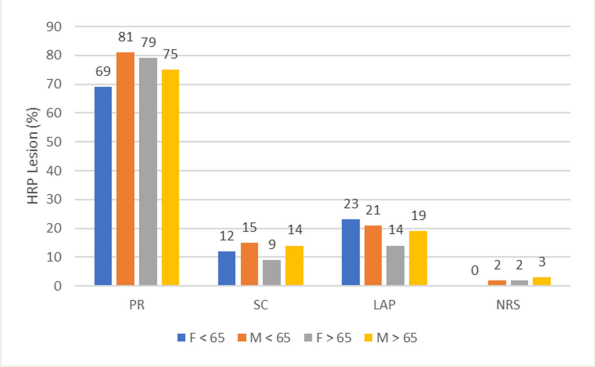

Figure 2 Prevalence of qualitative high-risk plaque features according to age and sex. All differences reported in the present figure did not reach statistical significance as outlined in *Table 5*. LAP, low-attenuation plaque; NRS, napkin-ring sign; PR, positive remodelling; SC, spotty calcification.

follow-up,[22] even if high-risk plaque features' presence could be associated to early-ACS occurrence after CCTA (Supplementary data online, *Table S1*).

Among traditional risk factors in subjects that subsequently developed ACS, active smoking and positive family history prevalence were higher among the younger subgroup (*Table 1*), while no sex-related differences were identified (*Table 2*). These results further underline the importance of active smoking and positive family history in early identification of patients that may merit aggressive prevention programmes, irrespective of sex.

Study limitations

Since data are derived from a large observational cohort study in which CCTA was performed for clinical indication, there is the possibility of referral bias in our sample. Moreover, as the ICONIC trial is a case–control study of which we analysed only ACS cases, as the aim of the study was to better delineate differences in atherosclerosis expression across age and sex in patients who subsequently had ACS and our results do not represent the general population at risk, but rather a selected cohort of patients who had ACS. For the same reason, we were not able to provide age- and sex-specific CCTA cut-offs for ACS risk prediction, and future studies should cover this important topic. Moreover, no information is available regarding sex- or age-specific patterns in the progression of atherosclerosis progression because only baseline CCTA was evaluated. Finally, it should be underlined that atherosclerosis is only one factor contributing to the complex interplay that causes acute coronary syndromes and sex-related differences in acute coronary syndrome pathophysiology could not be adequately assessed as bio-humoral data were not included in the present study.

Conclusion

Our data emphasize the importance of age- and sex-related differences in the expression of coronary atherosclerosis within a population cohort of 234 patients who suffered from ACS. Our finding that female patients had lower non-calcified plaque volume must be considered when atherosclerosis quantification by CCTA is performed. We found no sex- or age-related differences, however, for either qualitative or quantitative plaque features using a lesion-based analysis, suggesting that the presence and characteristics of even a single high-risk plaque may have similar prognostic value in both males and females, regardless of age.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online

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Table 7 CCTA characteristics according to age and sex on per-culprit lesion basis

	Age < 65 (64)		Age > 65 (65)		ANOVA *P*-value
	F (16)	M (48)	F (27)	M (38)	
Maximal lumen stenosis (%), mean ± SD	50.1 ± 25.2	49.8 ± 22.8	62.6 ± 19.8	60.6 ± 20.5	0.530
Total plaque volume (mm^3), mean ± SD	146.7 ± 181.9	116.9 ± 119.7	120.2 ± 118.4	161.8 ± 164.4	0.287
Necrotic core plaque volume (mm^3), mean ± SD	1.9 ± 3.2	2.3 ± 5.6	4.8 ± 17.4	2.5 ± 5.3	0.112
Fibrofatty plaque volume (mm^3), mean ± SD	41.1 ± 67.3	28.1 ± 49.0	16.8 ± 31.4	32.7 ± 55.4	0.065
NC + FF plaque volume (mm^3), mean ± SD	43.1 ± 70.1	30.3 ± 53.7	21.5 ± 43.1	35.2 ± 60.5	0.228
Fibrous plaque volume (mm^3), mean ± SD	71.0 ± 105.2	56.9 ± 55.5	45.9 ± 49.4	63.9 ± 58.9	0.059
Calcified plaque volume (mm^3), mean ± SD	32.6 ± 39.1	29.7 ± 46.4	52.7 ± 59.6	62.7 ± 76.8	0.072
>2 PR, *n* (%)	9 (56.3)	37 (77.1)	24 (88.9)	29 (76.3)	0.3160
>2 SC, *n* (%)	3 (18.7)	11 (22.9)	3 (11.1)	6 (15.8)	0.5570
>2 LAP, *n* (%)	6 (37.5)	11 (22.9)	4 (14.8)	10 (26.3)	0.2631
>2 NRS, *n* (%)	0	2 (4.2)	1 (3.7)	1 (2.6)	0.8722

FF, fibrofatty; HRP, high-risk plaque; LAP, low-attenuation plaque; NC, necrotic core; NRS, napkin-ring sign; PR, positive remodelling; SC, spotty calcification.

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Conflict of interest: none declared.

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IMAGE FOCUS

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Reverse Rivero-Carvallo's sign

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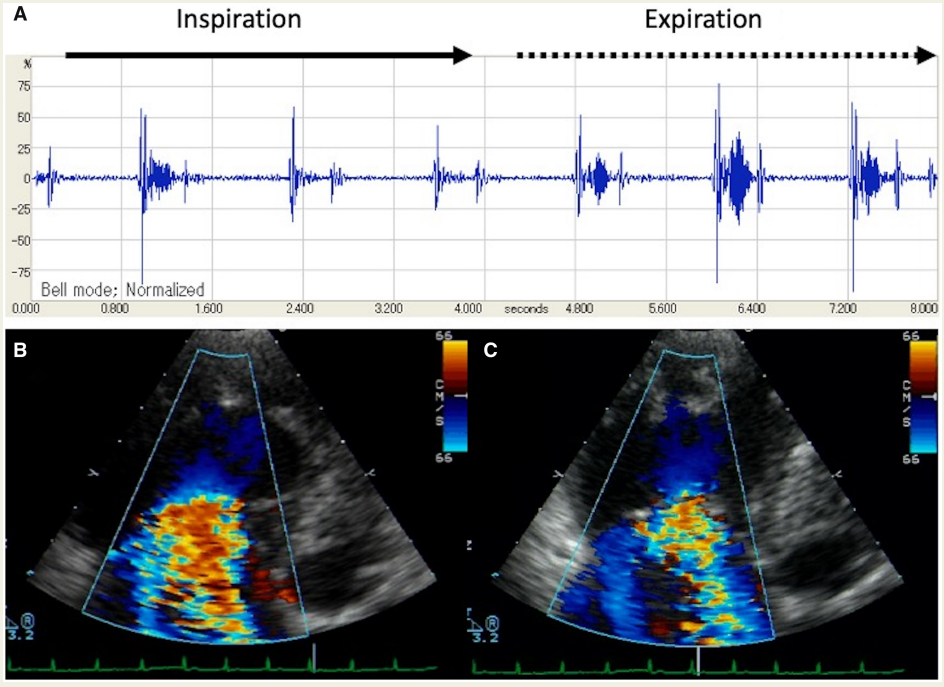

A middle-aged woman with chronic atrial fibrillation (AF) presented with dyspnoea on exertion. Physical examination showed a distended jugular vein, peripheral oedema, and positive Kussmaul's sign. In contrast to the Rivero-Carvallo's sign, the systolic murmur reduced during inspiration and increased during expiration (*Panel A*, Supplementary data online, *Sound S1*). The electrocardiogram showed sinus bradycardia instead of AF. Echocardiography confirmed dilated right atrium and ventricle with severe tricuspid regurgitation (TR). Furthermore, tricuspid annular (TA) dilatation during inspiration led to incomplete valve closure, increasing TR severity (*Panel B*, inspiration; *Panel C*, expiration, Supplementary data online, *Video S1*). Sudden changes from AF to sinus bradycardia were assumed to be the cause of right-sided heart failure. Cilostazol was administered to increase the heart rate and diuretics for volume reduction. Two weeks later, the patient improved with an increased heart rate, no jugular vein distension, and resolution of oedema. No cardiac murmurs were heard on inspiration or expiration, and echocardiography showed only mild TR. The Rivero-Carvallo's sign shows increase in systolic murmur of TR during inspiration. As venous return increases during inspiration, blood volumes in the right side of the heart and TR increase. This patient originally had severe TR, and the increased venous return during inspiration caused TA dilation and incomplete valve closure, thereby increasing TR. This resulted in a laminar flow through the tricuspid valve, and the systolic murmur reduced. This phenomenon may be considered as very severe TR, where the tricuspid valve was separated during inspiration.

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.