ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2022) **23**, 1314–1323
https://doi.org/10.1093/ehjci/jeac114

ORIGINAL PAPER

Early versus late acute coronary syndrome risk patterns of coronary atherosclerotic plaque

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Received 19 February 2021; revised 2 May 2022; accepted 31 May 2022; online publish-ahead-of-print 29 July 2022

See the editorial comment for this article 'Coronary plaque in the fourth dimension: associating coronary computed tomography plaque components and the time to acute coronary syndrome', by Jay Voit and Kelley R.H. Branch, https://doi.org/10.1093/ehjci/jeac170.

Aims The temporal instability of coronary atherosclerotic plaque preceding an incident acute coronary syndrome (ACS) is not well defined. We sought to examine differences in the volume and composition of coronary atherosclerosis between patients experiencing an early (≤90 days) versus late ACS (>90 days) after baseline coronary computed tomography angiography (CCTA).

Methods and results From a multicenter study, we enrolled patients who underwent a clinically indicated baseline CCTA and experienced ACS during follow-up. Separate core laboratories performed blinded adjudication of ACS events and quantification of CCTA including compositional plaque volumes by Hounsfield units (HU): calcified plaque >350 HU, fibrous plaque

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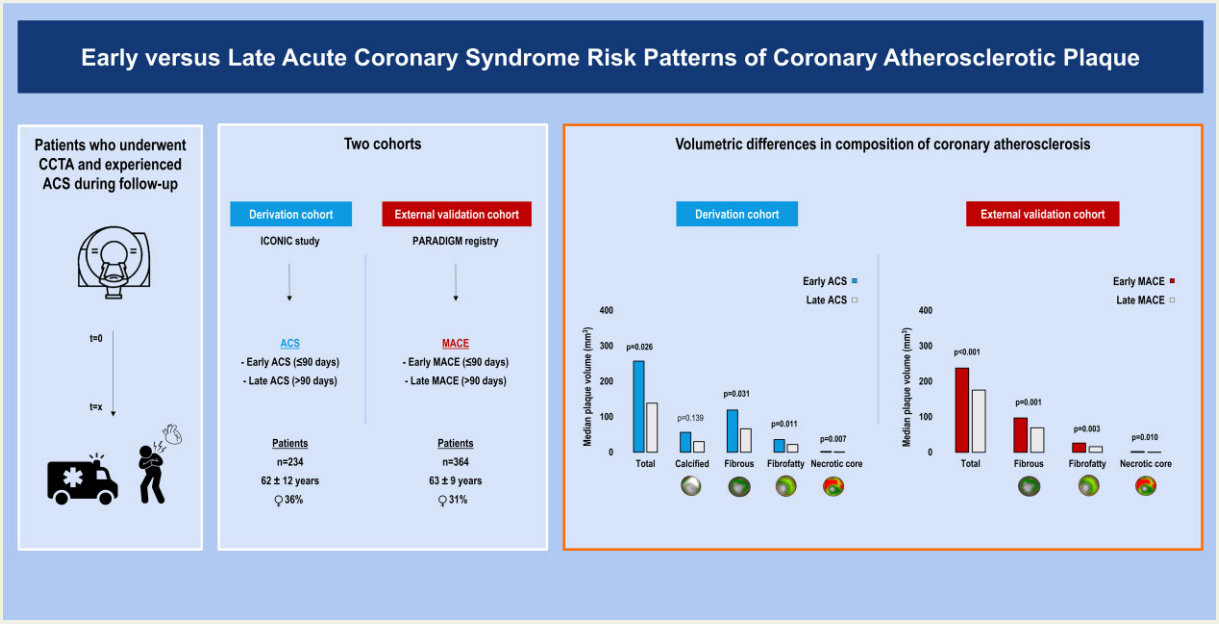
131–350 HU, fibrofatty plaque 31–130 HU and necrotic core <30 HU. In 234 patients (mean age 62 ± 12 years, 36% women), early and late ACS occurred in 129 and 105 patients after a mean of 395 ± 622 days, respectively. Patients with early ACS had a greater maximal diameter stenosis and maximal cross-sectional plaque burden as compared to patients with late ACS ($P < 0.05$). Larger total, fibrous, fibrofatty, and necrotic core volumes were observed in the early ACS group ($P < 0.05$). Findings for total, fibrous, fibrofatty, and necrotic core volumes were reproduced in an external validation cohort ($P < 0.05$).

Conclusions Volumetric differences in composition of coronary atherosclerosis exist between ACS patients according to their timing antecedent to the acute event. These data support that a large burden of non-calcified plaque on CCTA is strongly associated with near-term plaque instability and ACS risk.

Graphical Abstract



Early versus late ACS risk patterns of coronary atherosclerotic plaque. Schematic representation of the study design and patients (left panel), specifics of the two cohorts (middle panel), and the volumetric differences in composition of coronary atherosclerosis between patients with early versus late ACS (right panel). ACS, acute coronary syndrome; CCTA, coronary computed tomography angiography; MACE, major adverse cardiac events.

Keywords acute coronary syndrome • atherosclerosis • coronary artery disease • coronary computed tomography angiography

Introduction

It has been believed for decades that the majority of acute coronary syndromes (ACS) results from rupture of coronary lesions with a previously documented mild degree of luminal stenosis.[1] However, discrepancies exist amongst studies with regard to their timing antecedent to the ACS.[2–4] To this end, the volumetric progression of coronary lesions is thought to be the fundamental step for whether or not an ACS will occur.[5–7] Coronary computed tomography angiography (CCTA) has the ability to non-invasively detect, characterize and quantify coronary atherosclerotic plaque.[8,9] In this context, a larger volume of non-calcified plaque on CCTA has been related to vulnerable plaque and future myocardial infarction (MI).[10–13] We previously reported findings from the Incident COroNary Syndromes Identified by Computed Tomography (ICONIC) study, highlighting the importance of a comprehensive coronary plaque evaluation for the identification of patients at high risk for ACS.[12] The current analysis sought to examine differences in the volume and composition of coronary atherosclerosis between patients experiencing an early versus late ACS after clinically indicated baseline CCTA.

Methods

Study design and patients

Derivation cohort, ICONIC study

ICONIC is a nested case-control study within the prospective, dynamic, multicenter, observational *CO*ronary CT Angiography Evaluatio*N* *F*or

Clinical Outcomes: an *InteRnational Multicenter* registry, enrolling patients at 13 sites in 8 countries across Asia, Europe, and North-America between 2002 and 2009.[12,14] The study design including in- and exclusion criteria has been published in detail.[12] Of those enrolled in the ICONIC study, a total of 234 patients underwent a clinically indicated baseline CCTA for suspected coronary artery disease (CAD) and experienced an ACS during follow-up. Separate core laboratories performed blinded adjudication of ACS events and culprit lesions according to World Health Organization (WHO) and Third Universal MI definitions, as well as blinded qualitative and quantitative analysis of baseline CCTA according to an 18-segment Society of Cardiovascular Computed Tomography (SCCT) model.[15–17] ACS patients were 1:1 propensity-matched to within-site non-ACS controls based on age, sex, cardiac risk factors and CAD severity on CCTA defined as non-obstructive <50%, 1-vessel, 2-vessel, and 3-vessel or left main obstructive disease ≥50%. The study protocol was approved by institutional review boards or ethics committees at each participating site, and all patients provided written informed consent. For the present analysis, non-ACS controls ($n = 234$) were omitted. Thus, 234 ACS patients were included. Data including the non-ACS controls are presented in Supplementary data online, *Table S1*.

External validation cohort, PARADIGM registry

The cohort used to externally validate differences in the volume and composition of coronary atherosclerosis between patients experiencing early versus late ACS was the *Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging* (PARADIGM) registry. PARADIGM is a prospective, dynamic, multicenter, observational registry, enrolling patients for serial CCTA with an interscan interval of ≥2 years at 13 sites in 7 countries across Asia, Europe, North- and South-America between 2003 and 2015.[18] The study design including in- and exclusion criteria has been published in detail.[19] Of those enrolled in the PARADIGM registry, a total of 452 patients underwent a clinically indicated baseline CCTA for suspected CAD and experienced a major adverse cardiac event (MACE) during follow-up. MACE included MI, cardiac, and non-cardiac death, as well as early and late percutaneous coronary intervention or coronary artery bypass grafting surgery. The study protocol was approved by each site's institutional review board or ethics committee, and all patients provided written informed consent. For the present analysis, patients with a non-interpretable baseline CCTA due to prior stents or grafts ($n = 35$), artefacts ($n = 28$), missing or file-errors of images ($n = 12$) or a combination of the reasons above ($n = 13$) were excluded. Thus, 364 MACE patients were included.

Event adjudication

For the derivation cohort, a detailed methodology for the adjudication of ACS events and culprit lesions was previously reported.[12] First, ACS events were adjudicated by six experienced physicians at the Clinical and Data Coordinating Center (Dalio Institute of Cardiovascular Imaging, New York, NY, USA) according to WHO and Third Universal MI definitions.[15,17] Thorough review of electrocardiograms, cardiac biomarkers, and invasive coronary angiograms (ICAs) was completed, blinded to baseline CCTA. Second, for each ACS patient 1 culprit lesion was adjudicated based on availability of the ICA. In case 1 significant lesion was observed on ICA, this was deemed the culprit lesion. In case ≥2 lesions were observed on ICA, the culprit lesion was deemed based on a combination of both stenosis severity and ischaemia localization on the electrocardiogram. Reasons for unfeasible adjudication of culprit lesions on ICA ($n = 72$) were earlier described.[12] Third, culprit lesions were co-registered to culprit lesion precursors on baseline CCTA using fiduciary landmarks such as the distance from the ostium and side branches. Reasons for unfeasible co-registration to culprit lesion precursors on baseline CCTA ($n = 38$) were earlier described.[12] For a total of 124 culprit lesions, successful co-registration was achieved.

For the external validation cohort, definitions of MACE events and methodology for follow-up were previously reported.[19]

CCTA acquisition and image analysis

Patients from both cohorts were scanned with ≥64 detector row CT scanners in agreement with the SCCT guidelines and site-specific standards.[16,20] Scans were qualitatively and quantitatively analyzed by level III-experienced readers at the CCTA core laboratory (Severance Cardiovascular Hospital, Seoul, South-Korea) according to the 18-segment SSCT model, blinded to clinical data including event status.[16] For quantitative analysis, semi-automated validated software with appropriate manual correction was used at every 0.5–1.0 mm cross-section (QAngio CT Research Edition version 2.1.9.1, Medis Medical Imaging Systems, Leiden, the Netherlands).[8] All coronary segments ≥2 mm in diameter were evaluated, and a coronary lesion was defined as any tissue ≥1 mm^2 within or adjacent to the lumen that could be discriminated in >2 planes from the pericardial tissue, epicardial fat, or lumen.[11] Comprehensive evaluation included measurements of maximal diameter stenosis, maximal cross-sectional plaque burden, lesion length, total and compositional plaque volumes, and adverse plaque characteristics, amongst others. Maximal diameter stenosis and cross-sectional plaque burden were calculated in line with standardized definitions.[3] Compositional plaque volumes were uniformly categorized by Hounsfield units (HU): calcified plaque >350 HU, fibrous plaque 131–350 HU, fibrofatty plaque 31–130 HU and necrotic core <30 HU.[12] Adverse plaque characteristics included low-attenuation plaque <30 HU, positive remodeling ≥1.1, and spotty calcification ≤3 mm in any direction. High-risk plaque was defined as any coronary lesion exhibiting ≥2 of the features above.[11] All measurements were performed on a per-lesion and per-segment level, and summation of these values from the whole coronary artery tree generated patient-level data. Excellent intra- and interobserver intraclass correlations for measurements were previously reported for both cohorts.[12,18]

Study aims

The definition of early or late ACS was determined based on the time between the baseline CCTA and subsequent ACS. The cut-off for late ACS was fixed at 90 days after baseline CCTA in line with prior published reports, describing the interplay between the vulnerability and progression of coronary atherosclerosis.[5,6] Primary aim was the identification of differences in total and compositional plaque volumes between patients experiencing early (≤90 days) versus late ACS (>90 days). Secondary aims included identification of differences between proximal culprit lesion precursors of early and late ACS, within-patient identification of future culprit lesions and validation of (primary) patient-level findings using the external validation cohort.

Statistical analysis

Continuous data are reported as means ± standard deviations (SD) or medians with interquartile ranges (IQR). Categorical data are reported as counts with percentages. Continuous data were compared with the

Independent-Samples *T* test or Mann–Whitney *U* test based on skewness of distribution. Categorical data were compared with the χ^2 test or Fisher's Exact test based on minimum expected counts. First, patient-level comparisons were performed amongst patients with early and late ACS. Second, lesion-level comparisons were performed amongst all culprit lesion precursors of early and late ACS. Due to variability of absolute plaque volumes according to the location within the coronary artery tree, specific focus was given to proximal precursors in the left main artery, proximal left anterior descending artery, proximal right coronary artery, and proximal left circumflex artery (Supplementary data online, *Figure S1*). For visual interpretation of the time-dependent relationship, estimated plaque volumes derived from a general linear model were plotted against the time between the baseline CCTA and subsequent ACS.[21] Third, generalized estimating equations with a first-order autoregressive correlation structure were calculated to identify the compositions associated with culprit lesion precursors of either early or late ACS using within-patient non-culprit lesions as a comparator. Last, an external validation of statistically significant patient-level compositions was performed in the PARADIGM registry using early (≤90 days) versus late MACE (>90 days) after baseline CCTA. All statistical tests were two-sided and a *P*-value of <0.05 indicated statistical significance. All analyses were performed with R (version 3.6.1, R Development Core Team, Vienna, Austria) and SPSS software (version 26, SPSS IBM Corp., Armonk, NY, USA).

Results

Patients

A total of 234 patients (mean age 62 ± 12 years, 36% women) underwent baseline CCTA and experienced an ACS after a mean of 395 ± 622 days. ACS comprised 40 (17%) ST-segment elevation myocardial infarctions (STEMI), 114 (49%) non-ST-segment elevation myocardial infarctions (NSTEMI), 6 (3%) unclassified MI due to timing of the electrocardiogram preceding the ACS, and 74 (32%) unstable angina pectoris events. Patients who had an early ACS were largely comparable to patients who had a late ACS, as the majority was symptomatic with prevalent cardiac risk factors (*Table 1*). Distribution of ACS type and infarction size measured by cardiac biomarkers was similar amongst groups, whilst the left anterior descending artery was more frequently the culprit vessel in patients with early ACS (*Table 2*).

Table 1 Baseline characteristics of derivation cohort

	Patients with early ACS ≤90 days *n* = 129, mean ± SD or *n* (%)	Patients with late ACS >90 days *n* = 105	*P*-value
Age, years	62 ± 12	62 ± 11	0.722
Female	45 (35)	40 (38)	0.611
BMI, kg/m^2	27.1 ± 4.3	28.1 ± 5.9	0.447
Symptoms			
Typical angina	35 (29)	28 (28)	0.074
Atypical angina	60 (49)	34 (34)	
Non-cardiac pain	13 (11)	15 (15)	
Asymptomatic	15 (12)	22 (22)	
Dyspnoea	21 (20)	19 (24)	0.585
Cardiac risk factors			
Hypertension	80 (62)	68 (65)	0.649
Dyslipidaemia	67 (52)	62 (60)	0.268
Diabetes mellitus	25 (19)	21 (20)	0.905
Family history of CAD	46 (37)	48 (46)	0.204
Smoking current	40 (31)	32 (31)	0.899
Cardiac medication[a]			
Aspirin	57 (66)	35 (40)	0.001
Beta blockers	36 (42)	27 (31)	0.125
Calcium channel blockers	17 (20)	18 (22)	0.788
Renin-angiotensin system inhibitors	30 (35)	31 (35)	0.962
Statins	56 (68)	40 (49)	0.019
Interval coronary revascularization	60 (47)	58 (55)	0.184
ASCVD risk score, %	20 ± 14	19 ± 13	0.838

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAD, coronary artery disease.
[a]Cardiac medication prescribed at the time of baseline CCTA.

Patient-level comparison of early versus late ACS on baseline CCTA

As compared to patients with late ACS, early ACS patients demonstrated more often obstructive disease ≥50% with a corresponding greater maximal diameter stenosis and maximal cross-sectional plaque burden (*Table 3*). Total, fibrous, fibrofatty and necrotic core volumes were significantly larger in the early ACS group [256.9 mm^3 (IQR 86.2–398.4 mm^3) vs. 138.3 mm^3 (IQR 53.3–354.3 mm^3), $P = 0.026$; 118.9 mm^3 (IQR 36.0–192.4 mm^3) vs. 66.0 mm^3 (IQR 22.4–155.5 mm^3), $P = 0.031$; 35.5 mm^3 (IQR 9.0–90.6 mm^3) vs. 21.9 mm^3 (IQR 3.6–52.3 mm^3), $P = 0.011$; and 1.9 mm^3 (IQR 0.1–10.1 mm^3) vs. 0.8 mm^3 (IQR 0.0–3.6 mm^3), $P = 0.007$, respectively) (*Figure 1A*). Similar findings were observed with regard to fibrofatty plaque and necrotic core when compositional plaque volumes were vessel volume-normalized (*Figure 1B*). The time-dependent relationship for total and non-calcified plaque volumes, using estimated values derived from a general linear model, is illustrated in *Figure 2*.

Lesion-level comparison of early versus late ACS on baseline CCTA

As compared to precursors of late ACS, early culprit lesion precursors exhibited a greater maximal diameter stenosis and maximal cross-sectional plaque burden (Supplementary data online, *Table S2*). Total and compositional plaque volumes were not significantly larger in the early ACS group ($P > 0.05$). However, focused on proximal culprit lesion precursors only, fibrofatty volumes were significantly larger in early ACS as compared to late ACS [14.6 mm^3 (IQR 3.5–62.5 mm^3) vs. 5.5 mm^3 (IQR 1.0–34.4 mm^3), $P = 0.048$] (*Figure 3*). A trend towards

larger necrotic core volumes within the early ACS group was observed, that reached statistical significance when the volume of necrotic core was combined with fibrofatty plaque [0.5 mm^3 (IQR 0.0–4.1 mm^3) vs. 0.1 mm^3 (IQR 0.0–1.7 mm^3), $P = 0.065$; and 15.5 mm^3 (IQR 3.5–66.7 mm^3) vs. 5.9 mm^3 (IQR 1.0–37.4 mm^3, $P = 0.040$, respectively] (Supplementary data online, *Table S3*). The time-dependent relationship for fibrofatty volume, using estimated values derived from a general linear model, is illustrated in Supplementary data online, *Figure S2*.

Within-patient identification of future culprit lesions

As compared to within-patient non-culprit lesions, culprit lesion precursors of early ACS exhibited elevated risk for a greater maximal diameter stenosis [OR 1.050 (95% CI 1.032–1.068), $P < 0.001$], maximal cross-sectional plaque burden [OR 1.039 (95% CI 1.024–1.053), $P < 0.001$], lesion length [OR 1.033 (95% CI 1.019–1.047], $P < 0.001$), total plaque volume [OR 1.004 (95% CI 1.000–1.007), $P = 0.032$], and all compositional plaque volumes [for calcified plaque OR 1.006 (95% CI 1.000–1.011), $P = 0.042$; for fibrous plaque OR 1.009 (95% CI 1.002–1.017), $P = 0.013$; for fibrofatty plaque OR 1.010 (95% CI 1.000–1.019), $P = 0.047$; and for necrotic core OR 1.056 (95% CI 1.006–1.108), $P = 0.029$] (*Table 4*). Moreover, for culprit lesion precursors of late ACS an elevated risk was observed for a greater maximal diameter stenosis, lesion length, total, calcified and fibrous volumes as compared to within-patient non-culprit lesions ($P < 0.05$). For the significant volumetric findings, also risk measures according to tertiles were provided (Supplementary data online, *Table S4*).

Table 2 ACS event characteristics

	Patients with early ACS ≤90 days $n = 129$, median (IQR) or n (%)	Patients with late ACS >90 days $n = 105$	*P*-value
ACS type			
STEMI	17 (13)	23 (22)	0.189
NSTEMI	62 (48)	52 (50)	
Unclassified MI	3 (2)	3 (3)	
Unstable angina pectoris	47 (36)	27 (26)	
Culprit vessel[a]			
Left main artery	3 (2)	2 (2)	1.000
Left anterior descending artery	49 (38)	25 (24)	0.020
Right coronary artery	26 (20)	16 (15)	0.330
Left circumflex artery	21 (16)	20 (19)	0.580
Cardiac biomarkers			
Peak troponin I or T, *upper limit[b]	19.5 (4.5–93.4)	25.3 (8.7–106.7)	0.373
Peak creatine kinase, *upper limit[c]	2.8 (1.4–16.9)	1.8 (1.2–9.4)	0.238

[a]Only including cases with identified culprit lesions on ICA (non-significant lesions were omitted as culprits).
[b]Only including STEMI, NSTEMI, and unclassified MI.
[c]Only including cases without available troponin I or T.

External validation

In the external validation cohort, a total of 364 patients (mean 63 ± 9 years, 31% women) underwent baseline CCTA and experienced a MACE after a median of 531 days (IQR 31–1480 days). MACE comprised 17 (5%) MI, 10 (3%) cardiac deaths and 12 (3%) non-cardiac deaths, as well as 270 (74%) percutaneous coronary interventions and 55 (15%) coronary artery bypass grafting surgeries. Patients who had an early MACE were more often symptomatic with typical angina, dyslipidaemic, and current smokers (Supplementary data online, *Table S5*). As compared to patients with late MACE, patients with early MACE demonstrated significantly larger total, fibrous, fibrofatty, and necrotic core volumes [237.6 mm^3 (IQR 124.4–406.8 mm^3) vs. 175.3 mm^3 (IQR 56.2–303.1 mm^3), $P < 0.001$; 96.8 mm^3 (IQR 45.8–164.3 mm^3) vs. 69.0 mm^3 (IQR 23.1–140.8 mm^3), $P = 0.001$; 25.9 mm^3 (IQR 10.0–70.5 mm^3) vs. 15.8 mm^3 (IQR 2.3–53.2 mm^3), $P = 0.003$; and 1.9 mm^3 (IQR 0.1–7.2 mm^3) vs. 0.6 mm^3 (IQR 0.0–3.9 mm^3); $P = 0.010$, respectively] (*Figure 4*). Furthermore, when restricting to patients with early versus late MI or cardiac death only, trends according to compositional plaque volumes were comparable (Supplementary data online, *Figure S3*).

Discussion

The current report from the ICONIC study compared early versus late ACS risk patterns of coronary atherosclerotic plaque across the whole coronary artery tree using CCTA. We revealed that volumetric differences in composition of coronary atherosclerosis are present between patients and proximal culprit lesion precursors of ACS according to their timing antecedent to the acute event (Graphical Abstract). On a per-patient level, total and non-calcified plaque volumes were associated with early ACS, whilst on a proximal per-lesion level this was only seen for fibrofatty volumes. Importantly, patient-level findings were externally validated in the PARADIGM registry. These data suggest a potentially important role for CCTA in the future regarding the early identification of near-term plaque instability and ACS risk.

Severity and extent of coronary atherosclerosis and ACS

The *P*roviding *R*egional *O*bservations to *S*tudy *P*redictors of *E*vents in the *C*oronary *T*ree (PROSPECT) study revealed, using intravascular ultrasound, that coronary lesions responsible for ACS were

Table 3 Patient-level CCTA findings according to ACS timing

	Patients with early ACS ≤90 days $n = 129$, median (IQR) or n (%)	Patients with late ACS >90 days $n = 105$	P-value
Severity by number of vessels			
None	4 (3)	11 (11)	0.005
Non-obstructive	49 (38)	55 (52)	
1-vessel obstructive	49 (38)	20 (19)	
2-vessel obstructive	15 (12)	10 (10)	
3-vessel or left main obstructive	12 (9)	9 (9)	
Severity by quantification			
Maximal diameter stenosis, %	47.0 (33.4–61.0)	36.9 (19.3–49.8)	<0.001
Obstructive ≥50%	55 (43)	26 (25)	0.004
General measures			
Maximal cross-sectional plaque burden, %	74.3 (59.9–86.3)	66.5 (46.7–79.4)	0.001
Total plaque volume, mm^3	256.9 (86.2–398.4)	138.3 (53.3–354.3)	0.026
Vessel volume, mm^3	2560.8 (1793.7–3160.4)	2180.2 (1497.0–2822.1)	0.023
Lumen volume, mm^3	2145.9 (1541.0–2834.9)	2017.6 (1347.3–2498.6)	0.041
Number of lesions	4.0 (2.0–6.0)	4.0 (1.5–6.0)	0.172
Diffuseness	0.2 (0.1–0.4)	0.2 (0.1–0.4)	0.533
High-risk measures			
Low-attenuation plaque	60 (47)	41 (39)	0.252
Positive remodelling	118 (92)	87 (83)	0.047
Spotty calcification	43 (33)	29 (28)	0.346
Adverse plaque characteristics	121 (94)	89 (85)	0.023
High-risk plaque	72 (56)	50 (48)	0.212
Number of adverse plaque characteristics	4.0 (2.0–6.5)	3.0 (1.0–6.0)	0.066

predominantly angiographically mild, although characterized by large cross-sectional plaque burden and a relatively small luminal area.[3] In a large retrospective cohort study of 37 647 patients, Maddox *et al.* observed that the extent of obstructive CAD was associated with risk of MI.[22] These findings were evidently supported by a higher prevalence of obstructive disease ≥50 and ≥70% amongst ACS patients versus non-ACS controls in the primary analysis of the ICONIC study (34.6% vs. 19.2%, $P < 0.001$; and 12.8% vs. 5.1%, $P = 0.007$,

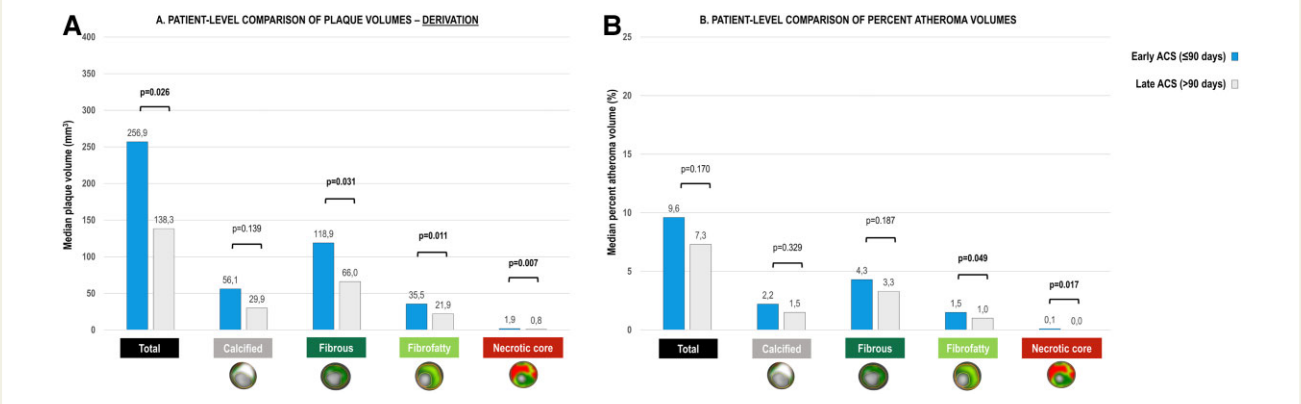


Figure 1 (*A*) Patient-level comparison of plaque volumes according to early versus late ACS. Patient-level comparison of plaque volumes between patients with early (blue bars, $n = 129$) versus late ACS (grey bars, $n = 105$). (*B*) Patient-level comparison of percent atheroma volumes according to early versus late ACS. Patient-level comparison of percent atheroma volumes between patients with early (blue bars, $n = 129$) versus late ACS (grey bars, $n = 105$). ACS, acute coronary syndrome.

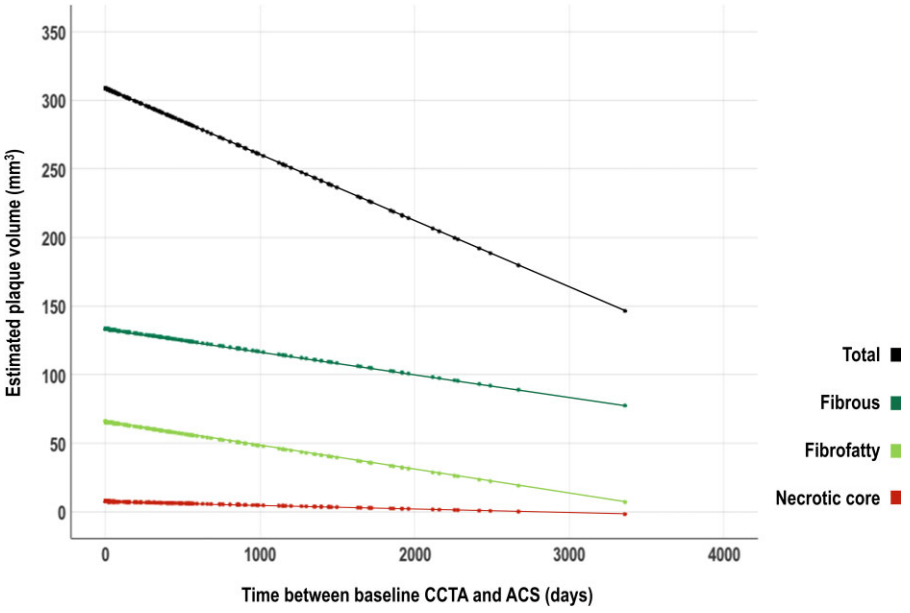


Figure 2 Patient-level visualization of plaque volumes according to ACS timing. Scatterplot depicts estimated plaque volumes (y-axis; increased values = increased amount of coronary plaque in mm^3) by the time between the baseline CCTA and subsequent ACS (x-axis; increased values = later occurrence of event in days). All data points are patient-level values, and estimated values were derived from a general linear model. Black, total plaque; dark-green, fibrous plaque; light-green, fibrofatty plaque; red, necrotic core. ACS, acute coronary syndrome; CCTA, coronary computed tomography angiography.

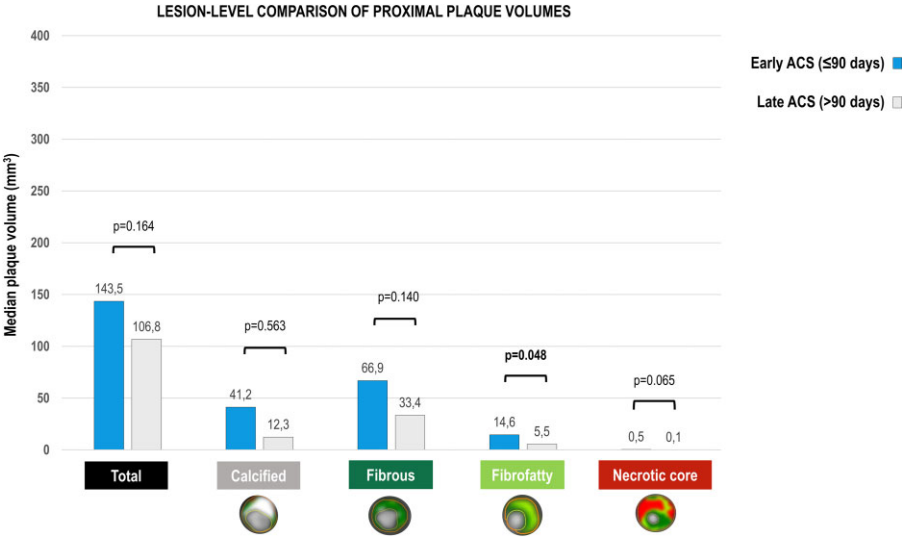


Figure 3 Lesion-level comparison of proximal plaque volumes according to early versus late ACS. Lesion-level comparison of proximal plaque volumes between culprit lesion precursors of early (blue bars, $n = 62$) versus late ACS (grey bars, $n = 33$). Precursors within the left main artery, proximal left anterior descending artery, proximal right coronary artery and proximal left circumflex artery were considered proximal. ACS, acute coronary syndrome.

respectively).[12] In the present analysis, the prevalence of obstructive disease ≥50% decreased significantly from early towards late ACS, suggesting that obstructive disease was mainly associated with relatively short-term events. Preceding imaging studies have investigated the relationship of the extent of coronary atherosclerosis in stable patients with the occurrence of ACS.[2,3,23–26]

Table 4 Identification of early or late culprit lesion precursors within ACS patients

	Early vs. non-culprit lesion precursors		Late vs. non-culprit lesion precursors	
	OR (95% CI)[a]	*P*-value	OR (95% CI)[a]	*P*-value
Maximal diameter stenosis, %	1.050 (1.032–1.068)	<0.001	1.023 (1.005–1.043)	0.014
Maximal cross-sectional plaque burden, %	1.039 (1.024–1.053)	<0.001	1.014 (0.996–1.033)	0.117
Lesion length, mm	1.033 (1.019–1.047)	<0.001	1.032 (1.020–1.043)	<0.001
Total plaque volume, mm^3	1.004 (1.000–1.007)	0.032	1.003 (1.000–1.005)	0.021
Calcified volume, mm^3	1.006 (1.000–1.011)	0.042	1.007 (1.003–1.011)	<0.001
Fibrous volume, mm^3	1.009 (1.002–1.017)	0.013	1.006 (1.002–1.011)	0.002
Fibrofatty volume, mm^3	1.010 (1.000–1.019)	0.047	1.004 (0.998–1.010)	0.214
Necrotic core volume, mm^3	1.056 (1.006–1.108)	0.029	0.994 (0.949–1.041)	0.792

[a]Including 124 culprit lesion precursors ($n = 81$ for early; $n = 43$ for late and 458 non-culprit lesion precursors). Individual variables were adjusted for the distance from the ostium to minimal luminal diameter and statins.

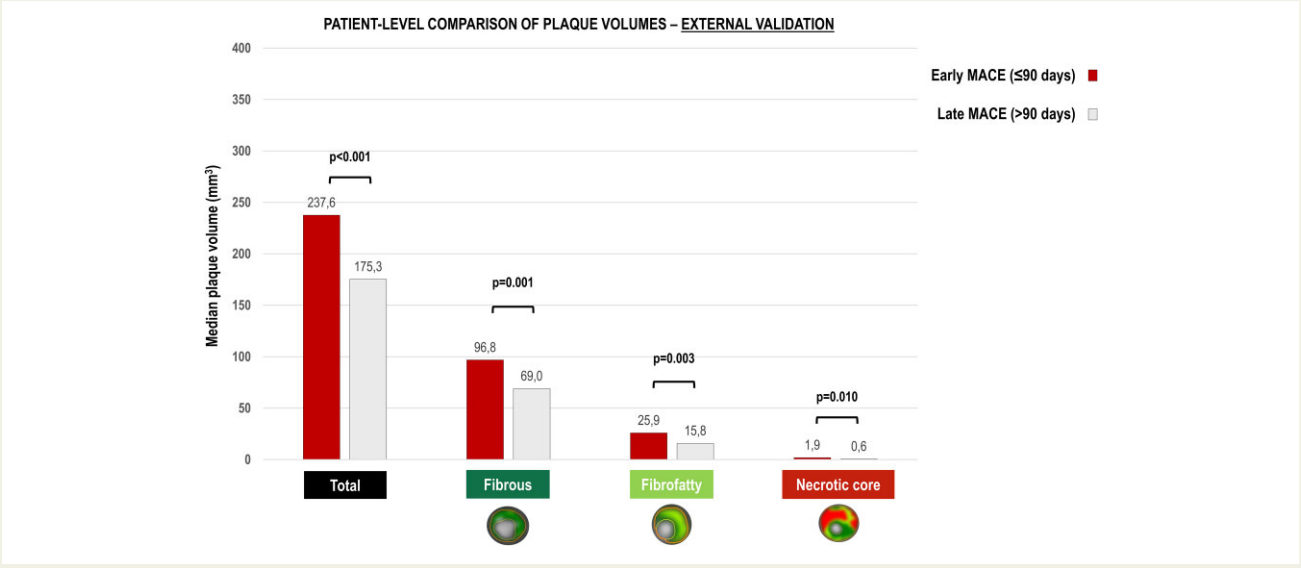


Figure 4 Patient-level comparison of plaque volumes according to early versus late MACE[a]. Patient-level comparison of plaque volumes between patients with early (red bars, $n = 137$) versus late MACE (grey bars, $n = 227$). MACE, major adverse cardiac events. [a]MACE after baseline CCTA.

Hadamitzky *et al.*[26] observed, in a 5-year follow-up study of 1584 patients, that the number of coronary segments containing any plaque predicted all-cause death and non-fatal MI in patients undergoing CCTA for suspected stable CAD. Similar findings were described in CCTA studies comparing patient-level or segment-level total plaque volumes between ACS patients and non-ACS controls.[2,24] Interestingly, the present analysis showed that the total plaque volume in patients with early ACS was larger than in those with late ACS, which may further substantiate the hypothesis that the extent of CAD is related to the temporal risk for ACS.

Composition of coronary atherosclerosis and ACS

Intravascular ultrasound studies have illustrated that echo-lucent areas within coronary lesions, likely representing necrotic core or lipid rich zones, are more frequently observed in ACS causing lesions as compared to non-ACS causing lesions.[23] Likewise, HU attenuation on CCTA has been demonstrated to depict different compositions of coronary atherosclerosis. Specific thresholds have been established to identify plaque components such as calcified plaque, fibrous plaque, fibrofatty plaque and necrotic core.[9] Especially, the lower HU attenuations on CCTA have been acknowledged as markers for rupture-vulnerable coronary lesions with associated risk for adverse events.[2,25,27–30] Plaque rupture is the leading cause of acute thrombus formation, next to plaque erosion and to a lesser extent eruptive calcified nodules.[10] The hallmark of plaque rupture is the disruption of a thin-cap fibroatheroma (<65 μm), exposing the underlying necrotic core to the lumen with subsequent luminal thrombosis.[31] Necrotic core is a progressive stage in CAD in which inflammatory cells, such as macrophages and T lymphocytes, penetrate the lipid pool and

undergo apoptosis or necrosis.[32] In the current analysis using CCTA, a trend towards larger necrotic core volumes in proximal culprit lesion precursors of early versus late ACS was observed, which reached statistical significance when the volume of necrotic core was combined with fibrofatty plaque (0.5 mm^3 vs. 0.1 mm^3, $P = 0.065$; and 15.5 mm^3 vs. 5.9 mm^3, $P = 0.040$, respectively). The combination of both necrotic core and fibrofatty plaque on CCTA might reflect the lipid pool in its totality that can be observed on histopathology (gold standard).[33] Lipid pool might progress into a necrotic core during the later inflammatory stages of CAD and is therefore contributory to ACS risk. To date, it is unknown how well CCTA can distinguish lipid pool from necrotic core given the current limits of spatial resolution. To this end, future research is warranted in order to evaluate if dual-energy as compared to single-energy CCTA can further improve the characterization of plaque components.

Limitations

The present findings were part of large observational cohort studies with intrinsic limitations, including unmeasured confounding factors and selection bias. Limited information was available on duration of or changes in medication use after baseline CCTA. In 18 ACS patients long-term medications were available, showing that those with early or late ACS had similar usage of cardiac medication at 5-year follow-up. Regarding the adjudication of ACS events, potentially an important group of patients experiencing ACS in an earlier revascularized segment or leading to death without sufficient available data was excluded from the derivation cohort. Additionally, culprit lesions that caused MACE were not adjudicated in the external validation cohort (as per earlier reported study design).[19] For instance, ICAs were not collected and therefore only a patient-level validation could be performed. Regarding the co-registration of culprit lesions to culprit lesion precursors, ACS patients having no or unmeasurable coronary lesions on baseline CCTA due to spatial resolution and artefacts could not be co-registered. Moreover, quantification of chronic total occlusions was not feasible with the software that was utilized. Finally, coronary atherosclerosis is a continuously dynamic process, which should always be considered when interpreting our results.

Conclusion

Volumetric differences in composition of coronary atherosclerosis exist between ACS patients experiencing an early versus late ACS after clinically indicated baseline CCTA. A large burden of non-calcified plaque across the whole coronary artery tree is strongly associated with near-term plaque instability and ACS risk, supporting the importance of plaque components related to vulnerable plaque.

Supplementary data

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

Funding

This trial was supported by NIH Grant No. HL115150 and the Leading Foreign Research Institute Recruitment Programme of the National Research Foundation of Korea, Ministry of Science, ICT, & Future Planning (Seoul, Korea).

Conflict of interest: Dr Chow receives support from CV Diagnostix and Ausculsciences, educational support from TeraRecon Inc., and has equity interest in General Electric. Dr Leipsic is a consultant and has stock options in Circle CVI and HeartFlow and receives research support from GE Healthcare. Dr Min is an employee of Cleerly, Inc. Dr Shaw serves on the scientific advisory board for Covanos, 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. The remaining authors have no relevant conflicts to disclose.

Data availability

Data may be available upon reasonable request to the corresponding author.

References

1. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation*. 1995; **92**(3): 657–71.
2. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, *et al.* Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol*. 2009; **54**(1):49–57.
3. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, *et al.* A prospective natural-history study of coronary atherosclerosis. *N Engl J Med*. 2011; **364**(3):226–35.
4. Ojio S, Takatsu H, Tanaka T, Ueno K, Yokoya K, Matsubara T, *et al.* Considerable time from the onset of plaque rupture and/or thrombi until the onset of acute myocardial infarction in humans: coronary angiographic findings within 1 week before the onset of infarction. *Circulation*. 2000; **102**(17):2063–9.
5. Ahmadi A, Argulian E, Leipsic J, Newby DE, Narula J. From subclinical atherosclerosis to plaque progression and acute coronary events: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019; **74**(12):1608–17.
6. Ahmadi A, Leipsic J, Blankstein R, Taylor C, Hecht H, Stone GW, *et al.* Do plaques rapidly progress prior to myocardial infarction? The interplay between plaque vulnerability and progression. *Circ Res*. 2015; **117**(1):99–104.
7. Kolodgie FD, Gold HK, Burke AP, Fowler DR, Kruth HS, Weber DK, *et al.* Intraplaque hemorrhage and progression of coronary atheroma. *N Engl J Med*. 2003; **349**(24):2316–25.
8. Boogers MJ, Broersen A, van Velzen JE, de Graaf FR, El-Naggar HM, Kitslaar PH, *et al.* Automated quantification of coronary plaque with computed tomography: comparison with intravascular ultrasound using a dedicated registration algorithm for fusion-based quantification. *Eur Heart J*. 2012; **33**(8):1007–16.
9. de Graaf MA, Broersen A, Kitslaar PH, Roos CJ, Dijkstra J, Lelieveldt BP, *et al.* Automatic quantification and characterization of coronary atherosclerosis with computed tomography coronary angiography: cross-correlation with intravascular ultrasound virtual histology. *Int J Cardiovasc Imaging*. 2013; **29**(5): 1177–90.
10. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol*. 2006; **47**(Suppl. 8):C13–8.
11. Motoyama S, Ito H, Sarai M, Kondo T, Kawai H, Nagahara Y, *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): 337–46.
12. Chang HJ, Lin FY, Lee SE, Andreini D, Bax J, Cademartiri F, *et al.* Coronary atherosclerotic precursors of acute coronary syndromes. *J Am Coll Cardiol*. 2018; **71**(22): 2511–22.
13. Williams MC, Kwiecinski J, Doris M, McElhinney P, D'Souza MS, Cadet S, *et al.* Low-attenuation noncalcified plaque on coronary computed tomography angiography predicts myocardial infarction: results from the multicenter SCOT-HEART Trial (Scottish computed tomography of the HEART). *Circulation*. 2020; **141**(18): 1452–62.
14. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah MH, Berman DS, *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.
15. Mendis S, Thygesen K, Kuulasmaa K, Giampaoli S, Mahonen M, Ngu Blackett K, *et al.* World Health Organization definition of myocardial infarction: 2008-09 revision. *Int J Epidemiol*. 2011; **40**(1):139–46.

16. Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ, *et al.* SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr*. 2014; **8**(5):342–58.
17. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, *et al.* Third universal definition of myocardial infarction. *Eur Heart J*. 2012; **33**(20):2551–67.
18. Lee SE, Chang HJ, Sung JM, Park HB, Heo R, Rizvi A, *et al.* Effects of statins on coronary atherosclerotic plaques: the PARADIGM study. *JACC Cardiovasc Imaging*. 2018; **11**(10):1475–84.
19. Lee SE, Chang HJ, Rizvi A, Hadamitzky M, Kim YJ, Conte E, *et al.* Rationale and design of the Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography IMaging (PARADIGM) registry: a comprehensive exploration of plaque progression and its impact on clinical outcomes from a multicenter serial coronary computed tomographic angiography study. *Am Heart J*. 2016; **182**:72–9.
20. Abbara S, Blanke P, Maroules CD, Cheezum M, Choi AD, Han BK, *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):435–49.
21. van Rosendael AR, van den Hoogen IJ, Gianni U, Ma X, Tantawy SW, Bax AM, *et al.* Association of statin treatment with progression of coronary atherosclerotic plaque composition. *JAMA Cardiol*. 2021; **6**(11):1257–66.
22. Maddox TM, Stanislawski MA, Grunwald GK, Bradley SM, Ho PM, Tsai TT, *et al.* Nonobstructive coronary artery disease and risk of myocardial infarction. *JAMA*. 2014; **312**(17):1754–63.
23. Yamagishi M, Terashima M, Awano K, Kijima M, Nakatani S, Daikoku S, *et al.* Morphology of vulnerable coronary plaque: insights from follow-up of patients examined by intravascular ultrasound before an acute coronary syndrome. *J Am Coll Cardiol*. 2000; **35**(1):106–11.
24. Versteylen MO, Kietselaer BL, Dagnelie PC, Joosen IA, Dedic A, Raaijmakers RH, *et al.* Additive value of semiautomated quantification of coronary artery disease using cardiac computed tomographic angiography to predict future acute coronary syndrome. *J Am Coll Cardiol*. 2013; **61**(22):2296–305.
25. Hoffmann U, Moselewski F, Nieman K, Jang IK, Ferencik M, Rahman AM, *et al.* Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. *J Am Coll Cardiol*. 2006; **47**(8):1655–62.
26. Hadamitzky M, Taubert S, Deseive S, Byrne RA, Martinoff S, Schomig A, *et al.* Prognostic value of coronary computed tomography angiography during 5 years of follow-up in patients with suspected coronary artery disease. *Eur Heart J*. 2013; **34**(42):3277–85.
27. Kitagawa T, Yamamoto H, Horiguchi J, Ohhashi N, Tadehara F, Shokawa T, *et al.* Characterization of noncalcified coronary plaques and identification of culprit lesions in patients with acute coronary syndrome by 64-slice computed tomography. *JACC Cardiovasc Imaging*. 2009; **2**(2):153–60.
28. Puchner SB, Liu T, Mayrhofer T, Truong QA, Lee H, Fleg JL, *et al.* High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. *J Am Coll Cardiol*. 2014; **64**(7):684–92.
29. Dey D, Achenbach S, Schuhbaeck A, Pflederer T, Nakazato R, Slomka PJ, *et al.* Comparison of quantitative atherosclerotic plaque burden from coronary CT angiography in patients with first acute coronary syndrome and stable coronary artery disease. *J Cardiovasc Comput Tomogr*. 2014; **8**(5):368–74.
30. Pflederer T, Marwan M, Schepis T, Ropers D, Seltmann M, Muschiol G, *et al.* Characterization of culprit lesions in acute coronary syndromes using coronary dual-source CT angiography. *Atherosclerosis*. 2010; **211**(2):437–44.
31. Burke AP, Farb A, Malcom GT, Liang YH, Smialek JE, Virmani R. Plaque rupture and sudden death related to exertion in men with coronary artery disease. *Jama-J Am Med Assoc*. 1999; **281**(10):921–6.
32. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death - a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscl Throm Vas*. 2000; **20**(5):1262–75.
33. Han D, Torii S, Yahagi K, Lin FY, Lee JH, Rizvi A, *et al.* Quantitative measurement of lipid rich plaque by coronary computed tomography angiography: a correlation of histology in sudden cardiac death. *Atherosclerosis*. 2018; **275**:426–33.