# Vessel-specific plaque features on coronary computed tomography angiography among patients of varying atherosclerotic cardiovascular disease risk

Bax, A.M.; Yoon, Y.E.; Gianni, U.; Rosendael, A.R. van; Lu, Y.; Ma, X.Y.; ... ; PARADIGM Investigators

ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2022) **23**, 1171–1179
https://doi.org/10.1093/ehjci/jeac029

**ORIGINAL PAPER**

# Vessel-specific plaque features on coronary computed tomography angiography among patients of varying atherosclerotic cardiovascular disease risk

**A. Maxim Bax [1], Yeonyee E. Yoon[1,2,3], Umberto Gianni[1], Alexander R. van Rosendael[4], Yao Lu[5], Xiaoyue Ma[5], Benjamin P. Goebel[1], Sara W. Tantawy[1], Daniele Andreini[6], Matthew J. Budoff [7], Filippo Cademartiri [8], Kavitha Chinnaiyan[9], Jung Hyun Choi[10], Edoardo Conte[6], Pedro de Araújo Gonçalves[11], Ilan Gottlieb[12], Martin Hadamitzky[13], Jonathon A. Leipsic[14], Erica Maffei[15], Gianluca Pontone [6], Sanghoon Shin[16], Yong-Jin Kim[2], Byoung Kwon Lee[17], Eun Ju Chun[3], Ji Min Sung[18,19], Sang-Eun Lee[16,19], Daniel S. Berman[20], Jagat Narula[21], Fay Y. Lin[1], Hyuk-Jae Chang [18,19], and Leslee J. Shaw [1]*; for the PARADIGM investigators**

[1]Department of Radiology, Dalio Institute of Cardiovascular Imaging, NewYork-Presbyterian Hospital, Weill Cornell Medicine, 413 East 69th Street, Suite 108, New York, NY 10021, USA; [2]Department of Internal Medicine, Seoul National University College of Medicine, Cardiovascular Center, Seoul National University Hospital, Seoul, South Korea; [3]Department of Radiology, Seoul National University Bundang Hospital, Sungnam, South Korea; [4]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; [5]Department of Healthcare Policy and Research, New York-Presbyterian Hospital, The Weill Cornell Medical College, New York, NY, USA; [6]Department of Medicine, Centro Cardiologico Monzino, IRCCS Milan, Milan, Italy; [7]Department of Medicine, Los Angeles Biomedical Research Institute, Torrance, CA, USA; [8]Department of Medicine, Cardiovascular Imaging Center, SDN IRCCS, Naples, Italy; [9]Department of Cardiology, William Beaumont Hospital, Royal Oak, MI, USA; [10]Division of Cardiology, Department of Internal Medicine, Pusan University Hospital, Busan, South Korea; [11]Department of Cardiology, UNICA, Unit of Cardiovascular Imaging, Hospital da Luz, Lisboa, Portugal; [12]Department of Radiology, Casa de Saude São Jose, Rio de Janeiro, Brazil; [13]Department of Radiology and Nuclear Medicine, German Heart Center Munich, Munich, Germany; [14]Department of Medicine and Radiology, University of British Columbia, Vancouver, BC, Canada; [15]Department of Radiology, Area Vasta 1/ASUR Marche, Urbino, Italy; [16]Division of Cardiology, Department of Internal Medicine, Ewha Womans University Seoul Hospital, Seoul, Korea; [17]Division of Cardiology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; [18]Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea; [19]Department of Cardiology, Yonsei-Cedars-Sinai Integrative Cardiovascular Imaging Research Center, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea; [20]Department of Imaging and Medicine, Cedars Sinai Medical Center, Los Angeles, CA, USA; and [21]Department of Cardiology, Icahn School of Medicine at Mount Sinai, Mount Sinai Heart, Zena and Michael A. Wiener Cardiovascular Institute, Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, New York, NY, USA

*Received 6 April 2021; editorial decision 20 January 2022; online publish-ahead-of-print 7 March 2022*

**See the editorial comment for this article 'Converging on the distribution profile of coronary artery disease', by Luis Eduardo Juarez-Orozco *et al.*, https://doi.org/10.1093/ehjci/jeab232.**

**Aims** The relationship between AtheroSclerotic CardioVascular Disease (ASCVD) risk and vessel-specific plaque evaluation using coronary computed tomography angiography (CCTA), focusing on plaque extent and composition, has not been examined. To evaluate differences in quantified plaque characteristics (using CCTA) between the three major coronary arteries [left anterior descending (LAD), right coronary (RCA), and left circumflex (LCx)] among subgroups of patients with varying ASCVD risk.

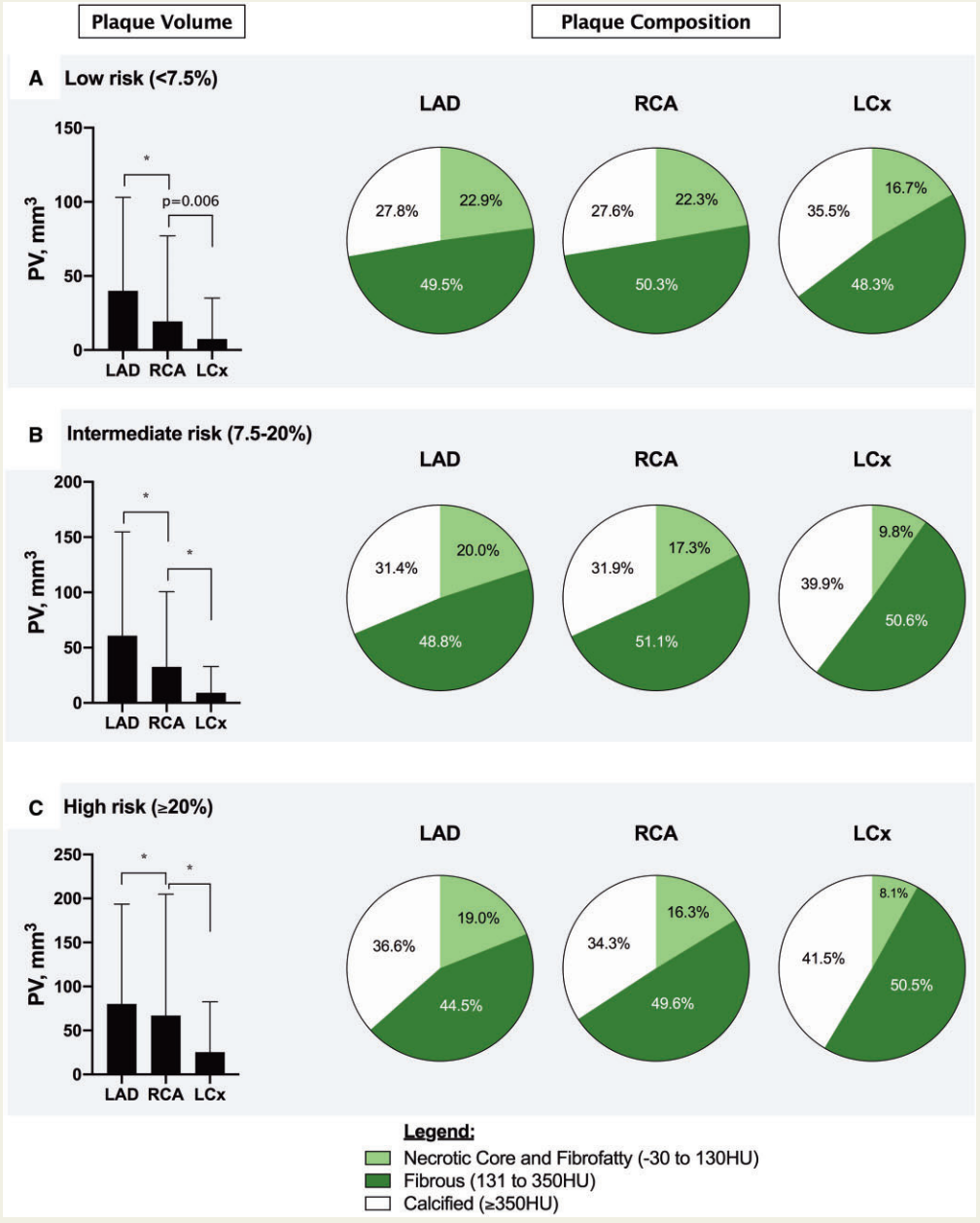
**Methods and results** Patients were included from a prospective, international registry of consecutive patients who underwent CCTA for evaluation of coronary artery disease. ASCVD risk groups were <7.5% (low), 7.5–20% (intermediate), and ≥20% (high). Among the ASCVD risk groups, the three coronary arteries were compared regarding quantified plaque volume and composition. Whole-heart plaque quantification was performed in 1340 patients (age 60 ± 9 years, 58% men). Across low, intermediate, and high ASCVD risk patients, the volume of plaque increased proportionally but was least in the LCx (7.4, 9.0, and 25.3 $mm^3$, respectively) as compared with the RCA (19.3, 32.6, and 67.0 $mm^3$,

* Corresponding author. Tel: +1 (404) 518 3021. E-mail: les2035@med.cornell.edu

respectively, all $P \leq 0.006$) and LAD (39.9, 60.8, and 93.3 $mm^3$, respectively, all $P < 0.001$). In each ASCVD risk group, the composition of plaque in the LCx exhibited the least necrotic core and fibrofatty plaque ($P < 0.05$ vs. LAD and RCA).

**Conclusion** Among patients with varying risk of ASCVD, plaque in the LCx is decidedly less and is comprised of less non-calcified plaque supporting prior evidence of the lower rates of acute coronary events in this vessel.

## Graphical Abstract




**Keywords** coronary artery disease • coronary computed tomography angiography • atherosclerotic cardiovascular disease • coronary arteries • plaque composition • plaque distribution

# Introduction

Coronary computed tomography angiography (CCTA) has become the non-invasive standard approach to diagnosing obstructive coronary artery disease (CAD) and serves as an effective alternative to invasive coronary angiography.[1] In addition to evaluation of stenosis severity,[2,3] CCTA allows for whole-heart quantification of plaque volume and composition, with results validated against intravascular ultrasound (IVUS).[4] Quantified plaque burden, as well as plaque composition, has been associated with clinical outcomes and the progression of coronary atherosclerosis.[5,6] Notably, low-density plaque has been reported as a precursor feature of an acute coronary syndrome (ACS),[7] while statin therapy results in a shift to more calcified plaque and is commonly thought to exert plaque stability and reduce risk for major coronary events.[8,9] Traditionally, data examining atherosclerotic burden have been pooled across the coronary arteries. However, our group recently published an overview of the differences in plaque burden and composition between the three major epicardial arteries [i.e. the left anterior descending (LAD), right coronary artery (RCA), and left circumflex (LCx) artery], based on quantitative CCTA analysis.[10] These findings may potentially underlie the observed differences in risk for ACS in the different coronary arteries.[11]

The AtheroSclerotic CardioVascular Disease (ASCVD) risk by pooled cohort equation (PCE) is associated with significant CAD burden detected on CCTA and is a reliable predictor for future ASCVD events.[12,13] Although the ASCVD risk score has well-established in asymptomatic individuals, the association between the 10-year ASCVD risk and volumetric measurement of coronary atherosclerotic plaque as derived from CCTA[10] has not been examined. Therefore, we aimed to evaluate the relationship between 10-year ASCVD risk and the presence, severity, and constitution of coronary atherosclerosis in the three major epicardial coronary arteries when quantitatively evaluated on CCTA.

# Methods

## Study design and patients

The PARADIGM (*P*rogression of *A*the*R*osclerotic *P*l*A*que *D*eterm*I*ned by Computed Tomo*G*raphic Angiography *I*Maging) study is an observational dynamic cohort that prospectively enrolled patients with suspected or known CAD from 13 sites across 7 countries, undergoing CCTA. Details on the study design have been published previously.[14] For the current analysis, exclusion criteria were prior diagnosis of CAD or revascularization ($n = 595$) or missing analysis from an individual coronary artery on CCTA ($n = 317$). Accordingly, the current population consists of 1340 patients (including 4020 coronary arteries).

## Cardiovascular risk factors and the ASCVD risk score

Demographic data, targeted medical history, and clinical cardiovascular risk factors were prospectively collected at each study site. Standardized definitions of cardiovascular risk factors were used.[15] The 10-year ASCVD risk was calculated for each patient using the pooled cohort equations.[12] Patients were categorized according to their 10-year ASCVD risk into groups of low risk (<7.5%), intermediate risk (≥7.5% to <20%), and high risk (≥20%). Diabetes mellitus was defined as fasting glucose ≥126 mg/dL or the use of insulin and/or oral hypoglycaemic agents. Hypertension was defined as a documented history of high blood pressure or treatment with antihypertensive medication. Hyperlipidaemia was defined as untreated high serum cholesterol or treatment with lipid-lowering medication. Smoking was defined as current smoking at the time of CCTA.

## CCTA acquisition and interpretation

All CCTAs were performed in accordance with the Society of Cardiovascular Computed Tomography guidelines.[16] Imaging datasets from each participating site were transferred to a core laboratory for blinded image analysis. All computations were performed by level III experienced readers blinded to clinical data, using quantitative plaque software (QAngioCT Research Edition v2.1.9.1, Medis Medical Imaging Systems, Leiden, The Netherlands).[17]

Details on the interpretation protocol have been described previously.[18] In short, all coronary segments with a diameter ≥2 mm were evaluated according to an adapted American Heart Association model for coronary segment classification.[19] Presence of coronary atherosclerotic plaque was defined as any tissue ≥1 $mm^2$ identified in >2 planes, within or adjacent to the lumen that could be discriminated from surrounding structures.[2,19] Plaque volume ($mm^3$) of segments was summed to generate vessel-level plaque volume, which was categorized according to pre-existing Hounsfield Unit thresholds into compositional subtypes of necrotic core (-30 to 30 HU); fibrofatty (30 to 130 HU); fibrous (131 to 350 HU); and calcified plaque (≥350 HU). Total plaque volume was adjusted for vessel volume ($mm^3$) to calculate PAV (%).[20] For each coronary artery, compositional build-up of plaque was expressed as the percentage of total plaque volume consisting of each compositional subtype (subtype volume/total plaque volume × 100, %). Within each patient, plaque distribution was expressed as the percentage of all patient plaque volume present in the separate coronary arteries (coronary artery plaque volume/patient plaque volume × 100). Furthermore, diameter stenosis (%) was quantified as the percentage of reduced lumen diameter.

## Study endpoints

Study endpoints included the total volume of atherosclerotic plaque as well as varying compositional subgroups, notable low density or necrotic core, and calcified plaque.

## Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range), while categorical variables are presented as absolute numbers (percentage). Continuous variables were compared with the Friedman test and Wilcoxon signed-rank test with post-hoc Bonferroni correction for multiple comparisons. Categorical variables were compared with the $\chi^2$ test. The distribution of plaque volume over the three major coronary arteries (expressed as % of all patient plaque volume in each coronary artery) was expressed for each ASCVD risk group in ternary plots. Two-tailed *P*-values <0.05 were considered statistically significant. All analyses were performed in SPSS version 25 (IBM Corporation, Armonk, NY, USA) and SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

# Results

## Patients

A total of 1340 patients (age 60.4 ± 9.3 years; 57.6% men) were included in the current study (*Table 1*). A majority of patients were referred for CCTA for evaluation of anginal symptoms (84.8%).

**Table 1 Patient characteristics at the time of CCTA**

| | Patients ($n$ = 1340) |
|---|---|
| Age, years | 60.4 ± 9.3 |
| Male | 772 (57.6%) |
| BMI, kg/m$^2$ | 25.3 ± 3.3 |
| ASCVD risk score, % | 9.5 (4.7–18.1) |
| Cardiovascular risk profile | |
| Diabetes mellitus | 276 (20.6%) |
| Hypertension | 706 (52.9%) |
| SBP, mmHg | 129.6 ± 17.7 |
| DBP, mmHg | 78.1 ± 10.8 |
| Hyperlipidaemia | 509 (38.2%) |
| Current smoker | 238 (17.9%) |
| Family history of CAD | 384 (28.7%) |
| Anginal symptoms[a] | 1129 (84.8%) |
| Medications | |
| Aspirin | 492 (37.2%) |
| β-blockers | 368 (27.9%) |
| Calcium channel blockers | 287 (21.8%) |
| Diuretics | 119 (9.0%) |
| RAAS inhibitors | 379 (28.8%) |
| Statins | 519 (40.4%) |
| Lipid panel, mg/dL | |
| Total cholesterol | 190.5 ± 40.2 |
| LDL-c | 115.9 ± 34.9 |
| HDL-c | 51.1 ± 13.9 |
| Triglycerides | 146.1 ± 87.5 |

All values are expressed as mean ± standard deviation, $n$ (%), or median (interquartile range).
ASCVD, AtheroSclerotic CardioVascular Disease; BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; RAAS, renin–angiotensin–aldosterone system; SBP, systolic blood pressure.
[a]Asymptomatic patients in this registry met clinical indications for CCTA, including pre-operative risk evaluation, prior stress testing, or a history of non-cardiac atherosclerosis.

Prevalence of clinical cardiovascular risk factors ranged from 17.9% (current smoking) to 52.5% (hypertension). Median ASCVD risk in the population was 9.5% (4.7–18.1%) with 545 patients (40.7%) being at low ASCVD risk, 513 patients (38.3%) at intermediate risk, and 282 patients (21.0%) at high risk. At the time of CCTA, 40.4% of patients were on statin therapy.

## Vessel-specific prevalence of atherosclerotic plaque according to ASCVD Risk

Findings regarding the presence and extent of coronary atherosclerosis across each ASCVD risk group are shown in *Table 2*. Approximately one-third of low-risk patients had no atherosclerotic plaque (36.7%) or had only one coronary artery with plaque (30.5%). The prevalence of multi-vessel atherosclerotic plaque was higher among patients with intermediate (51.3%), and high-risk scores (68.5%, $P < 0.001$ for trend).

Across all three major coronary arteries, there was a graded increase in the prevalence of atherosclerotic plaque by the ASCVD risk score, with high ASCVD risk patients exhibiting the greatest prevalence of plaque ($P < 0.001$ for the LAD, RCA, and LCx). Among low and intermediate ASCVD risk groups, vessel-specific prevalence of atherosclerotic plaque was lowest in the LCx (22.0% and 31.8%) as compared with the RCA (29.0% and 44.8%, $P = 0.01$ and $P < 0.001$) and LAD (58.7% and 74.5%, both $P < 0.001$). Among high-risk patients, prevalence of atherosclerotic plaque was also higher in LAD (83.7%, $P < 0.001$ vs. RCA and LCx) but was not significantly different between the RCA (56.7%) and LCx (52.5%, $P = 0.68$). Patients at higher ASCVD risk showed higher maximal diameter stenosis in all three coronary arteries (LAD: $P < 0.001$, RCA: $P = 0.029$, and LCx: $P = 0.006$). When a patient had single-vessel atherosclerotic plaque, it was most often located in the LAD across all ASCVD risk groups (*Table 3*; $P = 0.18$ for trend).

## Vessel-specific plaque quantification and composition according to ASCVD risk

An overview of vessel-specific atherosclerotic plaque quantification and composition for each ASCVD risk group is presented in *Figure 1* and Supplementary data online, *Table S1*.

*Among low-risk patients* (*Figure 1A*), plaque volume was lowest in the LCx (7.4 ± 27.7 mm$^3$), followed by the RCA (19.3 ± 57.8 mm$^3$; $P = 0.006$), and highest in the LAD (39.9 ± 63.2 mm$^3$; $P < 0.001$). Regarding plaque composition, percentages of necrotic core, and fibrofatty plaque were significantly lower in the LCx (16.7%) as compared with the RCA (22.3%) and LAD (22.9%; both $P < 0.001$). Percentages of calcified plaque were highest in the LCx (35.5%), albeit not statistically different from the RCA (27.6%; $P = 0.12$) or LAD (27.8%; $P = 0.10$).

*Among intermediate-risk patients* (*Figure 1B*), similar results were noted. Plaque volume was lowest in the LCx (9.0 ± 23.9 mm$^3$), followed by the RCA (32.6 ± 68.0 mm$^3$; $P < 0.001$) and LAD (60.8 ± 80.1 mm$^3$; $P < 0.001$). Percentages of necrotic core and fibrofatty plaque were lowest in the LCx ($P < 0.001$ vs. LAD and RCA), while percentages of calcified plaque were highest in the LCx ($P = 0.003$ vs. LAD and $P = 0.009$ vs. RCA).

*Similarly, among patients with high ASCVD risk scores* (*Figure 1C*), the LCx showed lowest plaque volume [25.3 ± 57.4 mm$^3$ vs. 67.0 ± 137.8 mm$^3$ (RCA) and 93.9 ± 113.5 mm$^3$ (LAD); both $P < 0.001$] and lowest percentage of necrotic core and fibrofatty plaque ($P < 0.001$ vs. RCA and LAD). Percentages of calcified plaque were highest in the LCx (41.5%), significantly so when compared to the RCA (34.3%; $P = 0.013$) but not to the LAD (36.6%; $P = 0.074$). Similar patterns were observed when using % atheroma volume as the comparator across the ASCVD risk groups (Supplementary data online, *Table S1*).

Differences between the coronary arteries existed among subgroups of patients with and without individual cardiovascular risk factors as well (Supplementary data online, *Table S2*), as well as among patients treated with and without statins (Supplementary data online, *Table S3*).

## Distribution of plaque volume over the coronary arteries

In *Figure 2*, the distribution of plaque over the three coronary arteries (expressed as percentages of all plaque volume in each separate coronary artery) is shown. Among patients with low- to borderline

**Table 2 Vessel-specific prevalence and extent of atherosclerotic plaque according to ASCVD risk**

| | 10-year ASCVD risk groups | | | *P*-value |
|---|---|---|---|---|
| | Low (*n* = 545) | Intermediate (*n* = 513) | High (*n* = 282) | |
| Number of coronary arteries with atherosclerotic plaque | | | | <0.001 |
| None | 200 (36.7%) | 100 (19.5%) | 33 (11.7%) | |
| One | 166 (30.5%) | 150 (29.2%) | 56 (19.9%) | |
| Two | 105 (19.3%) | 164 (32.0%) | 91 (32.3%) | |
| Three | 74 (13.6%) | 99 (19.3%) | 102 (36.2%) | |
| Vessel-specific prevalence of atherosclerotic plaque | | | | |
| LAD | 320 (58.7%)****** | 382 (74.5%)****** | 236 (83.7%)****** | <0.001 |
| RCA | 158 (29.0%)***** | 230 (44.8%)***** | 160 (56.7%)* | <0.001 |
| LCx | 120 (22.0%)*** | 163 (31.8%)*** | 148 (52.5%)* | <0.001 |
| Maximal diameter stenosis among diseased coronary arteries, % | | | | |
| LAD | 19.2 [10.7–28.6] | 23.3 [13.3–33.9] | 25.5 [15.3–39.1] | <0.001 |
| RCA | 15.3 [7.8–29.1] | 20.8 [11.8–32.2] | 22.6 [12.6–35.3] | 0.029 |
| LCx | 14.9 [7.9–23.7] | 15.5 [9.9–25.3] | 20.4 [10.5–30.5] | 0.006 |

ASCVD, AtheroSclerotic CardioVascular Disease; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery.
*Within each ASCVD risk group (vertically), significant differences (paired $P < 0.05$) between coronary arteries are marked as compared with LAD;
**compared with RCA;
***compared with LCx.

**Table 3 Location of atherosclerotic plaque among patients with single-vessel plaque**

| | 10-year ASCVD risk groups | | | *P*-value |
|---|---|---|---|---|
| | Low (*n* = 166) | Intermediate (*n* = 150) | High (*n* = 56) | |
| Location of atherosclerotic plaque | | | | 0.18 |
| LAD | 147 (88.6%) | 126 (84.0%) | 47 (83.9%) | |
| RCA | 12 (7.2%) | 15 (10.0%) | 4 (7.1%) | |
| LCx | 7 (4.2%) | 9 (6.0%) | 5 (8.9%) | |

ASCVD, AtheroSclerotic CardioVascular Disease; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery.

ASCVD risk scores, most plaque was located in the LAD [84.9% (46.4–100) %], with small percentages in the RCA [0% (0–35.7) %], and LCx [0% (0–9.0) %]. As indicated by the red-coloured area, having 100% of plaque located in the LAD was commonly observed. Among patients with intermediate ASCVD risk scores, percentage of the plaque located in the LAD was lower [73.5% (43.4–100) %], while the percentage of plaque located in the RCA [10.8% (0–40.9) %] and LCx [0% (0–11.3) %] were higher. This trend continued among patients with high ASCVD scores [RCA: 17.8% (0–48.5) %; LCx 5.1% (0–19.7) %], but the majority of plaque remained located in the LAD [60.9% (36.2–89.7) %].

# Discussion

This study demonstrates the greater extent of atherosclerotic plaque among patients in higher ASCVD risk groups. Plaque was predominantly located in the LAD in all risk groups. Quantified plaque volume was lowest in the LCx, followed by the RCA and LAD in each risk group. Interestingly, plaque in the LCx consisted of markedly less necrotic core and fibrofatty components across the ASCVD risk groups (supporting the evidence of a lower ACS risk and potentially more stable atherosclerosis[11]). Earlier, we reported differences between the coronary arteries on quantified CCTA analysis.[10] This study extends these prior findings by examining vessel-specific differences among patients of varying ASCVD risk.

## Relation between ASCVD risk and the extent of coronary atherosclerosis

As atherosclerotic plaque becomes more extensive across multiple diseased coronary arteries, acute coronary event risk increases, and ongoing symptoms more often lead to coronary revascularization.[21] This study further elaborates on the complex relationship between ASCVD risk and the burden of atherosclerosis across the three

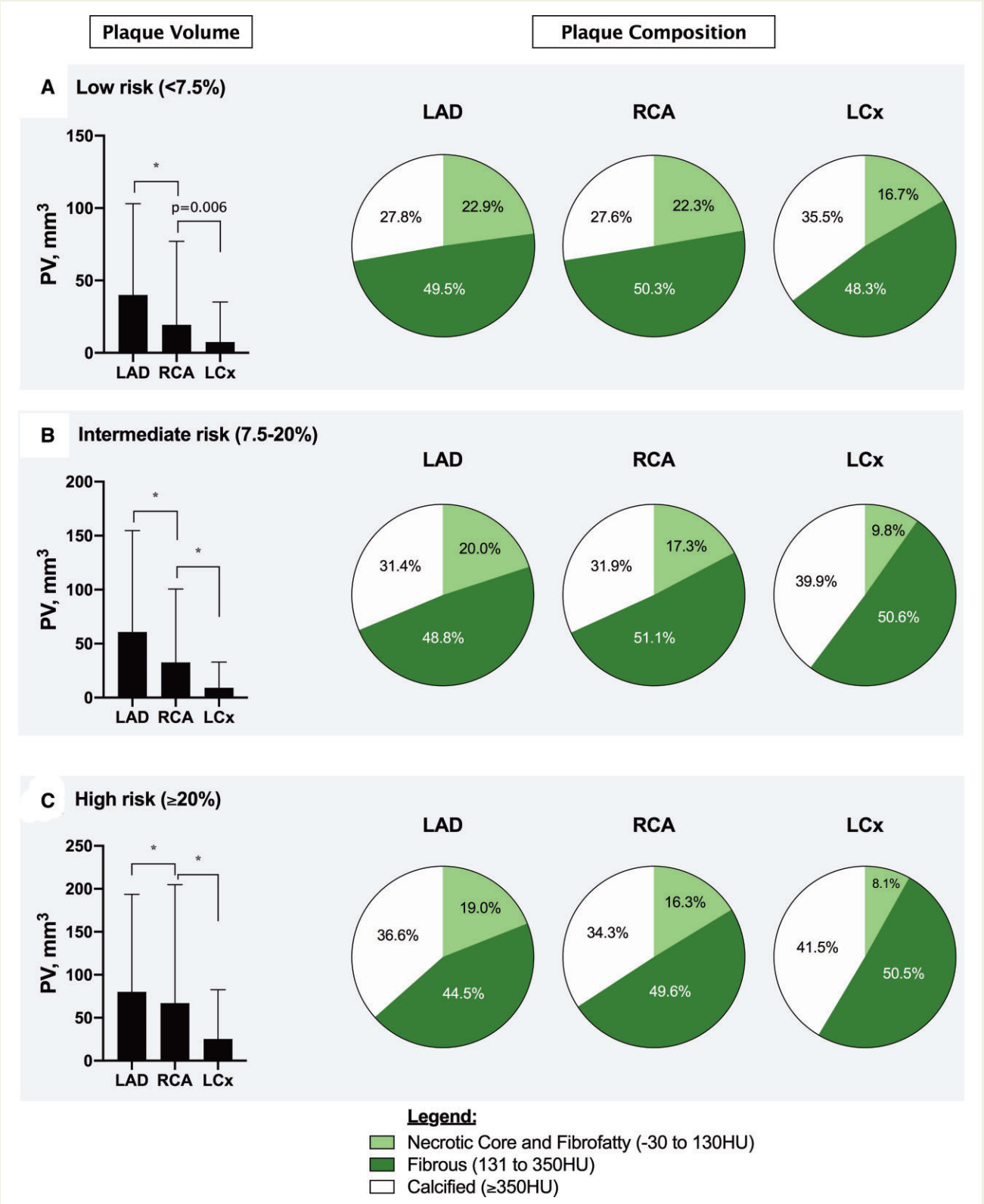



**Figure 1** Vessel-specific plaque volume and plaque composition in patients with (*A*) low ASCVD risk, (*B*) intermediate ASCVD risk, and (*C*) high ASCVD risk. Vessel-specific mean (SD) plaque volume is presented in bar charts on the left. In each ASCVD risk group, the LCx showed lowest plaque volume, followed by the RCA, and LAD. On the right, average plaque composition per coronary artery is presented as mean percentages of all plaque volume made up by the compositional plaque subtypes. In each ASCVD risk group, percentages of necrotic core and fibrofatty plaque types were lowest in the LCx as compared with the LAD and RCA. *$P < 0.001$.

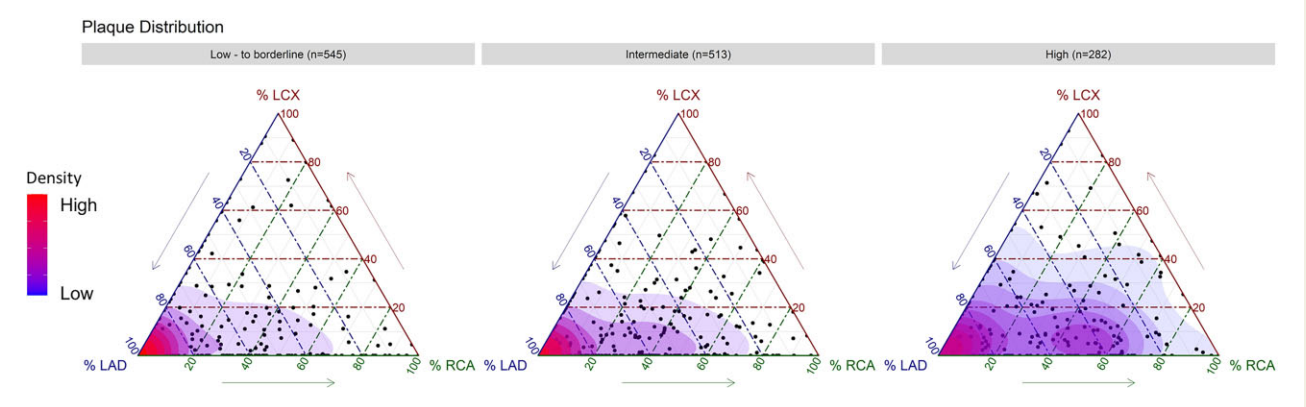



**Figure 2** Distribution of plaque volume over the three coronary arteries, expressed as the percentage of plaque volume located in the LAD (blue side), RCA (green side), and LCx (red side). Distribution of plaque volume over the three coronary arteries is presented in ternary plots. The sides of the triangle reflect percentages of plaque volume located in the LAD (blue side), RCA (green side), and LCx (red side). The coloured shade represents the plot density; the higher, the more patients have a plaque distribution represented in that area of the plot. The majority of plaque was located in the LAD in all ASCVD risk groups. From left to right: patients with low, intermediate, and high ASCVD risk.

major coronary arteries. Prior observations in asymptomatic individuals have similarly shown that higher risk patients have more prevalent coronary artery calcium.[22]

## CCTA provides individualized risk assessment over pooled ASCVD Risk

ASCVD risk from PCE is a reliable predictor of 10-year risk of cardiovascular events and is currently recommended for risk evaluation for primary prevention strategies.[23] However, there is recent evidence suggesting that the individual risk of a patient may not be completely reflected by their ASCVD risk. Data from the Progression of Early Subclinical Atherosclerosis study show the high prevalence of subclinical atherosclerosis in risk factor-free patients, with normal low-density lipoprotein cholesterol levels.[24] In a substudy from MESA, 17% of patients without any traditional ASCVD risk factors had CACS of >100. Importantly, patients without any ASCVD risk factors but high CACS (>300) showed markedly higher event rates than patients with ≥3 cardiovascular risk factors but no detected coronary calcium.[25] In this study, 63.3% of patients with low- to borderline ASCVD risk had atherosclerotic plaque, supporting the concept that CCTA could provide additional insights in the risk of individual patients over the pooled ASCVD risk.[15,26]

## Vessel-specific CCTA findings according to ASCVD risk

Most studies assess plaque burden on a patient- or lesion-level, whereas this study compared volumetric and compositional differences in the three coronary arteries. The highest prevalence of atherosclerotic was observed in the LAD within each ASCVD risk group. These findings potentially indicate earlier onset of atherosclerosis in the LAD, as compared with the RCA and LCx. Indeed, when stratifying for age, the prevalence of atherosclerotic plaque was consistently highest in the LAD and reaching half of patients ≤50 years old (Supplementary data online, *Figure S1*). This hypothesis is supported by results from the Multi-Ethnic Study of Atherosclerosis (MESA) study, where 3112 individuals with baseline coronary artery calcium scores (CACS) of 0 most frequently developed calcification in the LAD on follow-up (44% vs. 12% in the RCA and 10% in the LCx).[27] Furthermore, the lowest quantitative plaque volume was noted in the LCx (in comparison with the RCA and LAD) among all ASCVD risk groups. This is in line with evidence from IVUS, optical coherence tomography (OCT), and CCTA, showing the lesser degree of disease in the LCx.[28–30]

In this study, plaque composition in the LCx consisted of significantly less necrotic core and fibrofatty plaque (i.e. non-calcified or vulnerable plaque), as compared with the LAD and RCA. Among patients experiencing myocardial infarction following CCTA, culprit lesion precursors showed significantly higher necrotic core volumes on baseline CCTA than matched non-culprit lesion precursors.[7] The relationship between calcified plaque and cardiovascular events has been described as being more nuanced. Whereas absolute calcified plaque burden, often expressed as CACS, is a robust predictor of adverse events,[31,32] presence of 'hyperdense' calcified plaque (>1000 HU),[33] as well as a high percentages of total plaque consisting of calcified plaque,[8] are inversely related to adverse events and indicate stable plaque. For the current report, the higher percentages of calcified plaque in the LCx as compared to the LAD and RCA potentially indicate presence of more stable plaque.

## Registry limitations

The current study has several limitations. First, the observational nature of PARADIGM renders selection and other types of bias likely. Patients in this registry were followed up for a second CCTA, thereby excluding a majority of patients with normal coronary arteries or severe atherosclerosis at baseline, who were likely to undergo coronary revascularization soon after their baseline CCTA. Second, no differentiation was made between patients with controlled and uncontrolled risk factors. Despite this, patients with higher ASCVD risk did show higher extent and burden of atherosclerosis. Last, the semi-automated quantitative plaque analysis software requires manual adjustments.

# Conclusions

Examining patients undergoing CCTA for evaluation of CAD, we report existing differences between the coronary arteries among patients of varying ASCVD risk. The LCx showed the lowest quantified plaque volume, along with the least vulnerable plaque characteristics, as compared to the RCA and LAD. The majority of plaque was located in the LAD across all ASCVD risk groups. These findings have implications for vessel-specific outcome and underline the potential of CCTA to nuance the risk assessment as from the more general ASCVD risk scores.

# Supplementary data

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

## Acknowledgements

Dr James K. Min was involved in this registry prior to leaving Weill Cornell Medical College. Currently, he is an employee of Cleerly, Inc. He is not listed as an author as he did not contribute to the current manuscript, but we acknowledge and are grateful for his contributions to this registry. We also thank all PARADIGM investigators for their continued collaboration.

## Funding

This work was supported by the Leading Foreign Research Institute Recruitment Program through the National Research Foundation (NRF) of Korea funded by the Ministry of Science and ICT (MSIT) (grant no. 2012027176). The study was also funded in part by a grant from the Dalio Foundation (New York, NY, USA).

**Conflict of interest:** K.C. is a non-compensated medical advisor for Heartflow, Inc. L.J.S. is on the scientific advisory board for Covanos, Inc. J.A.L. is a consultant to and has stock options in Circle CVI and HeartFlow, receives research support from GE Healthcare and serves on the speakers' bureau for Philips and GE Healthcare. All other authors have no conflicts of interest to report.

## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

## References

1. Chow BJ, Small G, Yam Y, Chen L, Achenbach S, Al-Mallah M *et al.* Incremental prognostic value of cardiac computed tomography in coronary artery disease using CONFIRM: COroNary computed tomography angiography evaluation for clinical outcomes: an InteRnational Multicenter registry. *Circ Cardiovasc Imaging* 2011;**4**:463–72.
2. 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**:337–46.
3. 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**:684–92.
4. de Graaf MA, Broersen A, Kitslaar PH, Roos CJ, Dijkstra J, Lelieveldt BPF *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**:1177–90.
5. Hwang D, Kim HJ, Lee SP, Lim S, Koo BK, Kim YJ *et al.* Topological data analysis of coronary plaques demonstrates the natural history of coronary atherosclerosis. *JACC Cardiovasc Imaging* 2021;**14**:1410–21.
6. Lee SE, Sung JM, Rizvi A, Lin FY, Kumar A, Hadamitzky M *et al.* Quantification of coronary atherosclerosis in the assessment of coronary artery disease. *Circ Cardiovasc Imaging* 2018;**11**:e007562.
7. Chang HJ, Lin FY, Lee SE, Andreini D, Bax JJ, Cademartiri F *et al.* Coronary atherosclerotic precursors of acute coronary syndromes. *J Am Coll Cardiol* 2018;**71**:2511–22.
8. Jin HY, Weir-McCall JR, Leipsic JA, Son JW, Sellers SL, Shao M *et al.* The relationship between coronary calcification and the natural history of coronary artery disease. *JACC Cardiovasc Imaging* 2021;**14**:233–42.
9. Puri R, Nicholls SJ, Shao M, Kataoka Y, Uno K, Kapadia SR *et al.* Impact of statins on serial coronary calcification during atheroma progression and regression. *J Am Coll Cardiol* 2015;**65**:1273–82.
10. Bax AM, van Rosendael AR, Ma X, van den Hoogen IJ, Gianni U, Tantawy SW *et al.*; PARADIGM Investigators. Comparative differences in the atherosclerotic disease burden between the epicardial coronary arteries: quantitative plaque analysis on coronary computed tomography angiography. *Eur Heart J Cardiovasc Imaging* 2021;**22**:322–30.
11. Antoni ML, Yiu KH, Atary JZ, Delgado V, Holman ER, van der Wall EE *et al.* Distribution of culprit lesions in patients with ST-segment elevation acute myocardial infarction treated with primary percutaneous coronary intervention. *Coron Artery Dis* 2011;**22**:533–6.
12. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R *et al.* 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;**63**(25 Pt B):2935–59.
13. Han D, Berman DS, Miller RJH, Andreini D, Budoff MJ, Cademartiri F *et al.* Association of cardiovascular disease risk factor burden with progression of coronary atherosclerosis assessed by serial coronary computed tomographic angiography. *JAMA Netw Open* 2020;**3**:e2011444.
14. 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.
15. van Rosendael AR, Bax AM, Smit JM, van den Hoogen IJ, Ma X, Al'Aref S *et al.* Clinical risk factors and atherosclerotic plaque extent to define risk for major events in patients without obstructive coronary artery disease: the long-term coronary computed tomography angiography CONFIRM registry. *Eur Heart J Cardiovasc Imaging* 2020;**21**:479–88.
16. 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**:435–49.
17. Park HB, Lee BK, Shin S, Heo R, Arsanjani R, Kitslaar PH *et al.* Clinical feasibility of 3D automated coronary atherosclerotic plaque quantification algorithm on coronary computed tomography angiography: comparison with intravascular ultrasound. *Eur Radiol* 2015;**25**:3073–83.
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**:1475–84.
19. 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**:342–58.
20. van Rosendael AR, Lin FY, Ma X, van den Hoogen IJ, Gianni U, Al Hussein O *et al.* Percent atheroma volume: optimal variable to report whole-heart atherosclerotic plaque burden with coronary CTA, the PARADIGM study. *J Cardiovasc Comput Tomogr* 2020;**14**:400–6.
21. Silverman MG, Harkness JR, Blankstein R, Budoff MJ, Agatston AS, Carr JJ *et al.* Baseline subclinical atherosclerosis burden and distribution are associated with frequency and mode of future coronary revascularization: multi-ethnic study of atherosclerosis. *JACC Cardiovasc Imaging* 2014;**7**:476–86.
22. Li Y, Zhu G, Ding V, Jiang B, Ball RL, Ahuja N *et al.* Assessing the relationship between American Heart Association atherosclerotic cardiovascular disease risk score and coronary artery imaging findings. *J Comput Assist Tomogr* 2018;**42**:898–905.
23. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ *et al.* 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019;**74**:e177–232.

24. Fernandez-Friera L, Fuster V, Lopez-Melgar B, Oliva B, Garcia-Ruiz JM, Mendiguren J *et al.* Normal LDL-cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors. *J Am Coll Cardiol* 2017; **70**:2979–91.
25. Silverman MG, Blaha MJ, Krumholz HM, Budoff MJ, Blankstein R, Sibley CT *et al.* Impact of coronary artery calcium on coronary heart disease events in individuals at the extremes of traditional risk factor burden: the Multi-Ethnic Study of Atherosclerosis. *Eur Heart J* 2014;**35**:2232–41.
26. Han D, Beecy A, Anchouche K, Gransar H, Dunham PC, Lee JH *et al.* Risk reclassification with coronary computed tomography angiography-visualized nonobstructive coronary artery disease according to 2018 American College of Cardiology/American Heart Association Cholesterol Guidelines (from the Coronary Computed Tomography Angiography Evaluation for Clinical Outcomes: an International Multicenter Registry [CONFIRM]). *Am J Cardiol* 2019;**124**:1397–405.
27. Alluri K, McEvoy JW, Dardari ZA, Jones SR, Nasir K, Blankstein R *et al.* Distribution and burden of newly detected coronary artery calcium: results from the Multi-Ethnic Study of Atherosclerosis. *J Cardiovasc Comput Tomogr* 2015;**9**: 337–44.e1.
28. Fujii K, Kawasaki D, Masutani M, Okumura T, Akagami T, Sakoda T *et al.* OCT assessment of thin-cap fibroatheroma distribution in native coronary arteries. *JACC Cardiovasc Imaging* 2010;**3**:168–75.
29. Iwasaki K, Matsumoto T, Aono H, Furukawa H, Nagamachi K, Samukawa M. Distribution of coronary atherosclerosis in patients with coronary artery disease. *Heart Vessels* 2010;**25**:14–8.
30. Wykrzykowska JJ, Mintz GS, Garcia-Garcia HM, Maehara A, Fahy M, Xu K *et al.* Longitudinal distribution of plaque burden and necrotic core-rich plaques in nonculprit lesions of patients presenting with acute coronary syndromes. *JACC Cardiovasc Imaging* 2012;**5**:S10–8.
31. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR *et al.* Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008;**358**:1336–45.
32. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA* 2004;**291**:210–5.
33. van Rosendael AR, Narula J, Lin FY, van den Hoogen IJ, Gianni U, Al Hussein O *et al.* Association of high-density calcified 1K plaque with risk of acute coronary syndrome. *JAMA Cardiol* 2020;**5**:282–90.