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# Comparative differences in the atherosclerotic disease burden between the epicardial coronary arteries: quantitative plaque analysis on coronary computed tomography angiography

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## Aims

Anatomic series commonly report the extent and severity of coronary artery disease (CAD), regardless of location. The aim of this study was to evaluate differences in atherosclerotic plaque burden and composition across the major epicardial coronary arteries.

## Methods and results

A total of 1271 patients (age  $60 \pm 9$  years; 57% men) with suspected CAD prospectively underwent coronary computed tomography angiography (CCTA). Atherosclerotic plaque volume was quantified with categorization by composition (necrotic core, fibrofatty, fibrous, and calcified) based on Hounsfield Unit density. Per-vessel measures

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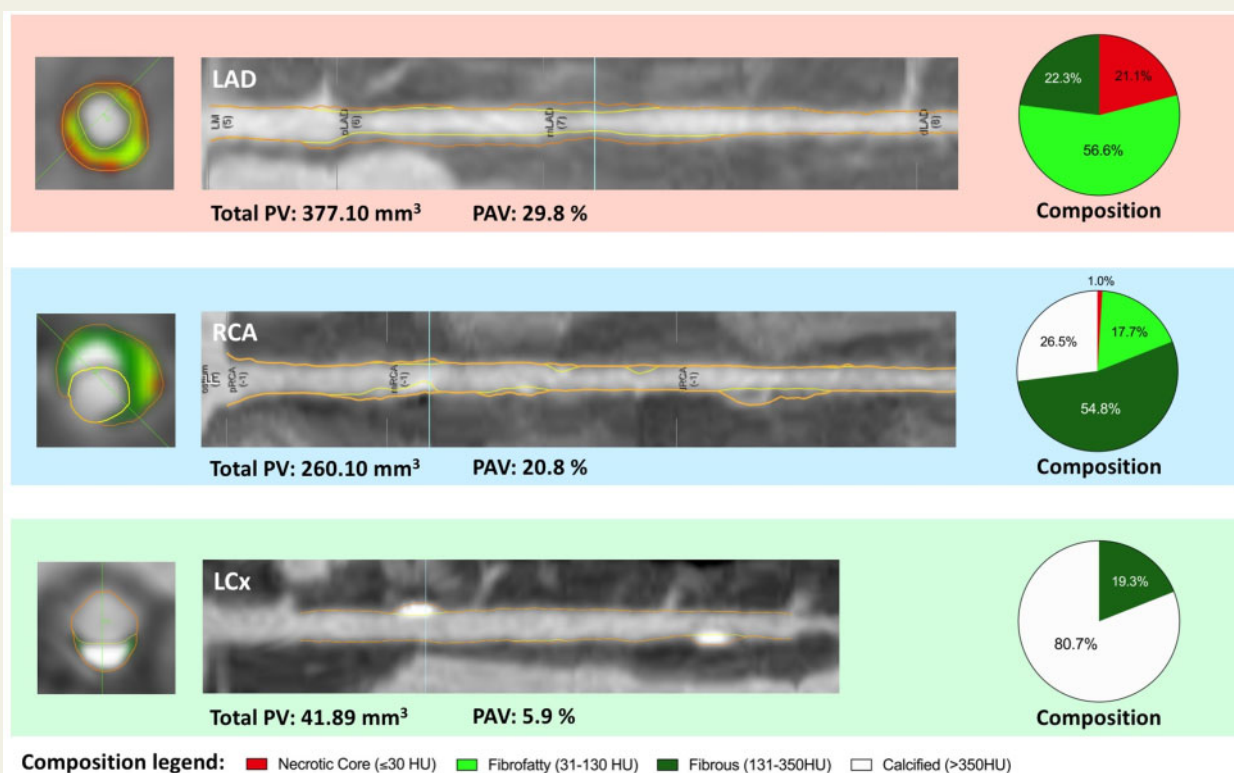
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were compared using generalized estimating equation models. On CCTA, total plaque volume was lowest in the LCx ( $10.0 \pm 29.4 \text{ mm}^3$ ), followed by the RCA ( $32.8 \pm 82.7 \text{ mm}^3$ ;  $P < 0.001$ ), and LAD ( $58.6 \pm 83.3 \text{ mm}^3$ ;  $P < 0.001$ ), even when correcting for vessel length or volume. The prevalence of  $\geq 2$  high-risk plaque features, such as positive remodelling or spotty calcification, occurred less in the LCx (3.8%) when compared with the LAD (21.4%) or RCA (10.9%,  $P < 0.001$ ). In the LCx, the most stenotic lesion was categorized as largely calcified more often than in the RCA and LAD (55.3% vs. 39.4% vs. 32.7%;  $P < 0.001$ ). Median diameter stenosis was also lowest in the LCx (16.2%) and highest in the LAD (21.3%;  $P < 0.001$ ) and located more distal along the LCx when compared with the RCA and LAD ( $P < 0.001$ ).

## Conclusion

Atherosclerotic plaque, irrespective of vessel volume, varied across the epicardial coronary arteries; with a significantly lower burden and different compositions in the LCx when compared with the LAD and RCA. These volumetric and compositional findings support a diverse milieu for atherosclerotic plaque development and may contribute to a varied acute coronary risk between the major epicardial coronary arteries.

## Graphical Abstract



## Keywords

coronary computed tomography angiography • coronary artery disease • coronary artery plaque composition

## Introduction

Atherosclerotic plaque imaging has rapidly advanced from initial studies using invasive techniques, such as intra-vascular ultrasound or optical coherence tomography<sup>1,2</sup> to more recent advancements using coronary computed tomography angiography (CCTA) as a non-invasive alternative for qualitative and quantitative measurement of atherosclerosis.<sup>3-5</sup> Within the field of anatomic imaging, there has

been extensive research establishing the prognostic significance and therapeutic benefit from intervention based on the severity and location of obstructive coronary artery disease (CAD).<sup>6-9</sup> Specifically, prior invasive angiographic data revealed that the left circumflex (LCx) coronary artery is more often observed with single when compared with multivessel CAD when compared with that in the left anterior descending (LAD) or right coronary artery (RCA).<sup>10</sup> Moreover, among patients with STEMI, the location of a culprit lesion

is reported less often in the LCx when compared with the LAD or RCA.<sup>11</sup> In stable patients, lower coronary artery calcium scores were also reported in the LCx when compared with the LAD or RCA.<sup>12</sup> These findings in largely smaller cohorts suggest a varied milieu for atherosclerosis development. To date, comprehensive comparisons between the epicardial coronary arteries concerning the presence and severity of coronary atherosclerosis have not been reported.

The Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography (PARADIGM) registry previously reported on alterations in atherosclerotic plaque with statin therapy.<sup>13</sup> In the current report, we undertook a comparative analysis of differences in the burden and composition of quantitative atherosclerotic plaque by the location of the epicardial coronary artery; primarily comparing the LCx with LAD and RCA. Differences were also compared based on correction for vessel volume, including analysis by the percent atheroma volume (PAV).

## Methods

### Study design

PARADIGM was a multinational, dynamic observational cohort that prospectively enrolled patients undergoing CCTA between 2003 and 2015.<sup>14</sup> The research protocol was approved by each centre's institutional review board. Details of the PARADIGM registry are found in the report by Lee et al.<sup>15</sup>

### Patient enrolment

A total of 2252 patients with suspected CAD undergoing CCTA were prospectively enrolled from 13 sites in 7 countries (Brazil, Canada, Germany, Italy, Portugal, South Korea, and the USA).<sup>14</sup> For this analysis, patients that had undergone revascularization (defined as percutaneous coronary intervention and/or coronary artery bypass grafting;  $n = 736$ ) were excluded, as well as patients with missing analysis of  $\geq 1$  coronary artery on CCTA ( $n = 245$ ). Thus, the current analysis included 1271 patients ( $n = 3813$  vessels).

### CCTA acquisition and interpretation

All CCTAs were performed in accordance with the Society of Cardiovascular Computed Tomography guidelines.<sup>16,17</sup> Datasets from each participating site were transferred to a core laboratory for blinded image analysis. Coronary atherosclerosis was evaluated on multiplanar and cross-sectional CCTA images. All computations were performed by level III experienced readers masked to clinical data, using quantitative plaque software (QAngioCT Research Edition v2.1.9.1, Medis Medical Imaging Systems, Leiden, the Netherlands).<sup>18</sup>

All coronary arteries with a diameter  $\geq 2$  mm were evaluated, according to the 17-segment American Heart Association model for coronary segment classification.<sup>17</sup> Presence of plaque was defined as any tissue  $\geq 1$  mm<sup>2</sup> identified in  $>2$  planes, within or adjacent to the lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or lumen.<sup>17,19</sup> Quantitative analysis was performed on a per-segment level. To generate vessel length (mm), vessel volume (mm<sup>3</sup>), lumen volume (mm<sup>3</sup>), and per-vessel plaque volume (mm<sup>3</sup>), measurements of all segments of each vessel, including side branches, were summed. PAV was calculated as follows:  $[(PV/vessel\ volume) \times 100] \%$ . Based on established Hounsfield Unit (HU) ranges, plaque composition was categorized as calcified ( $>350$  HU)<sup>20</sup>, fibrous (131–350 HU), and low-density [necrotic core ( $\leq 30$  HU) and fibrofatty (31–130 HU)]<sup>13,20,21</sup>. The proportion of total PV of the compositional

subtypes was calculated as:  $subtype\ \% = [(subtype\ PV/total\ per-vessel\ PV) \times 100] \%$ .

Furthermore, individual lesions were evaluated for composition (visually classified as calcified, mixed, or non-calcified), diameter stenosis (%), and high-risk plaque (HRP) defined as  $\geq 2$  of the following features: low-attenuation plaque, spotty calcification, positive remodelling, or napkin ring sign<sup>19,22</sup> and distance from the ostium to the point of minimal lumen diameter (mm). Low-attenuation plaque was defined as any lesion containing  $\geq 1$  voxel(s) with  $HU \leq 30$ .<sup>19,23</sup> Spotty calcification was defined by the presence of intra-lesional calcification  $<3$  mm.<sup>22,24</sup> A remodelling index was calculated as a maximal lesion vessel area divided by proximal reference vessel area, with positive remodelling defined by a remodelling index  $\geq 1.1$ .<sup>25</sup> A napkin ring sign was defined cross-sectionally with a central area of low attenuation plaque and a surrounding ring with higher attenuation plaque.

### Study endpoints

All analyses were performed on a per-vessel basis. The primary aim of this report was to compare differences in CCTA-derived atherosclerotic plaque volume between the three major epicardial coronary arteries. Secondary endpoints included comparisons by atherosclerotic plaque compositional subgroups and the location of the most stenotic lesion in the coronary artery.

### Statistical analysis

Continuous variables are presented as mean  $\pm$  SD or median with inter-quartile range (IQR), while categorical variables are presented as absolute numbers and percentages. Differences between categorical variables were compared using a  $\chi^2$  or Fisher's exact test. Continuous variables were compared using either a paired test (Friedman test for three-way or a Wilcoxon signed-rank test) or unpaired test (Mann–Whitney  $U$  test for per-lesion comparison), as appropriate. To account for within patient clustering of data, generalized estimating equations (GEE) models were used, including linear and logistic models. Odds ratios (ORs) and 95% confidence intervals were calculated. When noted, the GEE models included the atherosclerotic cardiovascular disease risk score, as a covariate. Two-tailed  $P$ -values  $<0.05$  were considered statistically significant. All analyses were performed in SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) and SPSS Statistics version 25 (IBM Corporation, Armonk, NY, USA).

## Results

### Baseline characteristics

From 2252 patients enrolled in the PARADIGM registry, 1271 (mean age  $60.3 \pm 9.3$  years; 57% men) were included in the current analysis (Table 1). A majority of enrolled patients were symptomatic prior to their CCTA (81%). The overall prevalence of CAD risk factors was 51.8% for hypertension, 37.5% for hyperlipidaemia, 19.8% for diabetes mellitus, and 18.4% for smoking.

### Quantitative measurement of atherosclerotic plaque on CCTA

CCTA measurements of the three major coronary arteries are presented in Table 2. On average, the LAD was the longest vessel ( $169.0 \pm 57.8$  mm), whereas the RCA was the largest vessel in terms of volume ( $1042.5 \pm 604.0$  mm<sup>3</sup>). The LCx was smaller in terms of vessel length ( $98.5 \pm 43.8$  mm) and vessel volume ( $476 \pm 305.9$  mm<sup>3</sup>) than the LAD and RCA ( $P < 0.001$  for both). Total plaque



**Table 2** Comparison of atherosclerotic plaque volume and composition between the major epicardial coronary arteries

| Vessel analysis                  | Mean ± SD or % |                |                | P-value              |                          |                          |
|----------------------------------|----------------|----------------|----------------|----------------------|--------------------------|--------------------------|
|                                  | LAD (N = 1271) | RCA (N = 1271) | LCx (N = 1271) | Overall <sup>a</sup> | LCx vs. LAD <sup>b</sup> | LCx vs. RCA <sup>b</sup> |
| Vessel length (mm)               | 169.0 ± 57.8   | 154.1 ± 51.5   | 98.5 ± 43.8    | <0.001               | <0.001                   | <0.001                   |
| Vessel volume (mm <sup>3</sup> ) | 900.4 ± 401.2  | 1042.5 ± 604.0 | 476.3 ± 305.9  | <0.001               | <0.001                   | <0.001                   |
| Lumen volume (mm <sup>3</sup> )  | 841.7 ± 381.6  | 1009.8 ± 586.8 | 466.3 ± 301.3  | <0.001               | <0.001                   | <0.001                   |
| Plaque volume (mm <sup>3</sup> ) | 58.6 ± 83.3    | 32.8 ± 82.7    | 10.0 ± 29.4    | <0.001               | <0.001                   | <0.001                   |
| Necrotic core (≤30 HU)           | 1.6 ± 5.3      | 0.6 ± 3.3      | 0.1 ± 1.2      | <0.001               | <0.001                   | <0.001                   |
| Fibrofatty (31–130 HU)           | 12.0 ± 24.2    | 5.8 ± 18.3     | 1.1 ± 5.2      | <0.001               | <0.001                   | <0.001                   |
| Fibrous (131–350 HU)             | 25.3 ± 36.8    | 15.8 ± 40.9    | 4.7 ± 14.6     | <0.001               | <0.001                   | <0.001                   |
| Calcified (>350 HU)              | 19.7 ± 41.2    | 10.7 ± 37.4    | 4.1 ± 14.4     | <0.001               | <0.001                   | <0.001                   |
| PAV (%)                          | 6.4 ± 8.1      | 2.8 ± 6.3      | 2.0 ± 5.2      | <0.001               | <0.001                   | <0.001                   |
| Number of lesions per vessel     | 1.10 ± 0.99    | 0.72 ± 1.15    | 0.42 ± 0.77    | <0.001               | <0.001                   | <0.001                   |
| ≥2 HRP features (%)              | 21.3           | 10.9           | 3.8            | <0.001               |                          |                          |
| Low-attenuation plaque (%)       | 15.1           | 7.2            | 1.8            | <0.001               |                          |                          |
| Spotty calcification (%)         | 13.8           | 6.3            | 2.9            | <0.001               |                          |                          |
| Positive remodelling (%)         | 56.1           | 33.0           | 22.7           | <0.001               |                          |                          |
| Napkin-ring sign (%)             | 0.5            | 0.2            | 0.0            | 0.002                |                          |                          |
| Number of HRP lesions per vessel | 0.21 ± 0.43    | 0.11 ± 0.37    | 0.04 ± 0.20    | <0.001               | <0.001                   | <0.001                   |

HRP, high-risk plaque; HU, Hounsfield Units; LAD, left anterior descending; LCx, left circumflex; PAV, percent atheroma volume; RCA, right coronary artery.

<sup>a</sup>Friedman test.

<sup>b</sup>Wilcoxon signed-rank test.

has been little attention to differences in the burden and composition of atherosclerotic plaque between the major epicardial coronary arteries. Our results revealed that the LCx contained a lower burden of plaque, even when correcting for vessel volume ( $P < 0.001$ ). Compared with the other coronary arteries, the LCx also showed a different compositional structure of plaque, containing a larger proportion of calcified plaque along with smaller proportions of low-density plaque. Moreover, low-density plaque, which is often associated with higher risk for future coronary events, was less often present in the LCx when compared with the LAD and RCA. These findings have implications for disease detection and support the variable findings reported for ischaemia provocation across the epicardial coronary tree. Importantly, the occurrence of more distal disease that is more calcified with a lower plaque burden and fewer high-risk plaque features is congruent with more stable atherosclerosis and a reduced likelihood for future ischaemic events.

### Jeopardized myocardium and risk across the epicardial coronary arteries

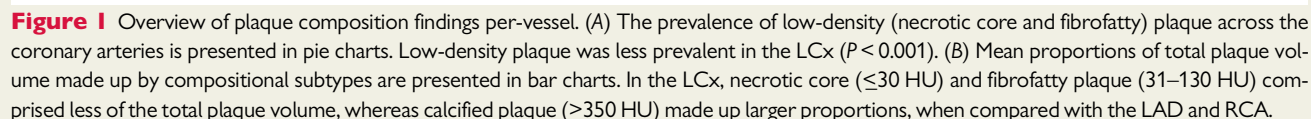
Risk assessment of patients based on angiographic findings have been previously reported. Several risk scores, such as the Duke CAD prognostic index<sup>6</sup> or SYNTAX score,<sup>26</sup> uniquely identify risk associated with an LAD stenosis, especially in a proximal location. This higher risk status relates to the sizeable proportion of jeopardized myocardium subtended by the LAD.<sup>27</sup> Additionally, the prevalence of culprit lesions when examined in STEMI series is notably less in the LCx. Additional research findings also reveal that lateral electrocardiographic leads or LCx stress imaging vascular territory

abnormalities have a significantly lower diagnostic accuracy; albeit also impacted upon by suboptimal localization and visualization.

The evidence is far from robust and for most of the analyses ranking disease burden and risk, the LCx has historically been the focus of fewer and smaller patient series. Several studies including patients with suspected CAD have shown a lower prevalence of significant stenosis in the LCx.<sup>28,29</sup> The absence of coronary stenosis occurs more often in the LCx (44%) when compared with the LAD (14%); in addition, a more severe stenosis ( $\geq 50\%$ ) is more often observed in the LAD when compared with the RCA and LCx.<sup>28</sup> In addition, Kang et al.<sup>29</sup> examined patients with significant stenosis on invasive coronary angiography, revealing the lowest prevalence of obstructive CAD in the LCx. These data support the improved survival reported for patients with one-vessel obstructive CAD in the LCx when compared with that of patients with isolated obstructive CAD in the LAD or RCA.<sup>30</sup>

### Potential mechanisms influencing atherosclerotic plaque between the epicardial coronary arteries

Our analysis reveals a lower burden of atherosclerosis in the LCx on CCTA, suggesting the possibility of a more stable and less turbulent atherosclerotic milieu in that vessel. These data are supported by prior evidence noting higher fractional flow reserve measures in the LCx when compared with the LAD, despite equivalent percent stenosis.<sup>31</sup> It is purported that local haemodynamic forces play an important role in the development of atherosclerosis in the coronary arteries.<sup>32,33</sup> Wall shear stress, the drag force of circulating blood onto the endothelial surface of the artery, is not uniformly distributed across the coronary arteries, with areas of low wall shear stress



|               | Adjusted odds ratio (aOR) and 95% confidence interval (CI)      |         |                                         |         |
|---------------|-----------------------------------------------------------------|---------|-----------------------------------------|---------|
|               | LAD vs. LCx                                                     |         | RCA vs. LCx                             |         |
|               | aOR of any plaque (95% CI) <sup>a</sup>                         | P-value | aOR of any plaque (95% CI) <sup>a</sup> | P-value |
|               |                                                                 |         |                                         |         |
| Necrotic core | 3.5 (2.6–4.6)                                                   | <0.001  | 2.8 (2.0–3.9)                           | <0.001  |
| Fibrofatty    | 4.1 (2.8–6.0)                                                   | <0.001  | 2.3 (1.6–3.3)                           | <0.001  |
| Calcified     | 1.2 (0.8–1.9)                                                   | 0.379   | 0.8 (0.5–1.2)                           | 0.280   |
|               | Ratio of composition type volume/total per-vessel plaque volume |         |                                         |         |
|               | LAD vs. LCx                                                     |         | RCA vs. LCx                             |         |
|               | Ratio (95% CI) <sup>b</sup>                                     | P-value | Ratio (95% CI) <sup>b</sup>             | P-value |
|               |                                                                 |         |                                         |         |
| Necrotic core | 1.8 (1.3–2.6)                                                   | 0.001   | 1.7 (1.2–2.4)                           | 0.004   |
| Fibrofatty    | 1.8 (1.5–2.2)                                                   | <0.001  | 1.6 (1.2–2.0)                           | <0.001  |
| Calcified     | 0.8 (0.7–0.9)                                                   | <0.001  | 0.8 (0.6–0.9)                           | <0.001  |

<sup>b</sup> Calculated from a linear GEE-model, adjusted for atherosclerotic cardiovascular disease risk score, and stain use. Ratios were calculated by dividing the proportions of compositional subtypes, in two vessels. E.g. the ratio for necrotic core in the LAD vs. LCx = ([necrotic core volume/plaque volume]<sub>LAD</sub> / [necrotic core volume/plaque volume]<sub>LCx</sub>).



## Supplementary data

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

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## Data availability

The data underlying this article cannot be shared publicly due to the patients' privacy. Data may be available upon reasonable request to the corresponding author, pending investigator approval of the study hypothesis and presence of an institutional data use agreement.

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**Conflict of interest:** K.C. is a non-compensated medical advisory board member of Heartflow Inc. J.K.M. has equity interest and is an employee of Cleerly, Inc. H.S. serves on the scientific advisory board of Phillips, has equity interest in Covanos, Inc., and has research grants from Medtronic, Abbott Vascular, and Phillips. L.J.S. serves on the scientific advisory board for Covanos, Inc. All other authors report no conflict of interest.

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