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ORIGINAL PAPER

Invasive coronary angiography findings across the CAD-RADS classification spectrum

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Abstract

The recently introduced coronary artery disease reporting and data system (CAD-RADS) evaluated by computed tomography and based on stenosis severity, might not adequately reflect the complexity of CAD. We explored the relationship between CAD-RADS and the spatial distribution, burden, and complexity of lesions by invasive coronary angiography (ICA). Stable patients who underwent coronary computed tomography angiography (CCTA) and ICA comprised the study population. Patients were classified according to the CAD-RADS: 0, No plaque; 1, 1–24% stenosis; 2, 25–49%; 3, 50–69%; 4A, 70–99%; 4B, left main stenosis or 3-vessel obstructive disease; and 5, total occlusion. Based on ICA findings, we calculated the SYNTAX score and the CAD extension index. Ninety-one patients were included, with a mean age of 61.4 ± 10.5 years (74% male). We found significant relationships between CAD-RADS and both the SYNTAX score ($p < 0.0001$) and the CAD extension index ($p < 0.0001$), although the complexity of coronary anatomy differed among patients with CAD-RADS ≥ 4A. Among patients with CAD-RADS < 4, the mean segment involvement score (SIS) was 8.4 ± 4.0, 52% of them with a SIS > 5. Of the 30 patients with CAD-RADS 5, 9 (30%) affected distal segments or secondary branches, and 9 (30%) had concomitant severe non-extensive disease at ICA. Regarding the spatial distribution of the non-occluded most severe lesions, 27 (44%) comprised distal segments or secondary branches. In the present study including a high-risk population, we identified diverse coronary anatomy complexity scenarios and relevant differences in spatial distribution sharing the same CAD-RADS classification.

Keywords Computed tomography · SYNTAX score · Coronary artery stenosis · Plaque burden

Introduction

Several multi-disciplinary imaging societies have endorsed a consensus document entitled coronary artery disease reporting and data system (CAD-RADS), aimed at standardizing coronary computed tomography angiography (CCTA) reports [1]. More recently, an analysis of the large multinational CONFIRM registry validated the prognostic value of the CAD-RADS, allowing risk stratification with reasonable accuracy. However, this study did not demonstrate an improvement in the prediction of death or myocardial infarction compared to other established classification systems such as Duke CAD index of traditional CAD reporting (area under the receiver operating characteristic curve of 0.7052, 0.7073, and 0.7095, respectively) [2]. CAD-RADS might provide a standardized tool for data collection and communication, not only for research purposes but also to facilitate insurance audits. Besides, the application of CAD-RADS would imply ensuing suggestions for subsequent patient management; leading to a consensus to advocate the inclusion of CAD-RADS reporting in all CCTA scans [3]. Nonetheless, CAD-RADS categories depend mostly on stenosis severity, while not adequately considering highly relevant prognostic features such as spatial distribution and burden of disease. Relying on stenosis severity for decision-making would be helpful in the acute chest pain setting [4]. In patients with stable CAD, however, this approach might not be adequate for appropriate risk stratification [5].

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Furthermore, it remains uncertain whether CAD-RADS can reflect the full complexity of CAD manifestation.

We therefore attempted to explore the relationship between CAD-RADS and the complexity, extent, and spatial distribution of coronary lesions assessed using invasive coronary angiography.

Methods

We retrospectively included stable patients with known or suspected CAD who were clinically referred for invasive coronary angiography (ICA), and in whom a CCTA was performed within 3 months before the ICA. All patients were in sinus rhythm, > 18 years old, able to maintain a breath-hold for at least 10 s, and did not have a history of contrast related allergy, renal failure, or hemodynamic instability. Patients with unstable angina, a history of myocardial infarction within the previous 30 days, coronary bypass graft surgery (CABG), or chronic heart failure were excluded. Patients with previous CABG were excluded since we aimed to explore the relationship between ICA and CCTA findings among native vessels, and the role of spatial distribution of lesions.

All scans were performed using a multidetector high definition scanner (Discovery HD 750, GE Healthcare, Milwaukee, USA), after intravenous administration of iodinated contrast (iobitridol, Xenetix 350TM, Guerbet, France). A total of 60-80 ml of iodinated contrast was injected using a dual-phase injection protocol, and image acquisition was performed after sublingual administration of 2.5–5 mg of isosorbide dinitrate. Patients with a heart rate of more than 65 bpm received 5 mg intravenous propranolol if needed in order to achieve a target heart rate of less than 60 bpm. All CCTA scans were acquired using prospective ECG-gating, as they involved previous protocols of CT myocardial perfusion. Iterative reconstruction was performed in all cases at 40% ASIR (Adaptive Statistical Iterative Reconstruction). Other scanner-related parameters were a collimation width of 0.625 mm and a slice interval of 0.625 mm.

Image analyses were performed off-line on a dedicated workstation, using a commercially available dedicated software tool (AW 4.6, GE Healthcare) by consensus of two experienced level 3 observers blinded to the clinical data and to the ICA findings. Axial planes, curved multiplanar reconstructions, and maximum intensity projections were used at 1-5 mm slice thickness, according to the 18-segment Society of Cardiovascular Computed Tomography classification [6]. Segments with a reference diameter lower than 1.5 mm were not included in the analysis. Based on CAD-RADS maximal degree of stenosis, patients were classified as follows: CAD-RADS 0: no plaque or stenosis; CAD-RADS 1: 1–24% stenosis; CAD-RADS 2: 25–49% stenosis; CAD-RADS 3: 50–69% stenosis; CAD-RADS 4A: 70–99% stenosis; CAD-RADS 4B: left main > 50% stenosis or 3-vessel obstructive disease > 70%; and CAD-RADS 5: total occlusion.

CT effective radiation dose was derived by multiplying the dose-length product with the weighting (k) value of 0.014 mSv/mGy/cm for chest examinations, as suggested by the Society of Cardiovascular Computed Tomography [7].

All ICAs were performed in accordance to standardized techniques, with angiograms obtained at multiple projections after administration of intracoronary nitrates. ICA analysis was performed by an independent observer, blinded to the CCTA data, using the RadiAnt™ viewer 3.4.2. The catheter tip was cleared of contrast for accurate calibration. Lesion measurements were performed using the worst view of an end-diastolic frame. The SYNTAX score is a validated tool to grade the angiographic complexity originally aimed at aiding the decision making of revascularization strategies, reported as an independent predictor of major adverse cardiac events in all wide spectrum of patient populations [8]. The SYNTAX score algorithm was used to score all coronary lesions with a diameter stenosis ≥ 50% in vessels ≥ 1.5 mm [9].

Furthermore, based on the ICA findings, patients were classified according to the CAD extension, as follows: 0, normal ICA; 1, mild (< 50%) stenosis; 2, moderate (50–69%) non-extensive stenosis; 3, moderate extensive (≥ 2 vessel); 4, severe (≥ 70%) non-extensive stenosis; 5, severe extensive stenosis; and 6, left main coronary artery (LMCA) stenosis (≥ 50%) or three-vessel disease plus proximal left anterior descending artery (LAD).

The study was approved by the institutional ethics committee and all studies have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

Continuous variables are reported as mean ± standard deviation, or medians (interquartile range, IQR) for variables with non-Gaussian distribution, whereas discrete variables are reported as counts and percentages. Comparisons among groups were performed using parametric and non-parametric one-way analysis of variance. The interobserver variability for CAD-RADS measurements was assessed using intraclass correlation coefficients (using a two-way random effect model, absolute agreement, and average measurement) with 95% confidence intervals. We also evaluated the sensitivity, specificity, positive predictive value, and negative predictive value of CCTA for the detection of obstructive (≥ 70%) CAD by ICA. All statistical analyses were performed using SPSS software, version 22.0 (IBM SPSS Statistics for Windows,

Armonk, NY). A two-sided p value of less than 0.05 indicated statistical significance.

Results

Study population

We included 96 patients clinically referred for ICA, who underwent a CCTA in our institution using a multidetector high definition CT scanner within 3 months before ICA. Four patients were excluded due to a non-diagnostic CCTA, and one patient was excluded due to suboptimal ICA images for CAD extension/SYNTAX score calculation. Therefore, a total of 91 patients comprised the study population. The mean age was 61.4 ± 10.5 years old, and 67 (74%) were male. Demographical characteristics are depicted in Table 1. The mean heart rate was 62.8 ± 9.3 bpm, and the mean effective radiation dose of CCTA was 4.2 ± 1.1 mSv. Sixty-two patients (68%) had previously undergone single photon emission computed tomography myocardial perfusion imaging, of which 43 (69%) had evidence of myocardial ischemia. The remaining patients (n = 29), with symptoms of typical angina, only underwent CCTA and ICA.

Relationships between CAD-RADS, SYNTAX score, and CAD extension index

At ICA, 62 (68%) patients had evidence of obstructive (≥ 70%) stenosis. On a per patient basis, CCTA had a sensitivity, specificity, positive predictive value, and negative predictive value of 96.8% (95% CI 89–100%), 82.8% (95% CI 64–94%), 92.3% (95% CI 83–97%), and 92.3% (75–99%) for the detection of obstructive stenosis.

There was an excellent agreement between observers regarding the CAD-RADS, with an intraclass correlation coefficient of 0.94 (95% CI 0.91–0.96).

The CAD-RADS distribution was the following; CAD-RADS 0: 11 (12%), CAD-RADS 1: 7 (8%), CAD-RADS 2: 4 (4%), CAD-RADS 3: 11 (12%), CAD-RADS 4A: 21 (23%), CAD-RADS 4B: 7 (8%), CAD-RADS 5: 30 (33%). Among patients with CAD-RADS ≥ 4A, 55/58 (95%) had ≥ 70 stenosis at ICA, whereas amid patients without severe lesions at ICA, 3 (10%) had a CAD-RADS ≥ 4A.

The median SYNTAX score was 10 (IQR 2.0; 19.5), and 15 (17%) patients had a SYNTAX score ≥ 23. We identified a significant relationship between CAD-RADS and both the SYNTAX score ($p < 0.0001$) and the CAD extension index ($p < 0.0001$), although the complexity of coronary anatomy differed among patients with CAD-RADS ≥ 4A (Table 2; Figs. 1, 2).

Thirty patients had a CAD-RADS 5 (total occlusion), with a median SYNTAX score of 19.8 (IQR 15.0; 29.1). Of those, 9 (30%) had concomitant severe non-extensive disease at ICA, 16 (53%) had severe extensive disease or severe proximal LAD stenosis, and 5 (17%) had LMCA stenosis or three vessel plus proximal LAD.

Extent of disease among patients with CAD-RADS < 4, and spatial distribution

To assess the different extent of disease among patients with non-obstructive findings at CCTA, we evaluated the 21 patients with CAD-RADS < 4, and further excluded 5 patients who had previously undergone stenting. Among these patients, the mean segment involvement score (SIS) was 8.4 ± 4.0 (minimum 2 segments, maximum 15 segments), 52% of them with a SIS > 5.

Table 1 Demographical characteristics

Age (years ± SD)	61.4 ± 10.5
Males (%)	67 (74%)
Hypertension (%)	61 (67%)
Hypercholesterolemia (%)	59 (65%)
Diabetes (%)	19 (21%)
Smoking (previous or current, %)	53 (58%)
Previous myocardial infarction (%)	28 (31%)
Previous percutaneous coronary intervention (%)	14 (15%)
Body mass index (%)	28.3 ± 3.4
Statin use (%)	63 (69%)
Clinical presentation	
Typical chest pain	52 (57%)
Dyspnea on exertion	17 (19%)
Atypical symptoms with positive stress test	22 (25%)

Table 2 Relationship between coronary anatomy extension and complexity (evaluated by invasive angiography), and the CAD-RADS classification (evaluated by CT angiography)

	SYNTAX score		CAD extension index
	Mean	Median	Mean
CAD-RADS			
0	0	0 (0; 0)	0
1	1.4 ± 3.8	0 (0; 0)	1.1 ± 1.3
2	4.0 ± 1.4	4.5 (2.5; 5.0)	2.5 ± 1.0
3	5.8 ± 4.9	5.0 (1.0; 9.0)	2.8 ± 1.2
4A	12.6 ± 8.2	10.0 (7.5; 16.5)	4.5 ± 0.8
4B	22.2 ± 11.0	17.0 (13.0; 29.0)	5.0 ± 1.0
5	21.8 ± 11.8	19.8 (15.0; 29.1)	4.9 ± 0.7
p value	< 0.0001	< 0.0001	< 0.0001

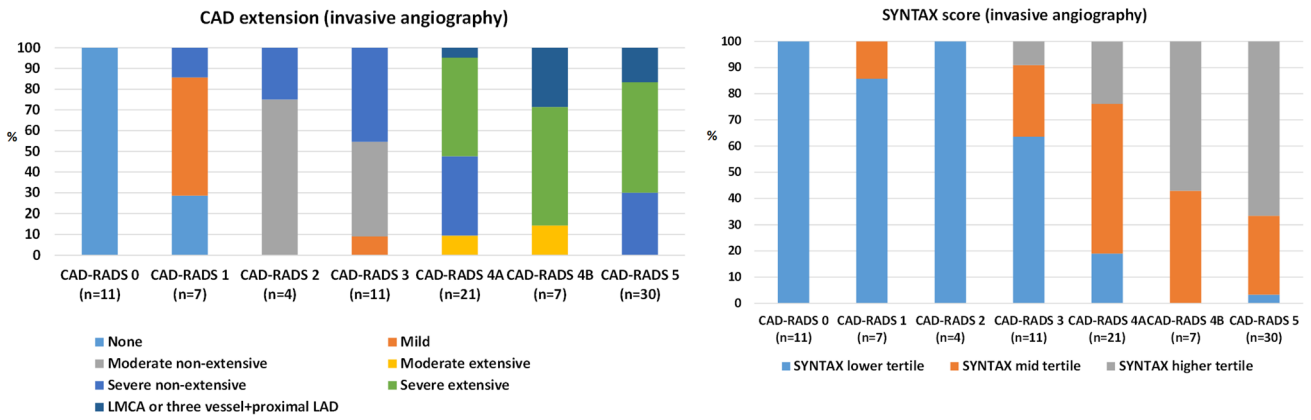

Fig. 1 Relationship between the CAD-RADS classification assessed by CT coronary angiography; and the extension (left panel) and complexity (right panel) of coronary atherosclerosis assessed by invasive coronary angiography

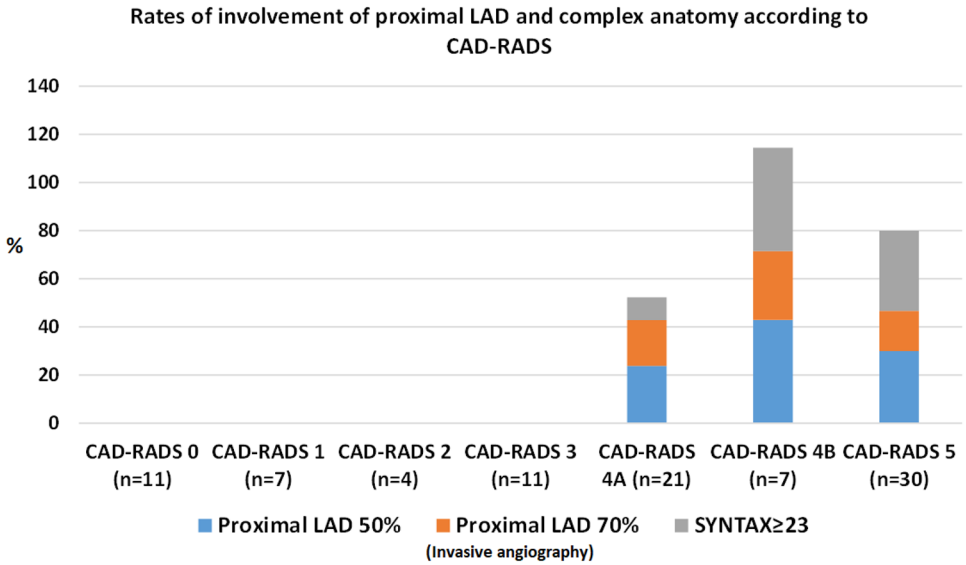

Fig. 2 Percent of patients with involvement of proximal left anterior descending (LAD) artery and complex coronary anatomy (defined as a SYNTAX score ≥ 23) according to CAD-RADS. Note that the y-axis exceeds 100% since variables reported are independent

Regarding the spatial distribution of the non-occluded most severe lesions, 27 (44%) comprised distal segments or secondary branches. Of the thirty patients with total occlusion at ICA, 9 (30%) comprised distal segments or secondary branches, whereas only six (20%) involved proximal segments. These results are shown in Fig. 3.

Discussion

CAD-RADS has recently been introduced as a tool to facilitate the communication of CCTA findings to general practitioners and clinical cardiologists, by providing standardized terminology. More importantly, it shows promise to regulate data collection across multiple sites, thus potentially aiding quality improvement, cost-effectiveness analyses, and insurance audits [1]. Although CAD-RADS has been recently shown to have reasonable accuracy for risk stratification, it was not superior to established CAD classification systems [2]. Furthermore, CAD-RADS is somewhat insensitive to the emerging significance of non-obstructive CAD and it does not adequately consider high-risk coronary anatomy [5]. Indeed, a recent analysis of the CONFIRM (Coronary CT angiography Evaluation for Clinical Outcomes: An International Multicenter) registry showed that a model including clinical variables plus a comprehensive CCTA score (comprising plaque extent, location, and composition) improved prediction of events compared with a model consisting of clinical variables plus CAD-RADS [10].

Accordingly, we undertook the current investigation to test the adequacy of CAD-RADS to capture the extent, complexity, and spatial distribution of CAD by ICA. We found CAD-RADS to correlate with the extent of CAD, and CAD-RADS < 4A was associated with a low risk anatomy,

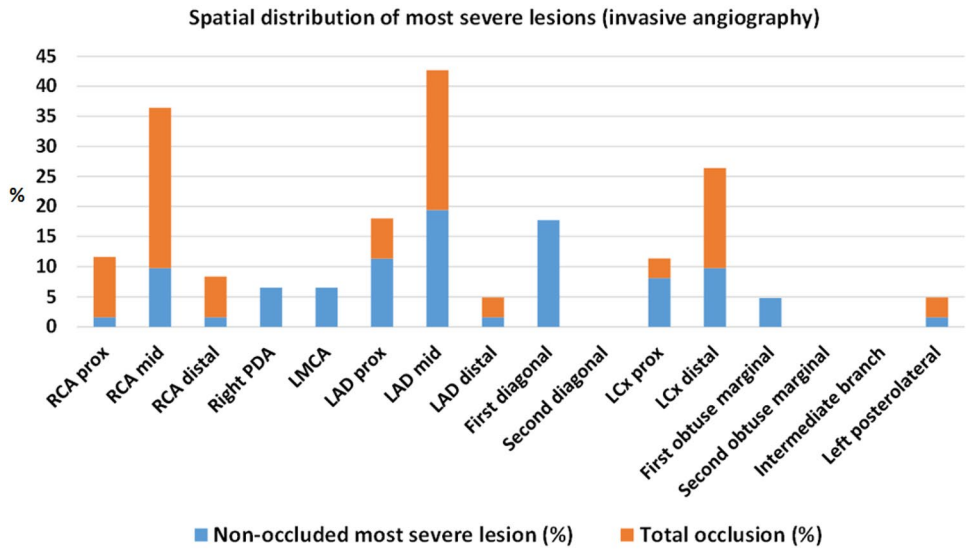

Fig. 3 Spatial distribution of most severe lesions. Note that the y-axis exceeds 100% since variables reported are independent

thus this threshold might potentially be safely used to rule out high-risk patients. However, we identified diverse coronary anatomy complexity scenarios sharing the same CAD-RADS classification despite different clinical implications. Indeed, half of patients with CAD-RADS < 4 had extensive disease. Despite some useful features, therefore, CAD-RADS has significant limitations. Indeed, Xie et al. reported a 38% rate of ICA among patients with CAD-RADS < 4A [2].

Among patients with total coronary artery occlusion, most of them assumed chronic considering a population of stable patients, the complexity of coronary anatomy differed widely, with a skewed distribution of the SYNTAX score across this subset of patients. Specifically, 30% of patients with total occlusion (CAD-RADS 5) had concomitant severe non-extensive disease at ICA, 53% had severe extensive or severe proximal LAD stenosis, and 17% had LMCA or three vessel plus proximal LAD. Furthermore, 30% of total occlusions were located at distal segments or secondary branches, whereas merely 20% comprised proximal segments. In parallel, almost half of non-occluded most severe lesions comprised distal segments of secondary branches.

A major omission of the CAD-RADS is the consideration of proximal LAD disease, since it indicates high-risk coronary anatomy, which should be distinguished from CAD that might be safely managed medically. Reporting the involvement of the proximal LAD (which supplies 45–55% of the left ventricle mass) is of outmost importance, since it has great prognostic implications in both patients with stable CAD and those presenting with acute myocardial infarction [11, 12].

Proximal LAD lesions are associated with lower left ventricular ejection fraction than non-proximal LAD lesions [13, 14]. Furthermore, lesion distance from the coronary ostium has been previously identified as an independent determinant of relative necrotic core content of plaques, and particularly the proximal LAD bears a worse plaque phenotype than other lesion locations [15, 16]. Indeed, most sites with the maximum necrotic core content, as well as most plaque ruptures, healed ruptures, and thin-cap fibroatheroma lesions are located at the proximal segments [17–21]. Nevertheless, ostial LAD and a distal LCX lesions would share the same classification according to CAD-RADS.

The number of diseased vessels is highly relevant from a prognostic perspective, regardless of its severity, sex, or the presence of diabetes [22–27]. In the past few years, the concept of non-obstructive coronary atherosclerosis has gained importance and insight, shifting longstanding dichotomous paradigms of the presence/absence of obstructive CAD to a more complex yet relevant concept [28]. Based on large prospective clinical studies demonstrating a risk continuum, patients with suspected CAD can be currently discriminated as follows: absence of coronary atherosclerosis; non-obstructive CAD (non-extensive and extensive); obstructive CAD (non-extensive and extensive); and with LMCA disease [22–24, 26]. Despite a significant relationship between CAD-RADS and the extent of CAD, we also demonstrated a considerable number of important scenarios in which CAD-RADS misrepresented the severity of CAD. Among patients with CAD-RADS 1 to 3 (non-obstructive CAD) we identified a very wide number of coronary segments involved, ranging from 2 to 15 segments, with half of these patients showing a SIS > 5 (extensive disease). It is noteworthy that patients with non-obstructive but extensive CAD are at similar risk of cardiac hard events than those with obstructive but non-extensive disease [26, 29].

Several other fields of radiology have preceded and inspired the creation of CAD-RADS. BI-RADS, TI-RADS, LI-RADS, and Lung-RADS are widely accepted diagnostic tools aimed at communicating the risk of developing

malignancy related to imaging findings. These classifications are typically a continuum, with increasing risk of malignancy with incremental RADS scores. Conversely, CAD-RADS categories are based on stenosis severity, a variable that accurately conveys risk and aids treatment strategies among patients with acute chest pain, though it might not be easily extrapolated to the stable setting [4].

Based on the new recommendations, referring physicians might expect that a CAD-RADS tool would be meant, among other uses, to communicate the risk of subsequent major adverse cardiac events. Our findings however, suggest that CAD-RADS might not adequately represent the aforementioned continuum [30].

Nonetheless, it is noteworthy that the CAD-RADS classification is meant to be complementary to the final, more comprehensive, impression of the CCTA report.

We recognize that CAD-RADS was conceived as a living document. Both proximal LAD lesion location and the presence of extensive disease have an established prognostic impact as well distinct management implication and thus should be considered in further CAD-RADS updates [31].

Limitations

A number of limitations of our study should be recognized. The relatively small population included might lead to selection bias, although it should be stressed that ICA was performed in all patients. Furthermore, data on the chronicity of total occlusions could not be verified, even though these were most likely to be chronic given our study population of patients with stable symptoms. Since the aim of the study was to address the limitations of focusing on lumen narrowing by confronting findings with ICA, we did not explore plaque characteristics, therefore, the CT-adapted Leaman score was not calculated. The SYNTAX II score was not calculated since data regarding left ventricular ejection fraction was incomplete. Finally, our population comprised a very high prevalence of CAD therefore extrapolation of our findings to CCTA studies in lower risk patients may not be appropriate.

Conclusion

In the present study including high risk patients referred to invasive coronary angiography, although CAD-RADS was related to the extent of CAD and complexity of CAD disease, we identified diverse coronary anatomy complexity scenarios sharing the same CAD-RADS classification. Furthermore, location of total occlusion, SYNTAX score, and rates of involvement of proximal left anterior descending differed significantly among patients with total occlusion.

Compliance with ethical standards

Conflict of interest We declare that Dr. Patricia Carrascosa is consultant of GE Healthcare. There are no competing interests related to the manuscript for any of the other authors.

Ethical approval The protocol was approved by the institutional ethics committee and all studies have been performed in accordance with the ethical standards as laid down in the 1975 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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