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Research Paper

Importance of coronary artery lumen size in the relationship between coronary artery plaque and vessel-specific ischemia: A post hoc analysis of CREDENCE and PACIFIC-1

Yipu Ding [a,b,*], Putri Annisa Kamila [a,c], Nick S. Nurmohamed [d,e], Ibrahim Danad [f], Ruurt A. Jukema [d], Pieter G. Raijmakers [g], Roel S. Driessen [d], Gianluca Pontone [h,i], Daniele Andreini [j], Hyuk-Jae Chang [k], Andrew D. Choi [l], Paul Knaapen [d], Hongbin Liu [b], Jeroen J. Bax [a,m], Alexander van Rosendael [a], on the behalf of the CREDENCE and PACIFIC-1 Investigators

[a] Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands
[b] School of Medicine, Nankai University, Tianjin, China
[c] Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia
[d] Department of Cardiology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands
[e] Department of Vascular Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
[f] Department of Cardiology, Radboud University Medical Center, Nijmegen, the Netherlands
[g] Department of Radiology and Nuclear Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, the Netherlands
[h] Department of Cardiovascular Imaging, Centro Cardiologico Monzino, IRCCS, Milan, Italy
[i] Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy
[j] Department of University Cardiology and Cardiac Imaging, IRCCS Ospedale Galeazzi Sant'Ambrogio, Milan, Italy
[k] Division of Cardiology, Severance Cardiovascular Hospital and Severance Biomedical Science Institute, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea
[l] Division of Cardiology, The George Washington University School of Medicine, Washington, DC, USA
[m] Turku University Hospital and University of Turku, Turku, Finland

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ABSTRACT

Background: While coronary artery plaque burden and stenosis are important for development of ischemia, the role of lumen size remains underexplored. This study evaluated the relationship between average lumen area (ALA) and vessel-specific ischemia beyond diameter stenosis (DS) and percent atheroma volume (PAV).

Methods: This post-hoc analysis included coronary arteries from the CREDENCE (n = 1716) and PACIFIC-1 (n = 612) trials, involving patients with suspected stable coronary artery disease (CAD) who underwent coronary computed tomography angiography (CTA) and invasive fractional flow reserve (FFR) measurement. AI-enabled quantitative CTA was used to assess plaque burden and composition. Ischemia was defined as FFR≤0.80. Each major coronary artery was analyzed. ALA was stratified into tertiles.

Results: Larger ALA was associated with younger age, higher body mass index, and more nitrate use in both cohorts (all $p < 0.05$). Increasing ALA correlated with lower diameter stenosis, reduced ischemia prevalence, and smaller plaque burden despite greater total plaque and non-calcified plaque volumes. In both cohorts, ischemia prevalence increased with stenosis severity, yet within each stenosis category, vessels with smaller ALA showed consistently higher ischemia rates. E.g., in CREDENCE vessels with 50 %–70 % stenosis, ischemia was observed in 60.0 % of small, 43.8 % of medium, and 27.8 % of large vessels (all $p < 0.05$). Similar patterns were observed within PAV strata across all plaque subtypes. Multivariable analysis confirmed ALA independently associated with lower ischemia prevalence in both studies (both $p < 0.001$).

Conclusions: Coronary artery lumen size significantly attenuates the relationship between atherosclerosis/stenosis and ischemia. These findings support integrating lumen assessment in coronary CTA-based risk stratification.

* Corresponding author. Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands.
E-mail address: dingyipu123@126.com (Y. Ding).

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1. Introduction

Cardiovascular disease remains the leading cause of mortality globally, and the burden of coronary artery disease (CAD) continues to rise despite advances in prevention and treatment strategies.[1,2] A central pathological feature of CAD is the progression of atherosclerotic plaque, leading to luminal encroachment, myocardial ischemia, and ultimately adverse cardiovascular events [3–5]. While current risk assessments have largely focused on plaque burden and degree of stenosis, the potential influence of lumen size on ischemic risk has received comparatively less attention.

Small lumen size has long been associated with a higher risk of restenosis and major adverse cardiovascular events (MACE) in patients undergoing percutaneous coronary intervention (PCI).[6,7] This observation underscores the inherent vulnerability of small vessels to pathological changes, which may only be detected with the use of ischemia imaging. Yet, whether small lumen size contributes to increased ischemic risk during the pre-intervention period has not been thoroughly investigated.

To better quantify this relationship, previous studies have proposed the coronary lumen volume to left ventricular mass (V/M) ratio as a risk marker for ischemia.[8] More recently, average lumen area (ALA) has emerged as a potentially more accurate and direct measure. For example, Tsugu et al. demonstrated a strong correlation between ALA and distal CT-derived fractional flow reserve (CT-FFR),[9] while the ISCHEMIA study found ALA to be associated with cardiovascular death or myocardial infarction, although the mechanistic basis for this association was not fully elucidated.[10]

In this study, we aim to investigate the role of lumen size, specifically quantified by ALA, in relation to coronary ischemia, and explore its function in the relationship between atherosclerosis/stenosis and ischemia, and assess whether ALA provides incremental predictive value beyond traditional measures such as diameter stenosis and plaque burden.

2. Materials and methods

2.1. Study population

The current study is a post hoc analysis of the CREDENCE study (612 patients) and the PACIFIC-1 study (208 patients).[11,12] CREDENCE included patients without known CAD scheduled to undergo clinically indicated nonemergent invasive coronary angiography (ICA). Patients underwent coronary CTA and ICA with fractional flow reserve (FFR) measurements. PACIFIC-1 included patients without known CAD with an intermediate pretest likelihood and normal left ventricular ejection fraction, and all patients underwent coronary CTA and ICA with 3-vessel FFR. Full inclusion and exclusion criteria, study design, as well as imaging techniques of both studies have been published previously.[11,12] Both studies were approved by the local ethics committee, with all patients visiting the study sites providing informed consent, and complied with the Declaration of Helsinki.

2.2. Coronary CTA acquisition

All coronary CTA scans were performed using single- or dual source computed tomography (CT) scanners with ≥64 detector rows (CREDENCE) or using a 256-detector row CT scanner (PACIFIC-1) (Philips Brilliance iCT, Philips Healthcare) in accordance with the SCCT (Society of Cardiovascular Computed Tomography) guidelines, as described previously (Supplemental Methods) [11–14].

2.3. AI-QCT from coronary CTA

Coronary CTA scans from both studies were analyzed using the previously described AI-QCT algorithm.[15,16] The quantitative coronary CTA evaluation was performed blinded to the clinical and outcomes data. This Food and Drug Administration (FDA)-cleared software (Cleerly Lab; Cleerly, Inc) uses a series of validated convolutional neural networks (3-dimensional U-Net and Visual Geometry Group [VGG] network variants) for image-quality assessment, coronary artery segmentation and labeling, lumen wall evaluation and vessel contour determination, and plaque characterization. The analysis included coronary segments having a diameter of 2 mm or greater based on a modified 18-segment SCCT model.[14] Total plaque volume (TPV) (mm^3) was defined as the sum of all plaque volumes calculated for each coronary lesion among all vessels. Total noncalcified plaque (tNCP) was defined as a lesion with a CT density lower than 350 HU, and calcified plaque (CP) above 350 HU.[17] The percentage of atheroma volume (PAV) was calculated by dividing plaque volume (PV)/vessel volume × 100 %; with compositional subgroups (PAV-TP, PAV-CP, and PAV-tNCP). Lumen volume, defined as total lumen of the coronary segments included in the analysis, was divided by vessel length to calculate ALA across the coronary tree.

2.4. Invasive coronary angiography and FFR

In CREDENCE, ICA was performed in agreement with clinical indications and local standards. The major coronary arteries and side branches ≥2.0 mm with >40 % or ≤90 % lumen diameter stenosis underwent FFR measurement distal to the stenosis during intracoronary or intravenous adenosine infusion. Images were transferred to a blinded core laboratory for performance of quantitative coronary angiography and FFR accuracy.[18]

In PACIFIC-1, ICA was performed following a standardized protocol with at least 2 orthogonal imaging directions per evaluated segment. Epicardial coronary vasodilation was induced using 0.2 mL of intracoronary nitroglycerin. Per PACIFIC-1 protocol, FFR measurements were performed in all 3 major coronary arteries in the distal part of the vessel, regardless of severity of stenosis, except for (subtotally) occluded (>90 %) lesions. Intracoronary (150 mg) or intravenous (140 mg/kg/min) adenosine infusion was used to induce maximal coronary artery hyperemia. All images and FFR signals were interpreted by experienced interventional cardiologists blinded to the noninvasive imaging results. In both studies, FFR was calculated as the ratio of the mean distal intracoronary and the mean aortic pressure.[18] FFR of 0.80 or less was graded as abnormal.

2.5. Statistical analysis

Continuous variables were described as mean ± standard deviation or median (interquartile range), and compared between the groups using either 2 sample *t*-test or nonparametric Wilcoxon rank sum test. Categorical variables were summarized as counts (percentages) and compared using the Pearson chi-square test or Fisher exact test if cell frequencies were insufficient.

The ALA was stratified into tertiles (small, medium, large) in both the CREDENCE (ALA≤3.40 mm^2, 3.40 mm^2<ALA≤4.45 mm^2, ALA>4.45 mm^2) and PACIFIC (ALA≤3.24 mm^2, 3.24 mm^2<ALA≤4.68 mm^2, ALA>4.68 mm^2) studies. Uni- and multivariable logistic regression analyses were performed to evaluate the association between ALA and ischemia. Sensitivity analyses were conducted with additional adjustment for clinical covariates and vessel type to assess the robustness of these associations. Logistic regression analyses were also conducted separately in patients with and without nitrate use to examine potential effects of nitrates on the results. To account for potential clustering effects arising from multiple vessels within the same patient, an additional sensitivity analysis was performed using generalized estimating equations (GEE), with patient ID specified as the subject variable and an exchangeable working correlation structure. This approach was used to assess whether within-patient correlation influenced the observed associations.

The prediction models were developed to assess the incremental predictive value of ALA beyond diameter stenosis and PAV. The models were structured as follows: Model 1 included diameter stenosis ≥50 %; Model 2 incorporated Model 1 plus PAV ≥2.6 % (which was proved to be associated with MACE[19]); and Model 3 further added ALA. Model performance was assessed using receiver operating characteristic (ROC) curve analysis, with the area under the curve (AUC) and corresponding 95 % confidence intervals (CI) reported. Reclassification improvements between models were evaluated using net reclassification improvement (NRI). Additional sensitivity analyses were performed using categorized diameter stenosis and continuous PAV when constructing the prediction models, to examine the consistency of the results across different variable specifications. A two-sided p value ≤ 0.05 was considered to constitute statistical significance for all analyses. Statistical analysis was performed using SPSS version 22.0 (SPSS, IL, USA), GraphPad Prism 8.0 (GraphPad Software, USA), MedCalc 19.0.4 (MedCalc Software, Belgium) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Clinical characteristics

A total of 1716 vessels from the CREDENCE trial and 612 vessels from the PACIFIC trial were included in this analysis. As shown in Table 1A, vessels with larger ALA in CREDENCE were associated with younger age (large ALA: 64.00 years [IQR 57.00–71.00] vs. medium ALA: 65.00 years [IQR 58.00–72.00] vs. small ALA: 66.00 years [IQR 59.00–73.00]) and higher BMI (large ALA: 26.44 kg/m^2 [IQR 24.39–29.02] vs. medium ALA: 25.61 kg/m^2 [IQR: 23.83–27.99] vs. small ALA: 25.10 kg/m^2 [IQR 22.86–27.99]) ($p < 0.001$ for both). Use of nitrates was also significantly higher in the vessels with large ALA compared to the others (18.5 % [106/573] vs. 12.8 % [146/1143], $p = 0.002$).

Similar patterns were observed in the PACIFIC trial (Table 1B), where larger vessels were associated with younger age, higher BMI, and more use of nitrates (large ALA: 14.1 % vs. small/medium ALA: 8.6 %, $p = 0.034$). Other cardiovascular risk factors were comparable across ALA tertiles in both cohorts ($p > 0.05$).

3.2. AI-QCT features and ischemia according to tertiles of average lumen area

In CREDENCE, for vessels with larger ALA, the average lumen volume was also larger, while the diameter stenosis was progressively smaller (0.49 vs. 0.41 vs. 0.33, $p < 0.001$) (Table 2A). Moreover, the prevalence of abnormal FFR declined with larger ALA (40.7 % [233/572] vs. 28.5 % [163/571] vs. 10.3 % [59/573], $p < 0.001$). Meanwhile, TP and NCP were larger, but plaque burden (which was normalized for the vessel volume, whether total, calcified, or non-calcified), was consistently smaller in vessels with larger ALA (all $p < 0.05$).

In PACIFIC, similar trends were observed for lumen volume, stenosis severity, and ischemia prevalence across tertiles of ALA (Table 2B). Total and non-calcified plaque volumes showed a gradual increase, although these differences were not statistically significant. Interestingly, calcified plaque volume became less across tertiles of ALA (15.10 mm^3 vs. 11.50 mm^3 vs. 6.00 mm^3, $p = 0.044$). For all plaque components, plaque burden decreased with increasing ALA (all $p < 0.05$).

3.3. The impact of ALA in the relationship between diameter stenosis or PAV with ischemia

As shown in Fig. 1, the prevalence of ischemia increased significantly with higher degrees of diameter stenosis in both CREDENCE and PACIFIC. Within each diameter stenosis category, vessels with larger ALA exhibited a lower prevalence of ischemia. For example, in CREDENCE, vessels with 50 %–70 % stenosis, 60.0 % of the small vessels showed

Table 1
Clinical characteristics of CREDENCE and PACIFIC.

A. CREDENCE

Characteristics	Overall patients (612 patients)	Small ALA (572 vessels)	Medium ALA (571 vessels)	Large ALA (573 vessels)	p
Age, years	65.00 [58.00, 72.00]	66.00 [59.00, 73.00]	65.00 [58.00, 72.00]	64.00 [57.00, 71.00]	<0.001
Male, %	428 (69.9)	380 (66.4)	399 (69.9)	414 (72.3)	0.099
BMI, kg/m^2	25.71 [23.72, 28.29]	25.10 [22.86, 27.52]	25.61 [23.83, 27.99]	26.44 [24.39, 29.02]	<0.001
Diabetes, %	186 (30.4)	200 (35.0)	163 (28.5)	160 (27.9)	0.017
Hypertension, %	394 (64.4)	360 (62.9)	362 (63.4)	382 (66.7)	0.356
Hyperlipidemia, %	308 (50.3)	269 (47.0)	300 (52.5)	291 (50.8)	0.163
Family history of CAD, %	120 (19.6)	109 (19.1)	108 (18.9)	107 (18.7)	0.986
Smoking history, %	290 (47.7)	265 (46.3)	270 (47.3)	278 (48.5)	0.759
Aspirin, %	360 (58.8)	341 (59.6)	334 (58.5)	320 (55.8)	0.415
Statin, %	357 (58.3)	318 (55.6)	331 (58.0)	345 (60.2)	0.286
Beta blocker, %	161 (26.3)	167 (29.2)	141 (24.7)	141 (24.6)	0.130
CCB, %	189 (30.9)	165 (28.8)	172 (30.1)	188 (32.8)	0.332
Nitrates, %	87 (14.3)	76 (13.3)	70 (12.3)	106 (18.5)	0.006

B. PACIFIC

Characteristics	Overall patients (208 patients)	Small ALA (203 vessels)	Medium ALA (204 vessels)	Large ALA (205 vessels)	p
Age, years	59.00 [51.75, 64.00]	61.00 [53.00, 65.00]	58.00 [51.00, 63.25]	58.00 [51.00, 63.00]	0.058
Male, %	132 (63.5)	120 (59.1)	120 (58.8)	146 (71.2)	0.012
BMI, kg/m^2	26.80 [24.34, 29.13]	26.29 [23.71, 28.69]	26.79 [24.36, 29.07]	27.74 [25.11, 29.74]	0.018
Diabetes, %	33 (15.9)	34 (16.7)	33 (16.2)	30 (14.6)	0.833
Hypertension, %	96 (46.2)	87 (42.9)	102 (50.0)	93 (45.4)	0.341
Hyperlipidemia, %	83 (39.9)	87 (42.9)	81 (39.7)	76 (37.1)	0.490
Family history of CAD, %	107 (51.4)	100 (49.3)	114 (55.9)	101 (49.3)	0.304
Smoking history, %	99 (47.6)	101 (49.8)	99 (48.5)	95 (46.3)	0.783
Aspirin, %	182 (87.5)	180 (88.7)	176 (86.3)	179 (87.3)	0.766
Statin, %	162 (77.9)	173 (85.2)	147 (72.1)	158 (77.1)	0.005
Beta blocker, %	135 (64.9)	133 (65.5)	134 (65.7)	131 (63.9)	0.916
CCB, %	61 (29.3)	58 (28.6)	59 (28.9)	61 (29.8)	0.964
Nitrates, %	22 (10.6)	17 (8.4)	18 (8.8)	29 (14.1)	0.105

Values are n (%) or median [IQR].
Abbreviation: ALA, average lumen area; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker.

Table 2
Vessel-level imaging characteristics of CREDENCE and PACIFIC.

A. CREDENCE					
Characteristics	Overall vessels ($n = 1716$)	Small ALA ($n = 572$)	Medium ALA ($n = 571$)	Large ALA ($n = 573$)	p
Diameter stenosis,	0.41 (0.27)	0.49 (0.31)	0.41 (0.25)	0.33 (0.21)	<0.001
Lumen volume, mm^3	788.00 [546.40, 1087.47]	482.75 [332.92, 660.03]	795.10 [629.65, 987.00]	1199.80 [934.90, 1474.70]	<0.001
ALA, mm^2	3.87 [3.17, 4.84]	2.94 [2.60, 3.17]	3.87 [3.61, 4.14]	5.37 [4.84, 6.27]	<0.001
Prevalence of ischemia (%)	455 (26.5)	233 (40.7)	163 (28.5)	59 (10.3)	<0.001
Plaque volume, mm^3					
Total plaque	138.70 [54.03, 273.30]	108.95 [40.70, 243.52]	141.70 [60.45, 267.85]	167.30 [70.90, 303.40]	<0.001
Calcified plaque	26.25 [4.27, 90.90]	27.00 [4.38, 104.60]	29.10 [6.25, 97.00]	22.70 [2.30, 73.90]	0.007
Total non-calcified plaque	89.80 [37.85, 169.20]	64.75 [26.45, 122.10]	87.30 [42.70, 166.30]	123.80 [53.10, 227.70]	<0.001
Percent atheroma volume, %					
Total plaque	14.70 [7.29, 24.81]	18.04 [8.60, 29.33]	15.32 [7.58, 25.04]	11.86 [5.72, 20.20]	<0.001
Calcified plaque	2.95 [0.53, 8.59]	5.11 [0.86, 13.22]	3.17 [0.82, 8.57]	1.65 [0.18, 4.91]	<0.001
Total non-calcified plaque	9.62 [4.97, 15.22]	10.10 [5.45, 16.08]	9.54 [4.99, 15.12]	9.00 [4.49, 14.47]	0.048
B. PACIFIC					
Characteristics	Overall vessels ($n = 612$)	Small ALA ($n = 203$)	Medium ALA ($n = 204$)	Large ALA ($n = 205$)	p
Diameter stenosis, %	0.16 [0.04, 0.50]	0.27 [0.05, 0.70]	0.18 [0.05, 0.52]	0.11 [0.03, 0.29]	<0.001
Lumen volume, mm^3	435.80 [282.55, 627.88]	252.00 [159.15, 382.25]	432.15 [318.85, 547.00]	702.50 [567.20, 885.40]	<0.001
ALA, mm^2	3.78 [2.97, 5.43]	2.72 [2.42, 2.95]	3.77 [3.50, 4.19]	6.25 [5.42, 7.53]	<0.001
Prevalence of ischemia (%)	165 (27.0)	85 (41.9)	51 (25.0)	29 (14.1)	<0.001
Plaque volume, mm^3					
Total plaque	37.55 [6.47, 139.38]	40.20 [3.80, 170.50]	38.35 [7.15, 142.95]	36.00 [7.40, 116.30]	0.921
Calcified plaque	10.20 [0.00, 55.30]	15.10 [0.00, 68.75]	11.50 [0.00, 57.73]	6.00 [0.00, 34.30]	0.044
Total non-calcified plaque	22.80 [5.30, 72.95]	18.00 [3.40, 77.15]	23.65 [6.38, 63.67]	23.90 [7.30, 74.20]	0.416
Percent atheroma volume, %					
Total plaque	8.58 [1.46, 22.39]	13.50 [1.57, 33.57]	8.78 [1.92, 23.45]	4.47 [0.98, 14.25]	<0.001
Calcified plaque	2.15 [0.00, 9.23]	4.84 [0.00, 16.58]	2.35 [0.00, 9.59]	0.62 [0.00, 4.53]	<0.001
Total non-calcified plaque	4.56 [1.34, 11.52]	7.20 [1.37, 15.26]	4.94 [1.51, 12.02]	3.24 [0.94, 8.61]	0.001

Values are n (%) or median [IQR].
Abbreviation: ALA, average lumen area.

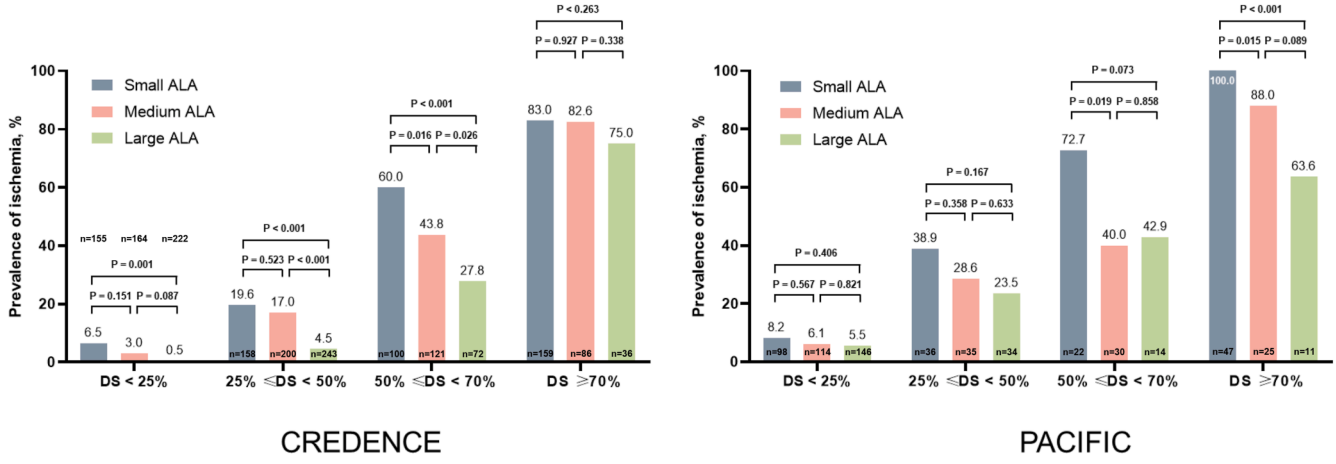


Fig. 1. The impact of ALA on prevalence of ischemia, across categories of DS
Abbreviation: ALA, average lumen area; DS, percentage diameter stenosis.

ischemia, while 43.8 % of the medium vessels and 27.8 % of the large vessels had abnormal FFR (all $p < 0.05$).

A similar pattern was observed in relation to PAV and ALA: the prevalence of ischemia increased as the PAV increased, while within each PAV tertile (for total, calcified, or non-calcified plaque), ischemia prevalence decreased steadily as ALA increased (Fig. 2 and Fig. S1).

The logistic analysis further addressed that after adjusting for diameter stenosis and PAV, the ALA remained independently associated with lower ischemia prevalence (CREDENCE: OR per 1 mm^2 increase = 0.57, 95 % CI 0.50–0.66; PACIFIC: OR = 0.77, 95 % CI 0.67–0.89; both $p < 0.001$) (Table 3), adjusted for diameter stenosis and PAV. Sensitivity analyses with additional adjustment for clinical covariates, vessel type and GEE modeling were shown in Table S1–S3. Logistic analyses stratified by nitrate use were demonstrated in Table S4.

3.4. Incremental predictive value of ALA for ischemia beyond diameter stenosis and PAV

In CREDENCE, the use of diameter stenosis ≥50 % alone (Model 1) demonstrated strong predictive ability for ischemia, with an AUC of 0.82 (95 % CI 0.80–0.83) (Fig. 3). Adding PAV to the model (Model 2) significantly improved prediction, yielding an NRI of 0.21 (95 % CI 0.16–0.25) over Model 1, $p = 0.007$. Incorporation of ALA into model 2 further enhanced predictive performance, increasing the AUC to 0.87 (95 % CI 0.85–0.88; $p < 0.001$ compared to Model 2), yielding a substantial NRI of 0.49 (95 % CI 0.39–0.59; $p < 0.001$).

Similarly, in the PACIFIC cohort, the addition of ALA to the model combining diameter stenosis ≥50 % and PAV significantly improved ischemia prediction (AUC 0.87, 95 % CI 0.84–0.89 vs. AUC 0.84, 95 % CI

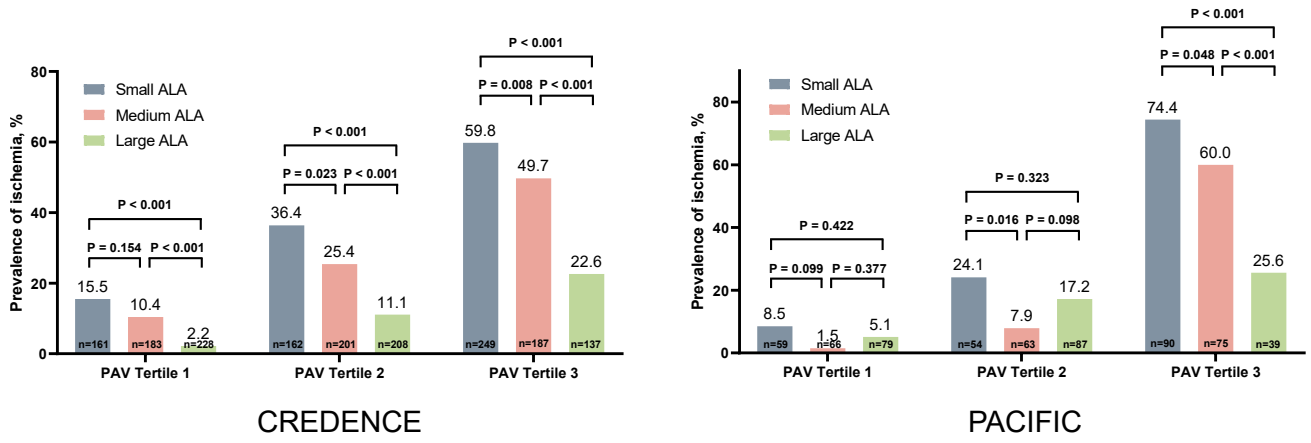


Fig. 2. The impact of ALA on prevalence of ischemia, across categories of PAV
Abbreviation: ALA, average lumen area; PAV, percent atheroma volume.

Table 3
Logistic analysis regarding the relationship between ALA and ischemia.

A. CREDENCE				
Parameters	Univariable Analysis		Multivariable Analysis	
	OR (95%CI)	*p*	OR (95%CI)	*p*
Diameter stenosis ≥50 %	19.64 (14.95–25.78)	<0.001	12.86 (9.59–17.24)	<0.001
PAV-TP, per 5 % increase	1.42 (1.36–1.49)	<0.001		
PAV-CP, per 5 % increase	1.45 (1.36–1.55)	<0.001		
PAV-tNCP, per 5 % increase	1.61 (1.49–1.73)	<0.001	1.25 (1.14–1.37)	<0.001
ALA, per 1 mm^2 increase	0.51 (0.46–0.57)	<0.001	0.57 (0.50–0.66)	<0.001
B. PACIFIC				
Parameters	Univariable analysis		Multivariable analysis	
	OR (95%CI)	*p*	OR (95%CI)	*p*
Diameter stenosis ≥50 %	18.06 (11.58–28.17)	<0.001	5.13 (3.00–8.80)	<0.001
PAV-TP, per 5 % increase	1.57 (1.46–1.70)	<0.001		
PAV-CP, per 5 % increase	1.65 (1.48–1.83)	<0.001		
PAV-tNCP, per 5 % increase	2.59 (2.20–3.05)	<0.001	1.90 (1.57–2.31)	<0.001
ALA, per 1 mm^2 increase	0.70 (0.61–0.79)	<0.001	0.77 (0.67–0.89)	<0.001

Abbreviation: ALA, average lumen area; CI, confidence interval; CP, calcified plaque; tNCP, total non-calcified plaque; PAV, percent atheroma volume; TP, total plaque.

0.80–0.86; $p < 0.001$), with an associated NRI of 0.51 (95 % CI 0.35–0.67; $p < 0.001$). Sensitivity analyses using categorized diameter stenosis and continuous PAV similarly showed the incremental predictive value of ALA (Fig. S2–S4).

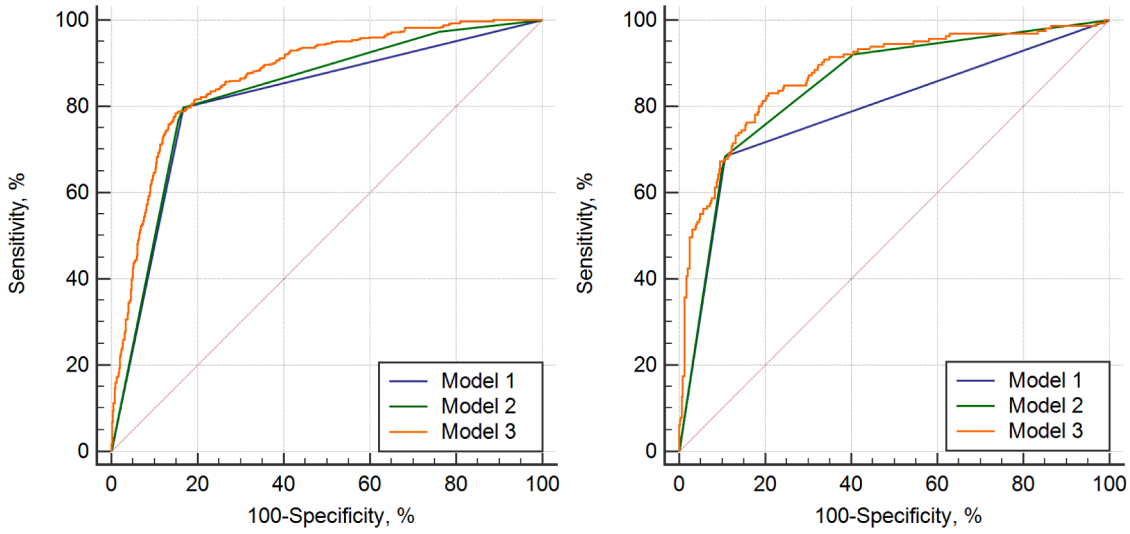
4. Discussion

In this post-hoc analysis of the CREDENCE and PACIFIC studies, we sought to clarify the importance of coronary lumen size defined by ALA in the diagnosis of vessel-specific ischemia. The current findings demonstrated that larger lumen size was consistently associated with a lower prevalence of ischemia, independent of strong predictors such as diameter stenosis and plaque burden. Conversely, smaller lumen size was linked to a higher ischemic prevalence. These findings translated to significantly lower prevalence of ischemia for vessels with an intermediate degree of stenosis or plaque burden, when the lumen size (ALA) was large, stressing the need for inclusion of ALA in clinical decision making.

4.1. Small lumen size as a risk factor

A reduction in ALA was found to be dynamically associated with an increase in plaque burden and stenosis severity. However, vessels with smaller luminal size may experience a greater physiological impact than vessels with larger lumen for the same degree of lumen loss. This concept has been repeatedly supported in post-PCI settings.[6] For instance, the rate of target lesion revascularization was significantly higher among patients with small-caliber vessels treated with drug-eluting stents ($p = 0.002$).[20] De Luca et al. further demonstrated that in patients undergoing primary angioplasty for ST-segment elevation myocardial infarction, smaller vessels were associated with severely reduced myocardial perfusion despite a lower occurrence of distal embolization.[21] Moreover, in patients with long lesions in small vessels (which implies a lower ALA), clinical outcomes were significantly worse, with a markedly increased rate of major adverse cardiovascular events at 2-year follow-up ($p < 0.001$).[22]

A recent study[9] investigated vessel lumen volume in non-obstructive right coronary arteries and reported that lower lumen volume was associated with lower CT-FFR. The current study builds upon that by expanding the analysis to all degrees of stenosis and across all coronary vessels—including RCA, LAD, LCX. We found a significant inverse correlation between ALA and FFR-defined ischemia. These findings may offer a mechanistic foundation for the observations reported by Nurmohamed et al., who suggested that a larger average lumen area was associated with a lower risk of MACE after adjusting for established predictors such as total plaque volume, low-density non-calcified plaque volume, and number of high risk plaques.[10] Together, these studies highlight the importance of lumen size, offering insight not only into the



CREDENCE	AUC (95%CI)	P value (Compared with the previous model)	NRI (95%CI) (Compared with the previous model)	P value (Compared with the previous model)
Model 1 (Diameter Stenosis ≥ 50%)	0.82 (0.80-0.83)	Reference	Reference	Reference
Model 2 (Model 1 + PAV ≥ 2.6%)	0.82 (0.80-0.84)	0.007	0.21 (0.16-0.25)	< 0.001
Model 3 (Model 2 + average lumen area)	0.87 (0.85-0.88)	< 0.001	0.49 (0.39-0.59)	< 0.001

PACIFIC	AUC (95%CI)	P value (Compared with the previous model)	NRI (95%CI) (Compared with the previous model)	P value (Compared with the previous model)
Model 1 (Diameter Stenosis ≥ 50%)	0.79 (0.75-0.82)	Reference	Reference	Reference
Model 2 (Model 1 + PAV ≥ 2.6%)	0.84 (0.80-0.86)	< 0.001	0.74 (0.62-0.86)	< 0.001
Model 3 (Model 2 + average lumen area)	0.87 (0.84-0.89)	< 0.001	0.51 (0.35-0.67)	< 0.001

Fig. 3. Incremental predictive value of average lumen area for ischemia beyond diameter stenosis and PAV
Abbreviation: AUC, area under the curve; CI, confidence interval; PAV, percent atheroma volume.

severity of atherosclerotic disease (represented by plaque volume and diameter stenosis) but also into the extent of preserved luminal capacity necessary to maintain adequate coronary blood flow and reduce future cardiovascular events.

4.2. Potential mechanisms underlying the relation between ALA and myocardial ischemia

One possible mechanism is that smaller coronary vessels are more susceptible to ischemia due to their limited capacity to accommodate plaque accumulation without compromising blood flow. Even a modest reduction in lumen diameter can significantly reduce perfusion in these vessels, leading to ischemia and worse outcomes.[7,20] This phenomenon underscores the protective role of a larger vessel lumen, which can protect against the hemodynamic consequences of atherosclerotic plaque formation. In addition, the plaque composition differs between small and large vessels. According to the Glagov phenomenon, vessels can undergo outward, positive remodeling in response to plaque accumulation, which helps preserve lumen size and delay the onset of flow-limiting stenosis.[23,24] However, this compensatory mechanism is less effective in vessels with a higher burden of calcified plaques, as seen more frequently in vessels with small ALA in our study. The stiffness caused by calcification limited the vessel's ability to adapt to plaque accumulation, exacerbating luminal narrowing and increasing ischemic risk.[25,26] Furthermore, the preservation of lumen area in non-diseased segments of the coronary arteries plays a crucial role in maintaining adequate myocardial perfusion.[27] Previous studies have shown that in the presence of proximal stenosis, distal coronary segments can undergo vasodilation, which is mediated by mechanisms such as adenosine-induced hyperemia to preserve blood flow, mitigating the overall ischemic burden.[28,29] Pharmacological interventions, such as the administration of nitrates, can enhance this compensatory mechanism by promoting vasodilation and improving blood flow through both diseased and non-diseased vessel segments.[28] In the current study, the use of nitrates was significantly more frequent in vessels with larger ALA, further supporting the protective role of preserved lumen dimension and vasodilatory capacity in reducing ischemic risk.

4.3. Comparison and connection with the V/M ratio

The V/M ratio, calculated as the ratio of coronary lumen volume to left ventricular mass was found significantly associated with ischemia, reflecting the balance between myocardial demand and coronary supply.[8] A lower V/M ratio is often observed in patients with male sex,

diabetes, or advanced CAD [30–32]. At the vessel level, however, it is difficult to determine the exact myocardial territory supplied by each artery, and small vessels may be masked by the relatively large lumen volumes of other vessels, reducing the sensitivity of the V/M ratio in detecting localized ischemic risk. Moreover, LV mass is not always accessible in standard analysis software. In contrast, vessel length is easily obtained during plaque quantification, making ALA a practical alternative. ALA offers vessel-specific insight into the risk of ischemia due to small lumen size and may serve as a useful surrogate when LV mass data are unavailable.

4.4. Clinical implications

We postulate that ALA would provide a measure in defining the lumen size in clinical practice. In the current study, vessels with smaller ALA were significantly associated with ischemia, independent of stenosis severity and plaque burden. This finding suggests that vessels with intrinsically small size or those that have become narrowed due to atherosclerosis are both at increased risk for ischemia. Therefore, more attention should be paid to small vessels, with timely initiation of anti-atherosclerotic therapies to prevent further ischemia and adverse cardiovascular events. On the other hand, in the presence of large plaque burden and higher stenosis degree, vessels with a large lumen volume were at significantly lower risk for ischemia, supporting the inclusion of ALA in clinical decision making.

4.5. Limitations

The current study has some limitations. First, this study is a post hoc analysis of the CREDENCE and PACIFIC-1 studies, which may introduce selection bias and limit generalizability. Second, the analysis was cross-sectional in nature and focused solely on diagnostic performance at a single time point. As such, it does not provide insight into the prognostic implications of small lumen size for long-term clinical outcomes. Prospective longitudinal studies are warranted to assess these relationships over time. Third, severe coronary calcification may lead to underestimation of lumen area due to blooming artifacts on CT imaging. In the current study, the overall calcified plaque burden was mild in both cohorts, which likely minimized this effect. However, when applying ALA measurements in routine clinical practice, particularly in patients with heavy calcification, this limitation should be carefully considered, as it may result in overestimation of ischemic risk and false-positive findings. Further studies including patients with severe calcification, as well as those incorporating photon-counting CT, are warranted to validate the robustness and generalizability of ALA assessments. Fourth, different protocols for FFR measurement were applied in CREDENCE (FFR measured only in coronary vessels with 40–90 % diameter stenosis) and PACIFIC-1 (FFR measured in all 3 coronary vessels), which may lead to potential bias. Fifth, due to the lack of myocardial mass measurements in the current dataset, we were unable to directly compare or integrate ALA with the V/M ratio, which could have provided additional insights into ischemic risk. Also, another explanation of the larger prevalence of ischemia in smaller vessels could be the inadequate lumen expansion to pre-CT provided nitroglycerin, instead of a blunted vasodilatory response to plaque development.

5. Conclusions

The relationship between coronary artery stenosis and plaque was significantly modified by the average lumen area, with less ischemia in vessels with large ALA, highlighting the importance of lumen assessment in ischemic risk evaluation, and its need for inclusion in coronary CTA interpretation.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2026.02.002.

References

1. GBDCoD Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2018;392(10159):1736–1788. https://doi.org/10.1016/S0140-6736(18)32203-7.
2. Mensah GA, Roth GA, Fuster V. The global burden of cardiovascular diseases and risk factors: 2020 and beyond. *J Am Coll Cardiol*. 2019;74(20):2529–2532. https://doi.org/10.1016/j.jacc.2019.10.009.
3. Mohammad MA, Stone GW, Koul S, et al. On the natural history of coronary artery disease: a longitudinal nationwide serial angiography study. *J Am Heart Assoc*. 2022;11(21):e026396. https://doi.org/10.1161/JAHA.122.026396.
4. Stone PH, Libby P, Boden WE. Fundamental pathobiology of coronary atherosclerosis and clinical implications for chronic ischemic heart disease management-the plaque hypothesis: a narrative review. *JAMA Cardiol*. 2023;8(2):192–201. https://doi.org/10.1001/jamacardio.2022.3926.
5. Barbato E, Toth GG, Johnson NP, et al. A prospective natural history study of coronary atherosclerosis using fractional flow reserve. *J Am Coll Cardiol*. 2016;68(21):2247–2255. https://doi.org/10.1016/j.jacc.2016.08.055.
6. Schunkert H, Harrell L, Palacios IF. Implications of small reference vessel diameter in patients undergoing percutaneous coronary revascularization. *J Am Coll Cardiol*. 1999;34(1):40–48. https://doi.org/10.1016/s0735-1097(99)00181-3.
7. Elezi S, Kastrati A, Neumann FJ, Hadamitzky M, Dirschinger J, Schomig A. Vessel size and long-term outcome after coronary stent placement. *Circulation*. 1998;98(18):1875–1880. https://doi.org/10.1161/01.cir.98.18.1875.
8. Taylor CA, Gaur S, Leipsic J, et al. Effect of the ratio of coronary arterial lumen volume to left ventricle myocardial mass derived from coronary CT angiography on fractional flow reserve. *J Cardiovasc Comput Tomogr*. 2017;11(6):429–436. https://doi.org/10.1016/j.jcct.2017.08.001.
9. Tsugu T, Tanaka K, Belsack D, et al. Impact of vessel morphology on CT-derived fractional-flow-reserve in non-obstructive coronary artery disease in right coronary artery. *Eur Radiol*. 2024;34(3):1836–1845. https://doi.org/10.1007/s00330-023-09972-8.
10. Nurmohamed NS, Min JK, Anthopolos R, et al. Atherosclerosis quantification and cardiovascular risk: the ISCHEMIA trial. *Eur Heart J*. 2024;45(36):3735–3747. https://doi.org/10.1093/eurheartj/ehae471.
11. Stuijfzand WJ, van Rosendael AR, Lin FY, et al. Stress myocardial perfusion imaging vs coronary computed tomographic angiography for diagnosis of invasive vessel-specific coronary physiology: predictive modeling results from the computed tomographic evaluation of atherosclerotic determinants of myocardial ischemia (CREDENCE) trial. *JAMA Cardiol*. 2020;5(12):1338–1348. https://doi.org/10.1001/jamacardio.2020.3409.
12. Danad I, Raijmakers PG, Driessen RS, et al. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. *JAMA Cardiol*. 2017;2(10):1100–1107. https://doi.org/10.1001/jamacardio.2017.2471.
13. Driessen RS, Danad I, Stuijfzand WJ, et al. Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. *J Am Coll Cardiol*. 2019;73(2):161–173. https://doi.org/10.1016/j.jacc.2018.10.056.
14. Leipsic J, Abbara S, Achenbach S, 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):342–358. https://doi.org/10.1016/j.jcct.2014.07.003.
15. Choi AD, Marques H, Kumar V, et al. CT Evaluation by Artificial Intelligence for Atherosclerosis, Stenosis and Vascular Morphology (CLARIFY): A Multi-center, international study. *J Cardiovasc Comput Tomogr*. 2021;15(6):470–476. https://doi.org/10.1016/j.jcct.2021.05.004.
16. Griffin WF, Choi AD, Riess JS, et al. AI evaluation of stenosis on coronary CTA, comparison with quantitative coronary angiography and fractional flow reserve: a CREDENCE trial substudy. *JACC Cardiovasc Imaging*. 2023;16(2):193–205. https://doi.org/10.1016/j.jcmg.2021.10.020.
17. Boogers MJ, Broersen A, van Velzen JE, 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):1007–1016. https://doi.org/10.1093/eurheartj/ehr465.
18. Nurmohamed NS, Danad I, Jukema RA, et al. Development and validation of a quantitative coronary CT angiography model for diagnosis of vessel-specific

coronary ischemia. *JACC Cardiovasc Imaging*. 2024;17(8):894–906. https://doi.org/10.1016/j.jcmg.2024.01.007.
19. Bar S, Knuuti J, Saraste A, et al. Derivation and validation of an artificial intelligence-based plaque burden safety cut-off for long-term acute coronary syndrome from coronary computed tomography angiography. *Eur Heart J Cardiovasc Imaging*. 2025. https://doi.org/10.1093/ehjci/jeaf121.
20. Elezi S, Dibra A, Mehilli J, et al. Vessel size and outcome after coronary drug-eluting stent placement: results from a large cohort of patients treated with sirolimus- or paclitaxel-eluting stents. *J Am Coll Cardiol*. 2006;48(7):1304–1309. https://doi.org/10.1016/j.jacc.2006.05.068.
21. De Luca G, Suryapranata H, de Boer MJ, et al. Impact of vessel size on distal embolization, myocardial perfusion and clinical outcome in patients undergoing primary angioplasty for ST-segment elevation myocardial infarction. *J Thromb Thrombolysis*. 2009;27(2):198–203. https://doi.org/10.1007/s11239-007-0179-5.
22. Claessen BE, Smits PC, Kereiakes DJ, et al. Impact of lesion length and vessel size on clinical outcomes after percutaneous coronary intervention with everolimus- versus paclitaxel-eluting stents pooled analysis from the SPIRIT (Clinical evaluation of the XIENCE V everolimus eluting coronary stent system) and COMPARE (Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice) randomized trials. *JACC Cardiovasc Interv*. 2011;4(11):1209–1215. https://doi.org/10.1016/j.jcin.2011.07.016.
23. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med*. 1987;316(22):1371–1375. https://doi.org/10.1056/NEJM198705283162204.
24. Korshunov VA, Schwartz SM, Berk BC. Vascular remodeling: hemodynamic and biochemical mechanisms underlying Glagov's phenomenon. *Arterioscler Thromb Vasc Biol*. 2007;27(8):1722–1728. https://doi.org/10.1161/ATVBAHA.106.129254.
25. Kinoshita D, Suzuki K, Yuki H, et al. Coronary plaque phenotype associated with positive remodeling. *J Cardiovasc Comput Tomogr*. 2024;18(4):401–407. https://doi.org/10.1016/j.jcct.2024.04.009.
26. Tauth J, Pinnow E, Sullebarger JT, et al. Predictors of coronary arterial remodeling patterns in patients with myocardial ischemia. *Am J Cardiol*. 1997;80(10):1352–1355. https://doi.org/10.1016/s0002-9149(97)00682-6.
27. Collet C, Katagiri Y, Miyazaki Y, et al. Impact of coronary remodeling on fractional flow reserve. *Circulation*. 2018;137(7):747–749. https://doi.org/10.1161/CIRCULATIONAHA.117.031478.
28. Duncker DJ, Bache RJ. Regulation of coronary blood flow during exercise. *Physiol Rev*. 2008;88(3):1009–1086. https://doi.org/10.1152/physrev.00045.2006.
29. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol*. 1974;33(1):87–94. https://doi.org/10.1016/0002-9149(74)90743-7.
30. Fairbairn TA, Dobson R, Hurwitz-Koweek L, et al. Sex differences in coronary computed tomography angiography-derived fractional flow reserve: lessons from ADVANCE. *JACC Cardiovasc Imaging*. 2020;13(12):2576–2587. https://doi.org/10.1016/j.jcmg.2020.07.008.
31. Kuneman JH, El Mahdiui M, van Rosendael AR, et al. Coronary volume to left ventricular mass ratio in patients with diabetes mellitus. *J Cardiovasc Comput Tomogr*. 2022;16(4):319–326. https://doi.org/10.1016/j.jcct.2022.01.004.
32. Kageyama S, Taylor CA, Updegrove A, et al. Cardiac computed tomography-derived coronary artery volume to myocardial mass in patients with severe coronary artery disease. *J Cardiovasc Comput Tomogr*. 2024;18(5):478–488. https://doi.org/10.1016/j.jcct.2024.06.010.