Full Title: CCTA-Derived Coronary Plaque Burden Offers Enhanced Prognostic Value Over CAC Scoring In Suspected CAD Patients

Running Title: CCTA Plaque Quantification Outperforms CAC Prognostic Value

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Abbreviations

CAC, Coronary Artery Calcium

CAD, Coronary Artery Disease

CCTA, Coronary Computed Tomography Angiography

CPV, Calcified Plaque Volume

NCPV, Non-calcified Plaque Volume

PAV, Percent Atheroma Volume

TPV, Total Plaque Volume

Abstract

Aim: To assess the prognostic utility of coronary artery calcium (CAC) scoring and coronary computed tomography angiography (CCTA) - derived quantitative plaque metrics for predicting adverse cardiovascular outcomes.

Methods and Results: The study enrolled 2,404 patients with suspected CAD but without prior history of CAD. All participants underwent CAC scoring and CCTA, with plaque metrics quantified using an artificial intelligence (AI)-based tool (Cleerly, Inc). Percent atheroma volume (PAV) and non-calcified plaque volume percentage (NCPV%), reflecting total plaque burden and the proportion of non-calcified plaque volume normalized to vessel volume, were evaluated. The primary endpoint was a composite of all-cause mortality and non-fatal myocardial infarction (MI). Cox proportional hazards models, adjusted for clinical risk factors and early revascularization, were employed for analysis.

During a median follow-up of 7.0 years, 208 patients (8.7%) experienced the primary endpoint, including 73 cases of MI (3%). The model incorporating PAV demonstrated superior discriminatory power for the composite endpoint (AUC = 0.729) compared to CAC scoring (AUC = 0.706, $p = 0.016$). In MI prediction, PAV (AUC = 0.791) significantly outperformed CAC (AUC = 0.699, $p < 0.001$), with NCPV% showing the highest prognostic accuracy (AUC = 0.814, $p < 0.001$).

Conclusions: AI-driven assessment of coronary plaque burden enhances prognostic accuracy for future adverse cardiovascular events, highlighting the critical role of comprehensive plaque characterization in refining risk stratification strategies.

Introduction

Coronary atherosclerosis is the fundamental pathological process driving the development of coronary artery disease (CAD), typically manifesting as a diffuse condition that involves the entire coronary artery system. Traditionally, CAD severity has been assessed by measuring coronary stenosis, which indicates the focal impact of the atherosclerotic process in a subset of patients. However, more than half of symptomatic patients presenting with cardiac events lack obstructive CAD, underscoring the limitations of conventional stenosis-based approaches for risk stratification.[1,2] Increasing evidence indicates that the total burden of coronary atherosclerosis, rather than isolated metrics such as diameter stenosis, is a more accurate predictor of future coronary events.[3,4]

Coronary computed tomography angiography (CCTA) is a non-invasive imaging modality that enables not only the evaluation of luminal stenosis but also a comprehensive assessment of the coronary vessel walls, including the extent of atherosclerotic burden and detailed plaque morphology. Recent advancements in technology, particularly the integration of artificial intelligence (AI), now support precise plaque quantification, with multiple AI-based tools receiving regulatory approval for clinical use.[5] The coronary artery calcium (CAC) score, obtained from non-contrast electrocardiography (ECG)-gated computed tomography (CT), serves as a surrogate for coronary atherosclerotic burden and is widely employed in cardiovascular risk assessment.[6] Its broad adoption is attributed to advantages such as ease of implementation, standardized reporting, and high reproducibility.[7] However, unlike the CAC score, CCTA enables the visualization of both calcified and non-calcified plaque, the latter of which is undetectable by CAC due to its intrinsic properties. Accordingly, the aim of this study is to compare the prognostic efficacy of CAC scoring with CCTA-derived coronary atherosclerotic plaque quantification in patients with suspected CAD.

Methods

Patient population

A total of 3,201 patients from Turku University Hospital, Turku, Finland and the Amsterdam University Medical Center, Amsterdam, the Netherlands, who underwent CCTA and CAC scoring for clinically suspected chronic coronary syndrome between 2007 and 2016 were evaluated for inclusion. Patients with a prior history of CAD or with unavailable imaging data were excluded from the study. Consequently, the final study population comprised 2,404 patients (Flowchart, Figure 1). The treatment decisions following CCTA were determined at the discretion of the referring physician, who had access to and was informed by the CCTA findings. Early revascularization was defined as any revascularization procedure performed within six months following CCTA. Given the retrospective design of the study, the ethics committees of both hospitals waived the requirement for written informed consent. The study complied with the principles of the Declaration of Helsinki.

CCTA and CAC score

Patients underwent CCTA and CAC scoring using a 64-row hybrid PET-CT scanner (n = 1,847; GE Discovery VCT or GE D690, GE Healthcare, Waukesha, WI, USA; n = 368, Philips Gemini TF 64, Philips Healthcare, Best, The Netherlands) or a 256-slice CT scanner (n = 189; Philips Brilliance iCT, Philips Healthcare, Best, The Netherlands). Both CCTA and CAC scoring were performed during the same scan session, independently of the results from either scan.

Detailed acquisition protocols have been previously published. [8,9] First, CAC scoring was conducted during a single breath-hold using a tube voltage of 120 kVp and a slice thickness of 2.5 mm. Coronary calcification was defined as a plaque with an area of at least 1 mm^2 and a density of ≥130 Hounsfield units. The CAC score was calculated by local cardiac imaging experts using the Agatston method, and the results were extracted directly from the imaging reports.[10]

Second, after administering sublingual nitrates and, if necessary, beta-blockers to achieve a heart rate below 65 beats per minute, CCTA was performed using a tube voltage of 100–120 kVp and a tube current of 600–1,000 mA, with prospective electrocardiogram gating. An iodine-containing contrast material bolus was administered according to local protocols.

Coronary plaque quantification

A U.S. Food and Drug Administration-cleared artificial-intelligence quantitative coronary computed tomography analysis (AI-QCT, Cleerly Inc.) software was utilized to analyze the CCTA images. Specific details about the software's technical aspects are available in previously published studies.[11,12] This software provides reproducible measurements with a relatively short computation time and has been validated against expert analyses, quantitative coronary angiography, fractional flow reserve (FFR), and intravascular ultrasound.[12-16] Anonymized imaging data were transferred to a core laboratory, where image analyses were conducted using AI-QCT, with the system blinded to clinical and outcome information. All CCTA scans were analyzed and only coronary segments with a diameter of ≥1.5 mm were included. Each segment was assessed for the presence of coronary atherosclerosis, defined as any tissue structure ≥1 mm^2 within the coronary artery wall that could be distinguished from surrounding epicardial tissue, epicardial fat, or the vessel lumen. Plaque volumes (in mm^3) were calculated for each coronary lesion and summed to determine the total plaque volume (TPV) at the patient level. Plaque types are categorized based on Hounsfield unit (HU) ranges: noncalcified plaque (NCP) as HU between −30 and +350, and calcified plaque (CP) as >350 HU. To account for variations in coronary artery size, plaque burden was normalized to the vessel volume and reported as percent atheroma volume (PAV), calculated as (TPV/vessel volume) × 100%. This normalization process was also applied to NCP and CP volumes, which were reported as percentages of NCP volumes (NCPV%) and CP volumes (CPV%), respectively (Figure 2). The vessel volume includes all coronary segments regardless of plaque presence, differing from other quantitative CT software that may

include only segments containing plaque. Segments with degraded image quality due to motion, insufficient opacification, beam hardening, or artifacts were excluded based automated image quality selection and finally a trained radiologic technologist provides the final image quality assessment. Furthermore, while AI-QCT performance in excluded segments is unknown, a prior study showed that total PAV per patient strongly correlates with regional PAV, suggesting that exclusion of a single segment will have minimal impact on the overall PAV results.[17]

Furthermore, Min et al. proposed a novel staging system for coronary artery disease based on PAV.[18] This classification is correlated with coronary stenosis severity and ischemia, supported by invasive coronary angiography and FFR data.[18,19] Additionally, this staging system has been recently proven as a significant prognostic marker for non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, and all-cause mortality.[11] Stages for NCPV% were defined according to the methodology reported by Nurmohamed et al, and the same staging system was applied to CPV%. [11] Table 1 provides the employed definitions for each stage. CAC score groups were classified according to the Society of Cardiovascular Computed Tomography consensus.[20]

Follow-up and endpoints

Follow-up was gathered through standardized electronic telephone interviews, medical records, and national registry databases. Investigators verified the identified events following the European Society of Cardiology guidelines.[21] The primary endpoint was defined as a composite of all-cause mortality and non-fatal myocardial infarction (MI). Periprocedural events associated with early revascularizations were excluded from the outcome analyses.

Statistical analysis

Continuous variables are represented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on their distribution. Categorical variables are reported as frequencies and percentages. Statistical comparisons of CT characteristics between individuals

with and without events were conducted using the chi-square test or Mann-Whitney U test, as appropriate. Spearman correlation was employed to assess the relationship between the plaque burden metrics and the CAC score. Kaplan-Meier analyses assessed the event-free survival across different stages of PAV, NCPV%, CPV% and CAC scores. The log-rank test was used to compare event rates over time between these categories. Cox proportional hazards regression models were employed to estimate hazard ratios (HRs) for the CAC score and plaque quantification metrics derived from CCTA, to evaluate their associations with both primary endpoint and MI. These regressions were conducted using both univariable and multivariable analyses, adjusted for symptoms, clinical risk factors, and early revascularization. The most relevant prognostic clinical risk factors were identified through backward selection in a multivariable Cox proportional hazards regression that incorporated all available clinical variables. Missing at random clinical factors were imputed using Fully Conditional Specification, creating 20 imputed datasets. The pooled results from these datasets were then used for analysis. The performance of non-nested prognostic models was compared using the Akaike Information Criterion (AIC), with a difference of more than 10 points between models considered significant. The timeROC R package was used to compute and compare the time-dependent receiver operating characteristic (ROC) area under the curve (AUC) of different prognostic models for predicting events occurring within the follow-up period.[22] To further control for the potential confounding effect of revascularization on outcomes, an additional sub-analysis was conducted, excluding patients who underwent early revascularization. A two-sided P value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS software version 28 (IBM Corporation, Armonk, New York, USA) and RStudio software (version 4.0.3, R Foundation).

Results

Of the 2,404 patients included in the study population, 1,080 (44.9%) were male, with a mean age of 61.6 ± 9.4 years. The prevalence of cardiovascular risk factors included hypertension in 1,301 patients (54.1%), hyperlipidemia in 1,391 patients (57.8%), and diabetes in 366 patients (15.2%). Baseline use of antiplatelet therapy, lipid-lowering therapy, and beta blockers was observed in 50.7%, 46.5%, and 48.2% of patients, respectively. A total of 1,273 patients (53.0%) presented with atypical angina or nonspecific symptoms, while 624 patients (26.0%) presented with typical angina. An early revascularization was performed in 299 patients (12.4%). These baseline characteristics are detailed in Table 2.

In the study population, the median CAC score was 39 Agatston Units (AU, [IQR: 0 – 271]), with 757 patients (31.5%) exhibiting a CAC score of 0 AU. The median TPV was 100.8 mm^3 (IQR: 31.2 - 295.3), CPV was 17.4 mm^3 (IQR: 0.2 - 95.9), and NCPV was 75.2 mm^3 (IQR: 27.2 - 187.6). Only 91 patients (3.8%) exhibited a complete absence of coronary plaques, with a TPV of 0 mm^3. When normalized to vessel volumes, the median PAV was 3.59% (IQR: 1.1 - 10.0), 0.59% (IQR: 0.01 - 3.3) for CPV%, and 2.53% (IQR: 0.9 - 6.3) for NCPV%, as shown in Table 3. The CAC score showed a strong correlation with TPV ($r = 0.89$, $p < 0.001$), CPV ($r = 0.96$, $p < 0.001$), and NCPV ($r = 0.82$, $p < 0.001$). CAC scores were also strongly correlated with normalized plaque volumes, including PAV ($r = 0.89$, $p < 0.001$), CPV% ($r = 0.95$, $p < 0.001$), and NCPV% ($r = 0.82$, $p < 0.001$).

Over a median follow-up period of 7.0 years (IQR: 4.9 - 8.7 years), 208 patients (8.7%) experienced the primary composite endpoint of all-cause mortality or non-fatal MI. MI occurred in 73 patients (3.0%). Patients who experienced the primary event had significantly higher CAC scores (274 AU vs. 31 AU, $p < 0.001$) and TPV (365.65 mm^3 vs. 91.05 mm^3, $p < 0.001$) compared to those without events. Similarly, both CPV (84.20 mm^3 vs. 13.15 mm^3) and NCPV (205.10 mm^3 vs. 67.40 mm^3) were significantly elevated in patients with events (both $p < 0.001$). These differences were also observed for plaque volumes normalized to vessel volumes (Table 3).

Quantitative Plaque Stages and CAC Score Groups: Relationship with Outcomes and Event-Free Survival

Advanced PAV, CPV%, NCPV% stages and CAC score groups were more prevalent in those who experienced the primary event (Table 3). This association is clearly illustrated in Figure 3, showing Kaplan-Meier curves demonstrating a progressive reduction in event-free survival with increasing PAV, NCPV%, CPV% stages and CAC scores groups.

Plaque Burden and CAC Score as Predictors of Events

In a baseline model with symptoms, clinical risk factors (age, sex, hypertension, diabetes, and smoking status), and adjustment for early revascularization, the prognostic value of PAV was compared with TPV for predicting the primary endpoint. The model including PAV (Akaike Information Criterion [AIC] = 2112.12) was a better predictor than TPV (AIC = 2123.16; AIC difference = 11.04). Therefore, PAV was used in the subsequent predictive models.

Cox proportional hazard regression analysis showed that the CAC score was significantly associated with the primary endpoint in univariable and multivariable analyses adjusted for symptoms, clinical risk factors, and early revascularization (Figure 4). The adjusted hazard ratio (aHR) for each 100-point increase in CAC score was 1.034 (95% CI: 1.021 - 1.046; $p < 0.001$). PAV was also a significant predictor of the primary endpoint, with an aHR of 1.199 (95% CI: 1.124 - 1.279; $p < 0.001$) per 5% increase. Moreover, CPV% and NCPV% were independently associated with the primary endpoint, with aHRs per 5% increase of 1.253 (95% CI: 1.138 - 1.379; $p < 0.001$) and 1.347 (95% CI: 1.204 - 1.506; $p < 0.001$), respectively.

Predictive Capacity of the CAC Score vs Plaque Burden

The ROC analysis indicated that the baseline model, which included symptoms, clinical risk factors, and early revascularization, achieved an AUC of 0.684 (95% CI: 0.626–0.744) for predicting all-cause mortality and non-fatal MI (Figure 5A). The inclusion of the CAC score significantly enhanced the model, raising the AUC to 0.706 (95% CI: 0.648–0.764; p = 0.026). A model incorporating PAV instead of the CAC score demonstrated superior discriminative ability, with an AUC of 0.729 (95% CI: 0.677–0.782; p = 0.016) compared to the CAC score model (Figure 5A). The final model, which included NCPV%, achieved an AUC of 0.731 (95% CI: 0.678–0.784); however, this difference was not statistically significant compared to the PAV (p = 0.907) and CAC score models (p = 0.061). A sub-analysis excluding patients with early revascularization revealed that the NCPV% model outperformed the CAC score model for predicting the primary endpoint (Supplement Figure 1A, AUC 0.773 vs. 0.737, p = 0.019).

When assessing predictive performance specifically for MI, the CAC score did not show incremental discriminative ability over the baseline model incorporating symptoms and traditional risk factors (AUC: 0.674 vs. 0.699, p = 0.164, Figure 5B). In contrast, the PAV model demonstrated significantly improved predictive performance (AUC: 0.791, p < 0.001, Figure 5B). Compared to the PAV model, the model with NCPV% did not exhibit a significant improvement in prognostic performance, with an AUC of 0.814 (p = 0.057, Figure 5B). In the supplementary analysis excluding early revascularization patients, the CAC score did not add significant prognostic value over the baseline clinical model (p = 0.555). Notably, the NCPV% model had the highest predictive ability compared to the PAV model for predicting future MI (AUC 0.852 vs. 0.825, p < 0.001).

Discussion

In this extensive, two-center study assessing the prognostic value of the CAC score and comprehensive coronary plaque quantification in patients with suspected CAD, the principal findings are: 1) PAV, NCPV%, CPV%, and CAC score categories demonstrated significant associations with the primary composite endpoint of death and non-fatal MI. 2) Coronary plaque normalized to vessel volume serves as a stronger predictor of adverse events than absolute plaque volume. 3) PAV exhibited enhanced discriminative performance for predicting the primary composite endpoint and MI compared to the CAC score, while NCPV% appears to be a more robust predictor of MI than the CAC score (Graphical Abstract). 4) The assessment of non-calcified plaque, particularly NCPV%, revealed prognostic capabilities comparable to PAV for predicting the primary endpoint and potentially greater performance in predicting MI.

Numerous studies have demonstrated that the extent of atherosclerosis holds significant prognostic value beyond clinical risk factors. For instance, Lin et al., in an external prognostic validation study of 1,611 patients from the SCOT-HEART trial, reported that a TPV ≥ 238 mm^3 was associated with MI (aHR of 5.36; 95% CI: 1.70–16.86).(16) Additionally, in an observational cohort of 536 patients followed for 10 years, Nurmohamed et al. showed that after adjusting for clinical risk factors, stage 3 PAV was strongly associated with a composite outcome of non-fatal MI, non-fatal stroke, revascularization, and death (aHR 3.57 [95% CI: 2.12–6.00]).(13) Our results are consistent with these previous findings, showing that a 5% increase in PAV is associated with an aHR of 1.199 (95% CI: 1.124–1.279, $p < 0.001$) for the primary outcome, after comprehensively controlling for other cardiovascular risk factors and revascularization. Importantly, the association was even more pronounced for non-calcified plaque, where a 5% increase in NCPV% was associated with an aHR of 1.347 (95% CI: 1.204–1.506, $p < 0.001$).

Additionally, we demonstrated that PAV exhibits greater prognostic value for future cardiovascular events compared to the traditional Agatston score, which does not account for the burden of non-calcified plaque. This difference was especially notable in predicting MI, where PAV significantly

outperformed the CAC score (AUC: 0.791 vs. 0.699, $p < 0.001$), and was even more pronounced for NCPV% (AUC: 0.814, $p < 0.001$). Importantly, non-calcified plaque represents a modifiable component of coronary atherosclerosis; statins are known to alter plaque composition by reducing non-calcified plaque while increasing the density of calcified plaque, thus stabilizing the plaque phenotype.[23] This effect complicates CAC-based risk stratification for patients on statin therapy, as statins increase CAC scores due to heightened calcium density, potentially overestimating coronary risk despite plaque stabilization(17). Notably, high-density calcium (>1,000 HU, the so-called “1K plaque”) is associated with a lower risk of acute coronary syndrome, independent of CAD extent and conventional cardiovascular risk factors (18). Indeed, the inclusion of the CAC score did not improve the performance of a model comprising clinical risk factors and symptoms for predicting MI. Consequently, serial imaging using CAC scoring presents challenges in evaluating changes in atherosclerotic burden and risk stratification for patients on statin therapy.

It is well-established that the burden of non-calcified coronary plaque is more closely associated with adverse cardiac outcomes.[24,25] In the PARADIGM study, which followed patients who had serial CCTA scans over two years apart due to symptoms, an annual increase of one standard deviation in PAV was linked to a 23% higher risk of experiencing a combined outcome of MI, death, or unplanned revascularization.[24] Importantly, only the progression of non-calcified plaque was independently associated with cardiovascular events, whereas the progression of calcified plaque was not.[24] Moreover, the nested case-control ICONIC study rigorously compared baseline CCTA findings from 234 patients who developed acute coronary symptoms during follow-up with those of propensity-score matched controls, based on baseline clinical and CCTA characteristics.[25] At a patient level multivariable analysis, calcified plaque was not significantly associated with acute coronary syndromes (aHR 0.999 [95% CI: 0.998-1.000, $p = 0.09$]).[25] Conversely, -30 to 130 HU plaque volume was positively related to events, with an aHR of 1.002 (95% CI: 1.000-1.001, $p = 0.037$).[25] Furthermore, our primary analysis revealed that NCPV%

demonstrated a numerically superior prognostic value compared to PAV for predicting MI, although this difference did not reach statistical significance ($p = 0.057$). Remarkably, in the sub-analysis that excluded patients who had undergone early revascularization, the difference reached statistical significance (AUC: 0.852 vs. 0.825, $p < 0.001$). These findings, combined with previous evidence, highlights that the non-calcified plaque component is likely a major determinant of future MI risk. Compared to the CAC score and PAV, NCPV% stands out as an important metric for MI risk prediction in patients with suspected CAD. Additionally, this quantitative metric may prove particularly valuable for continuous follow-up and risk reassessment in patients undergoing statin therapy, as it predominantly reflects modifiable patient risk and may facilitate a more precise evaluation of the impact of secondary prevention therapies on plaque composition and overall cardiovascular risk.

With advancements in temporal and spatial resolution of CCTA technology, along with relatively low radiation doses compared to mainstream perfusion imaging, high availability at a relatively low cost, and the rise of validated AI methods for quantifying and characterizing coronary atherosclerosis, risk assessment for patients with suspected CAD should be re-evaluated. A recent study demonstrated that AI-based quantitative CCTA analysis significantly improved 10-year prognostic discrimination compared to the contemporary recommended Coronary Artery Disease Reporting and Data System 2.0 (AUC: 0.82 vs 0.78; $p = 0.023$). Whether this enhanced classification capability provided by plaque quantification, compared to conventional CCTA evaluation, influences treatment decisions and, ultimately, outcomes remain a question for future investigation.

Study limitations

Due to the retrospective nature of data collection in this study, adjudication of more complex outcomes, such as cardiovascular death, was not feasible. Other causes of death could have influenced our composite outcome of death and MI. Nonetheless, our analysis revealed that the

discriminatory performance of plaque quantification, compared to the CAC score, in predicting myocardial infarction was even greater than for the composite primary outcome, underscoring its utility in forecasting specific cardiovascular events. Furthermore, we did not have access to information regarding patients' medical treatment following the scans. Inclusion of pharmacologic therapy—the cornerstone of stable CAD management—in our predictive models would likely have strengthened our findings. Although scanners with varying characteristics were utilized across the study sites, all devices were ≥64-slice scanners, a standard configuration widely used in clinical practice for cardiac CT and recommended by the SCCT.

Conclusions

In patients with suspected coronary artery disease, CCTA-derived PAV, obtained through an AI-based tool, has proven to be a stronger predictor of outcomes compared to the traditional CAC score. Notably, NCPV% emerges as an especially powerful metric for predicting myocardial infarction and may have potential as a valuable metric for assessing secondary prevention therapy effects and enhancing risk re-stratification.

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Table 1. Quantitative Coronary Artery Plaque Grading System.

Stage	PAV (%)	NCPV%	CPV%
0	0	0	0
1	>0-5	>0-2.5	>0-2.5
2	>5-15	>2.5-7.5	>2.5-7.5
3	>15	>7.5	>7.5

PAV: Percent atheroma volume; CPV%: Percentage of non-calcified plaque volume; CPV%: Percentage of calcified plaque volume

Table 2. Baseline Characteristics (N = 2404)

Age	61.58 ± 9.42
Male	1080 (44.9)
BMI	27.90 ± 4.91
Hypertension	1301 (54.1)
Hyperlipidaemia	1391 (57.9)
Diabetes Mellitus	366 (15.2)
Current smoker	407 (16.9)
Family history of CAD	1180 (49.1)
Medical therapy	
Anti-platelet drug	1219 (50.7)
Lipid lowering drug	1118 (46.5)
Betablocker	1158 (48.2)
Ace-inhibitor	434 (18.1)
ATR-blocker	472 (19.6)
Calcium channel blocker	422 (17.6)
Long-Acting Nitrate	139 (5.8)
Symptoms	
No chest pain	426 (17.7)
Atypical angina or non-specific symptoms	1273 (53.0)
Typical angina	624 (26.0)

Table 3. CT Characteristics of the Study Population Stratified by Primary Outcome (Death and Non-fatal Myocardial Infarction)

	Total (2404)	No Event (2196)	Event (208)	
CAC score				
CAC score	40 (0 – 271)	31 (0- 235)	274 (57 – 840)	<0.001
CAC score groups				
0	757 (31.5)	739 (33.7)	18 (8.7)	< 0.001
1-99	704 (29.3)	656 (29.9)	48 (23.1)	
100-299	386 (16.1)	341 (15.5)	45 (21.6)	
≥300	557 (23.2)	460 (20.9)	97 (46.6)	
Total Plaque				
TPV (mm^3)	100.80 (31.15-295.30)	91.05 (28.4-264.97)	326.65 (121.15-714.16)	<0.001
PAV (%)	3.49 (1.10-10.00)	3.06 (0.99-9.15)	10.51 (4.40-19.83)	<0.001
PAV stage				
0 (0%)	91 (3.8)	90 (4.1)	1 (0.5)	<0.001
1 (>0%-5%)	1314 (54.7)	1255 (57.1)	59 (28.4)	
2 (>5%-15%)	627 (26.1)	551 (25.1)	76 (36.5)	
3 (>15%)	372 (15.5)	300 (13.7)	72 (36.6)	
Calcified Plaque				
CPV (mm^3)	17.40 (0.20-95.97)	13.15(0.10-86.12)	84.20(24.40-275.25)	<0.001
CPV% (%)	0.59%(0.01-3.32)	0.45(0.01-2.88)	2.81(0.86-7.61)	<0.001
CPV% stage				
0 (0%)	91 (3.8)	90 (4.1)	1 (0.5)	< 0.001
1 (>0%-2.5%)	937 (39)	907 (41.3)	30 (14.4)	

2 (>2.5%-7.5%)	598 (24.9)	545 (24.8)	53 (25.5)	
3 (>7.5%)	778 (32.4)	654 (29.8)	124 (59.6)	
Non-Calcified Plaque				
NCPV (mm^3)	75.20 (27.22-187.55)	67.40 (24.53-171.08)	205.10 (85.25-358.42)	**<0.001**
NCPV %	2.53 (0.98 - 6.29)	2.36(0.90-5.75)	6.40(2.75-11.00)	**<0.001**
NCPV% stage				
0 (0%)	92 (3.8)	91 (4.1)	1 (0.5)	**<0.001**
1 (>0%-2.5%)	1100 (45.8)	1051 (47.9)	49 (23.6)	
2 (>2.5%-7.5%)	720 (30)	652 (29.7)	68 (32.7)	
3 (>7.5%)	492 (20.5)	402 (18.3)	90 (40.3)	

Figures

Figure 1. Study Workflow Diagram

Participant selection for the study. Abbreviations: CCTA, coronary computed tomography angiography; CAD, coronary artery disease.

Figure 2. Quantification of Coronary Plaque by AI-QCT

Case example of artificial intelligence quantitative coronary computed tomography (AI-QCT) analysis showing plaque volume quantification in the left anterior descending (LAD) artery. Plaque volume is normalized to vessel volume and reported as percent atheroma volume (PAV), calculated as (total plaque volume [TPV] / vessel volume) × 100%. Similarly, non-calcified (NCP) and calcified (CP) plaque volumes were normalized, yielding NCP volume percentage (NCPV%) and CP volume percentage (CPV%), respectively. Metrics are reported at a per-patient level. Abbreviations: AI-QCT, artificial intelligence quantitative coronary computed tomography; CCTA, coronary computed tomography angiography; LAD, left anterior descending artery; PAV, percent atheroma volume; CPV%, calcified plaque volume percentage; NCPV%, non-calcified plaque volume percentage; TPV, total plaque volume; NCP, non-calcified plaque; CP, calcified plaque.

Figure 3. Kaplan-Meier estimating event-free survival for primary outcome curves for CAC score categories and PAV, NCPV% and CPV% stages.

Kaplan-Meier survival curves estimating event-free survival for primary outcomes based on CAC score categories and plaque burden metrics, including PAV, NCPV%, and CPV%. A significant inverse association between survival and increased plaque burden was observed across all metrics, with a consistent trend toward lower event-free survival at higher CAC scores and plaque volume stages ($p < 0.001$ for all comparisons). Abbreviations: CAC, coronary artery calcium. Other abbreviations used in this figure were previously defined in Figure 2.

Figure 4. Univariable and Multivariable Cox Regression Analysis predicting the primary endpoint for CAC Score and Quantitative Plaque Metrics.

Univariable (A) and multivariable (B) Cox regression analyses predicting the primary endpoint based on CAC score (per 100 units) and AI-QCT plaque metrics: PAV, CPV%, and NCPV% (per 5% increments). Multivariable analysis adjusted for symptom characteristics, clinical risk factors (sex, age, hypertension, diabetes, smoking status), and early revascularization. Hazard ratios with 95% confidence intervals (CI) are shown for each metric, indicating a significant association ($p < 0.001$) between increased plaque burden and primary endpoint risk. Abbreviations used in this figure were previously defined in Figure 2

Figure 5. ROC Analysis of Models for Predicting Composite Primary Endpoint and Myocardial Infarction

ROC curves comparing models for predicting the composite primary endpoint (A) and MI (B). Models incorporate clinical variables including symptoms, cardiovascular risk factors (CVRF: sex, age, hypertension, diabetes, and smoking status), and early revascularization, with additional predictive metrics—CAC score, PAV, and NCPV%—to assess their incremental value. The area AUC with 95% confidence intervals is shown for each model. Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; CVRF, cardiovascular risk factors. Other abbreviations used in this figure were previously defined in Figure 2.

Graphical Abstract. Quantitative CCTA-Derived Coronary Plaque Burden Provides Enhanced Prognostic Value over CAC Score in Suspected CAD.

Using artificial intelligence-based tools, PAV and NCPV% were quantified to reflect total plaque and the proportion of non-calcified plaque volume, normalized to vessel volume. Over a median 7-year follow-up, 208 patients with suspected CAD (8.7%) experienced a composite outcome of all-cause mortality and non-fatal MI. Models incorporating PAV demonstrated superior predictive accuracy compared to CAC alone, with NCPV% achieving the highest prognostic accuracy for MI. These findings highlight the value of AI-driven, quantitative plaque assessment for enhancing risk stratification in adverse cardiovascular outcomes. Abbreviations: CAD, coronary artery disease; CAC, coronary artery calcium; CCTA, coronary computed tomography angiography; AI, artificial intelligence; PAV, percent atheroma volume; NCPV%, non-calcified plaque volume percentage; AUC, area under the curve; MI, myocardial infarction.