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ORIGINAL RESEARCH

# AI-Guided Quantitative Plaque Staging Predicts Long-Term Cardiovascular Outcomes in Patients at Risk for Atherosclerotic CVD

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## ABSTRACT

**BACKGROUND** The recent development of artificial intelligence–guided quantitative coronary computed tomography angiography analysis (AI-QCT) has enabled rapid analysis of atherosclerotic plaque burden and characteristics.

**OBJECTIVES** This study set out to investigate the 10-year prognostic value of atherosclerotic burden derived from AI-QCT and to compare the spectrum of plaque to manually assessed coronary computed tomography angiography (CCTA), coronary artery calcium scoring (CACS), and clinical risk characteristics.

**METHODS** This was a long-term follow-up study of 536 patients referred for suspected coronary artery disease. CCTA scans were analyzed with AI-QCT and plaque burden was classified with a plaque staging system (stage 0: 0% percentage atheroma volume [PAV]; stage 1: >0%-5% PAV; stage 2: >5%-15% PAV; stage 3: >15% PAV). The primary major adverse cardiac event (MACE) outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and all-cause mortality.

**RESULTS** The mean age at baseline was 58.6 years and 297 patients (55%) were male. During a median follow-up of 10.3 years (IQR: 8.6-11.5 years), 114 patients (21%) experienced the primary outcome. Compared to stages 0 and 1, patients with stage 3 PAV and percentage of noncalcified plaque volume of >7.5% had a more than 3-fold (adjusted HR: 3.57; 95% CI 2.12-6.00; $P < 0.001$) and 4-fold (adjusted HR: 4.37; 95% CI: 2.51-7.62; $P < 0.001$) increased risk of MACE, respectively. Addition of AI-QCT improved a model with clinical risk factors and CACS at different time points during follow-up (10-year AUC: 0.82 [95% CI: 0.78-0.87] vs 0.73 [95% CI: 0.68-0.79]; $P < 0.001$; net reclassification improvement: 0.21 [95% CI: 0.09-0.38]). Furthermore, AI-QCT achieved an improved area under the curve compared to Coronary Artery Disease Reporting and Data System 2.0 (10-year AUC: 0.78; 95% CI: 0.73-0.83; $P = 0.023$) and manual QCT (10-year AUC: 0.78; 95% CI: 0.73-0.83; $P = 0.040$), although net reclassification improvement was modest (0.09 [95% CI: −0.02 to 0.29] and 0.04 [95% CI: −0.05 to 0.27], respectively).

**CONCLUSIONS** Through 10-year follow-up, AI-QCT plaque staging showed important prognostic value for MACE and showed additional discriminatory value over clinical risk factors, CACS, and manual guideline-recommended CCTA assessment. (J Am Coll Cardiol Img 2024;17:269-280) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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**ABBREVIATIONS AND ACRONYMS**

**AI-QCT** = artificial intelligence-guided quantitative coronary computed tomography angiography analysis

**ASCVD** = atherosclerotic cardiovascular disease

**CACS** = coronary artery calcium scoring

**CAD** = coronary artery disease

**CCTA** = coronary computed tomography angiography

**CPV** = calcified plaque volume

**LD-NCP** = low-density noncalcified plaque

**MACE** = major adverse cardiac events

**NCPV** = noncalcified plaque volume

**NRI** = net reclassification improvement

**PAV** = percentage atheroma volume

**PR** = positive remodeling

**SIS** = segment involvement score

Atherosclerotic cardiovascular disease (ASCVD) risk stratification using traditional clinical risk factors may overestimate ASCVD events and current guideline-recommended 10-year risk stratification performs relatively poorly in identifying patients at high risk for ASCVD.[1-4] Coronary computed tomography angiography (CCTA) permits direct visualization of coronary artery disease (CAD) with high diagnostic performance and unique evaluation of atherosclerosis that allows for enhanced risk prognostication.

The multicenter prospective ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) as well as the multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes) registry have shown that CCTA-derived stenosis is associated with an up to 11-fold increased rate of major adverse cardiac events (MACE) during short-term follow-up (up to 4 years).[5-7] Recent CCTA studies such as ICONIC (Incident Coronary Syndromes Identified by Computed Tomography), SCOT-HEART (Scottish Computed Tomography of the Heart) and PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) have demonstrated that qualitative and quantitative assessment of atherosclerosis—plaque location, diffuseness, and high-risk plaque characteristics—provides independent predictive value for future ASCVD events in short- to intermediate-term follow-up.[7-12]

Nevertheless, the general semiautomated approaches to qualitative and quantitative plaque segmentation are time-consuming and challenging to implement in real-world clinical practice. In addition, the long-term prognostic value of atherosclerosis quantification is unknown.[13] The introduction of artificial intelligence-guided quantitative coronary computed tomography angiography analysis (AI-QCT) has enabled rapid analysis of atherosclerotic plaque burden and characteristics.[14,15] Several studies have shown that the objective and reproducible AI-QCT analysis achieves high diagnostic accuracy for both obstructive stenosis detection as well as atherosclerotic plaque burden quantification.[14-17]

This study set out to investigate the long-term prognostic value of atherosclerotic burden derived from AI-QCT and to compare the spectrum of quantified adverse plaque characterization to current guideline-based approaches to prognostication including CCTA-derived stenosis, coronary artery calcium scoring (CACS), and traditional clinical risk factors among patients referred for CCTA.

## METHODS

**PATIENT POPULATION.** This long-term follow-up study was performed in a previously published cohort of 539 patients.[18,19] All patients underwent CCTA imaging for suspected stable CAD between 2008 and 2014 at a university medical center (Amsterdam UMC). At time of imaging, the 539 patients had no history of CAD. Of the 539 patients in the study cohort, 2 patients had no imaging data available for the current analysis and 1 patient suffered from extensive coronary vasculitis requiring exclusion from the analysis, resulting in a final study population of 536 patients. The study complied with the Declaration of Helsinki. The current follow-up study was separately approved by the local ethics committee, with all patients visiting the study site providing informed consent.

**CCTA IMAGING.** All patients underwent combined CACS and CCTA using ≥64 slice CCTA scanners from the same manufacturer (Philips Healthcare), as described in detail in the Supplemental Methods and reported previously.[18,19]

**AI-QCT ANALYSIS.** A U.S. Food and Drug Administration-cleared, AI-based software approach

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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(Cleerly Inc) was used to analyze the CCTA images.[15] This U.S. Food and Drug Administration-cleared software service uses a series of validated convolutional neural networks for image quality assessment, coronary segmentation and labeling, lumen wall evaluation, vessel contour determination, and plaque characterization. Prior validation of AI-QCT has been reported in multicenter trials vs expert consensus, quantitative coronary angiography, and fractional flow reserve as previously published,[14,15,17] as well as intravascular ultrasound.[20] The algorithm first produces a centerline, lumen, and outer vessel wall contouring for every phase available and subsequently selects the 2 most optimal series for analysis. The choice for best-quality image is then made on a per-vessel basis. After automated segmentation and labeling in all vessels, plaques are characterized and quantified based on the HU attenuation. Finally, a trained radiologic technologist provides quality assurance overview of the AI analysis.

Coronary segments with a diameter ≥1.5 mm were included in the analysis using the modified 18-segment Society of Cardiovascular Computed Tomography model.[21] Coronary percentage stenosis was adjudicated on a per-vessel basis as per Society of Cardiovascular Computed Tomography guidelines and categorized by the Coronary Artery Disease Reporting and Data System (CAD-RADS).[22] Each segment was evaluated for the presence or absence of coronary atherosclerosis, defined as any tissue structure >1 $mm^2$ within the coronary artery wall that was differentiated from the surrounding epicardial tissue, epicardial fat, or the vessel lumen itself. Plaque volumes ($mm^3$) were calculated for each coronary lesion and then summated to compute the total plaque volume at the segment, vessel, and patient levels. Plaque volume was categorized using HU ranges, with low-density noncalcified plaque (LD-NCP) defined as plaques with any component on a pixel-level basis and quantified on an increment of 0.1 $mm^3$ as <30 HU, noncalcified plaque volume (NCPV) defined as HU between −30 and +350, and calcified plaque volume (CPV) defined as >350 HU.[23] Coronary plaque volume was normalized to the total per-patient vessel volume to account for variation in coronary artery volume, calculated as: plaque volume/vessel volume × 100%. These normalized volumes were reported as percentage atheroma volume (PAV), percentage NCPV, and percentage CPV. Arterial remodeling was calculated by examining the lesion diameter divided by the normal reference diameter. Positive remodeling was defined as a ratio ≥1.1. Two-feature-positive plaques were defined as coronary lesions with presence of both LD-NCP and positive remodeling.[23] When impaired image quality was present because of motion, poor opacification, beam hardening, or other artifact, only the part of the coronary artery with poor quality was excluded from the analysis.

**FOLLOW-UP FOR MAJOR CARDIOVASCULAR EVENTS.** Detailed prognostic data were collected during follow-up visits for the current study during 2021 and 2022. Patients who were unable to visit the study site were followed up using national registry databases, electronic medical records, and standardized telephone interviews, as previously described.[18,19] Events were adjudicated in accordance with current guidelines.[19,24] Complete follow-up was collected in 508 patients. For 28 patients who had no follow-up available but were confirmed alive, censoring was applied at the time of their last follow-up in the previous follow-up study.[18,19] For the current analysis, the primary outcome was defined as all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery). Revascularizations were adjudicated and early revascularizations resulting from the initial noninvasive imaging were excluded from this composite outcome. Additionally, for the calculation of 10-year ASCVD risk, a secondary outcome was used that consisted of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke, excluding all revascularizations.

**PLAQUE STAGING.** A proposed CAD staging of atherosclerotic plaque burden was evaluated using the following definitions as recently proposed by Min et al.[13,25] This plaque staging system was based on evidence from invasive angiographic stenosis and invasive fractional flow reserve data in a multicenter study to correspond to stenosis severity and ischemia. Patients without plaque were defined as stage 0, patients with a PAV >0%-5% were defined as stage 1, patients with a PAV >5%-15% were defined as stage 2, and patients with >15% PAV were defined as stage 3. Additionally, patients were further stratified by their NCPV: patients without plaque were defined as stage 0, patients with a NCPV >0%-2.5% were defined as stage 1, patients with a NCPV >2.5%-7.5% were defined as stage 2, and patients with >7.5% NCPV were defined as stage 3.

**STATISTICAL ANALYSIS.** Kaplan-Meier curves were plotted to compare event-free survival across different plaque stages using the log-rank test to analyze differences in event rates over time. Time to event was calculated starting from baseline CCTA imaging. HRs for PAV and NCPV stages were

**TABLE 1 Baseline Characteristics (N = 536)**

| | |
|---|---|
| Age at baseline, y | 58.6 ± 9.2 |
| Male | 297 (55) |
| Hypertension | 250 (47) |
| Hyperlipidemia | 195 (37) |
| Diabetes mellitus type 2 | 93 (18) |
| BMI, kg/m$^2$ | 27.0 ± 4.1 |
| Smoking history | 184 (35) |
| Family history of CAD | 284 (53) |
| Reason for referral | |
| Typical angina | 165 (31) |
| Atypical angina | 187 (35) |
| Aspecific chest pain | 178 (34) |
| Aspirin use | 403 (76) |
| Beta-blocker use | 324 (61) |
| Use of calcium antagonists | 140 (26) |
| Statin use | 354 (67) |
| MACE[a] | 116 (21) |
| Nonfatal myocardial infarction | 22 (4) |
| Nonfatal stroke | 13 (3) |
| Death | 44 (8) |
| Coronary revascularization | 37 (7) |
| CAD-RADS stage (based on AI-QCT) | |
| 0 | 15 (3) |
| 1 | 237 (44) |
| 2 | 91 (17) |
| 3 | 88 (16) |
| 4 | 75 (14) |
| 5 | 30 (6) |
| PAV, % | 5.0 (1.0-13.0) |
| Percentage NCPV | 3.5 (1.2-7.9) |
| Percentage CPV | 0.8 (0.0-4.2) |
| Presence of 2-feature-positive plaque | 192 (36) |
| SIS | 6 (4-9) |
| CACS, AU | |
| 0 | 147 (28) |
| 1-100 | 161 (30) |
| 101-300 | 87 (16) |
| >300 | 137 (26) |
| Median follow-up, y | 10.3 (8.6-11.5) |

Values are mean ± SD, median (IQR), or n (%). [a]Only first cardiac events are shown.

AI-QCT = artificial intelligence-guided quantitative coronary computed tomography analysis; BMI = body mass index; CACS = coronary artery calcium scoring; CAD = coronary artery disease; CAD-RADS = Coronary Artery Disease Reporting and Data System; CPV = calcified plaque volume; MACE = major adverse cardiac event; NCPV = noncalcified plaque volume; PAV = percentage atheroma volume; SIS = segment involvement score.

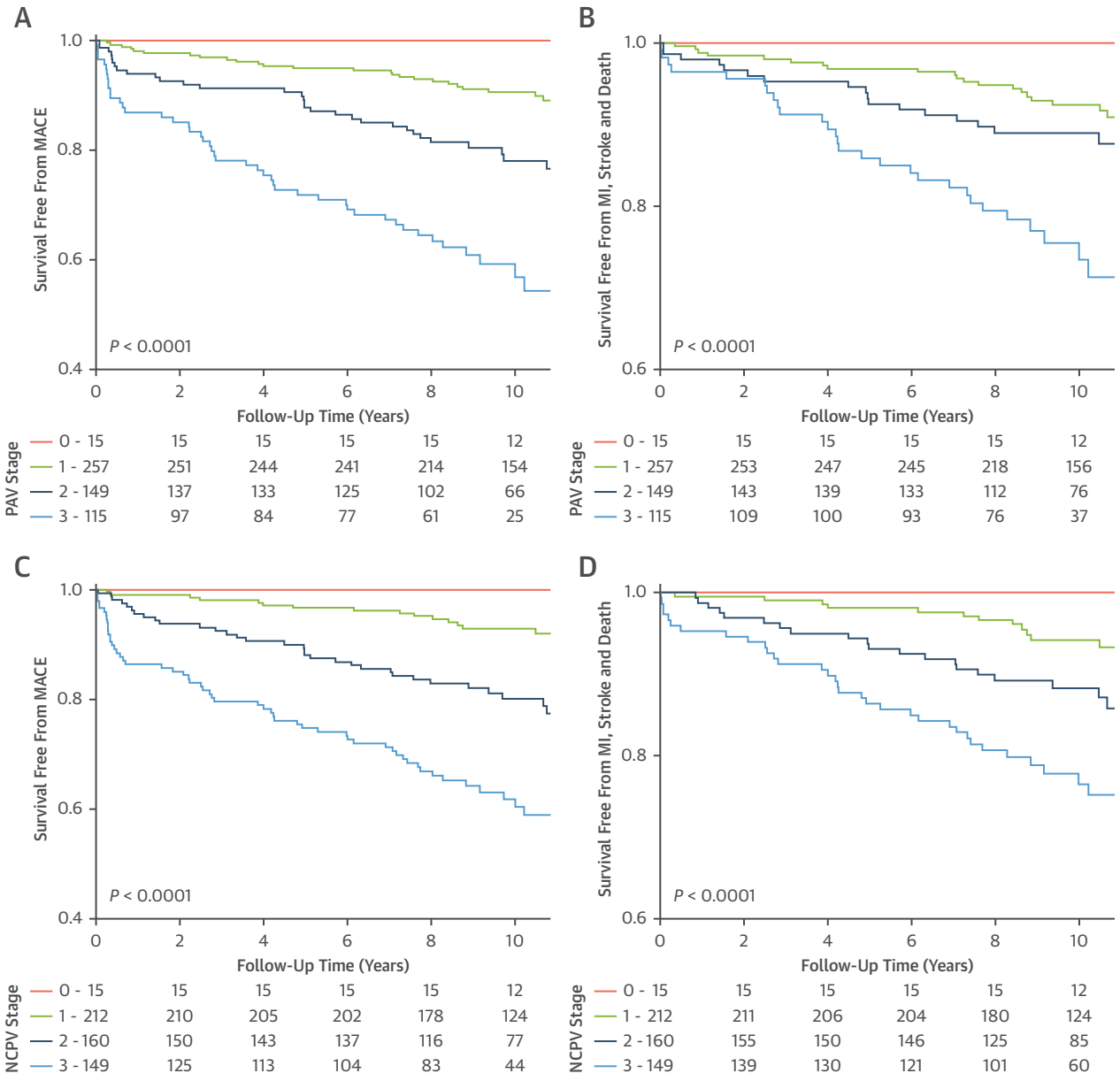
determined using Cox proportional hazards regression, both in an univariable analysis as well as a multivariable analysis adjusted for multiple clinical risk factors: age, sex, hypertension, dyslipidemia, diabetes mellitus, body mass index, smoking status, and family history of CAD. The proportional hazard assumptions were verified using Schoenfeld residuals. Missing clinical variables (≤1%) were imputed using multiple imputations by chained equations. A number of 25 imputed copies were created of the original data set and were pooled for the analysis. Because there were no events in patients with stage 0 PAV and NCPV, patients classified as stages 0 and 1 were combined as reference group in the Cox proportional hazards regression analysis. The other imaging parameters (CPV, CACS, and CAD-RADS score) were also classified into 3 categories; 2-feature-positive plaque was used as a binary variable. Subsequently, the performance of different Cox proportional hazards models was compared to AI-QCT. An overview of the models and variables is shown in the Supplemental Methods. Area under the curve was calculated using time-dependent receiver-operating characteristic curves derived from Cox proportional hazards models using the timeROC R package (R Foundation). Reclassification benefit was assessed using the net reclassification improvement (NRI) on a category basis using 3 risk categories based on the observed risk over time (2 years: low risk, <5%; intermediate risk, 5%-10%; high risk, ≥10%; 5 years: low risk, <7.5%; intermediate risk, 7.5%-15%; high risk, ≥15%; 10 years: low risk, <10%; intermediate risk, 10%-20%; high risk, ≥20%). The 95% CIs for point estimates of performance metrics were calculated using a bootstrap method (n = 1,000 replicates) when asymptotic intervals were not available. Ten-year survival probability estimates calculated from the PAV Cox regression model for different PAV were used to estimate the range of cardiovascular risk associated with the different plaque stages. For the current study population, survival probability estimates at 10 years were calculated from an additional Cox regression model with an interaction term between PAV and CAD-RADS. Similarly, this was also shown for NCPV and CAD-RADS.

Data are presented as mean ± SD for normally distributed variables or median (IQR) for non-normally distributed data. The normality of data distribution was assessed using histograms and probability plots. Categorical variables are expressed as absolute numbers and percentages. Independent sample Student's *t*-tests, Wilcoxon tests, Mann-Whitney U-tests, and Kruskal-Wallis tests were used where appropriate. All statistical analyses were performed using RStudio software (version 4.0.3, R Foundation).

## RESULTS

The 536 patients had a mean age of 58.6 ± 9.2 years and 297 (55%) were male (Table 1). Patients experienced a range of symptoms comprising typical angina (165 [31%]), atypical angina (187 [35%]), and

**FIGURE 1** **Kaplan-Meier Analysis of Plaque Stages for the Primary and Secondary Outcomes**




Shown are survival curves from a Kaplan-Meier analysis. (A) Coronary artery disease stages based on percentage atheroma volume (PAV), survival free from primary outcome (all-cause mortality, nonfatal myocardial infarction [MI], nonfatal stroke, and coronary revascularization). (B) Coronary artery disease stages, survival free from secondary outcome (all-cause mortality, nonfatal MI, and nonfatal stroke). (C) Noncalcified plaque volume (NCPV) stages based on percentage NCPV, primary outcome. (D) NCPV stages, secondary outcome. MACE = major adverse cardiac events.

nonspecific chest pain (178 [34%]). According to the AI-QCT analysis, 343 patients (64%) had nonobstructive CAD (<50% stenosis), 88 (16%) had moderate obstructive CAD (≥50%-69% stenosis) and 105 (20%) had a severe obstructive stenosis of ≥70%. CAD-RADS categorical distribution is shown in Table 1. During a median follow-up of 10.3 (IQR: 8.6, 11.5) years, 116 patients (22%) experienced the primary composite MACE outcome, 22 (4%) had a nonfatal myocardial infarction, 13 (3%) had a nonfatal stroke, 44 (8%) died, and 37 (7%) underwent coronary revascularization.

**FIGURE 2 Univariable and Multivariable Cox Regression for Clinical and AI-QCT Characteristics**

| Parameter | Univariable | HR (95% CI) | *P*-Value | Multivariable | HR (95% CI) | *P*-Value |
|---|---|---|---|---|---|---|
| **Clinical characteristics** | | | | | | |
| Age (per 10 years) | | 1.69 (1.39 to 2.06) | < 0.001 | | 1.68 (1.36 to 2.07) | < 0.001 |
| Sex | | 1.64 (1.12 to 2.40) | 0.010 | | 1.82 (1.23 to 2.69) | 0.003 |
| Hypertension | | 1.98 (1.36 to 2.88) | < 0.001 | | 1.67 (1.12 to 2.48) | 0.012 |
| Hypercholesterolemia | | 1.26 (0.87 to 1.83) | 0.214 | | 1.04 (0.71 to 1.53) | 0.844 |
| Diabetes | | 1.27 (0.82 to 1.97) | 0.284 | | 0.97 (0.60 to 1.56) | 0.896 |
| BMI (per 1 kg/m$^2$) | | 1.01 (0.97 to 1.05) | 0.688 | | 1.00 (0.95 to 1.05) | 0.936 |
| Smoking | | 1.24 (0.85 to 1.80) | 0.259 | | 1.22 (0.84 to 1.78) | 0.299 |
| Family history of CAD | | 1.02 (0.71 to 1.47) | 0.922 | | 1.23 (0.85 to 1.80) | 0.274 |
| **Percent atheroma volume** | | | | | | |
| Stage 0-1 (Reference) | | | | | | |
| Stage 2 | | 2.24 (1.39 to 3.60) | 0.001 | | 1.77 (1.08 to 2.90) | 0.023 |
| Stage 3 | | 5.23 (3.34 to 8.19) | < 0.001 | | 3.57 (2.12 to 6.00) | < 0.001 |
| **Percent non-calcified plaque volume** | | | | | | |
| Stage 0-1 (Reference) | | | | | | |
| Stage 2 | | 2.70 (1.58 to 4.62) | < 0.001 | | 2.13 (1.22 to 3.71) | 0.008 |
| Stage 3 | | 5.97 (3.62 to 9.85) | < 0.001 | | 4.37 (2.51 to 7.62) | < 0.001 |
| **Percent calcified plaque volume** | | | | | | |
| Stage 0-1 (Reference) | | | | | | |
| Stage 2 | | 2.31 (1.47 to 3.62) | < 0.001 | | 1.70 (1.06 to 2.72) | 0.027 |
| Stage 3 | | 3.97 (2.56 to 6.16) | < 0.001 | | 2.42 (1.46 to 4.01) | 0.001 |
| **Two feature positive plaque** | | | | | | |
| No (Reference) | | | | | | |
| Yes | | 1.96 (1.36 to 2.83) | < 0.001 | | 1.58 (1.05 to 2.36) | 0.027 |
| **Segment involvement score** | | | | | | |
| <5 (Reference) | | | | | | |
| 5-7 | | 2.00 (1.17 to 3.45) | 0.012 | | 1.63 (0.93 to 2.85) | 0.087 |
| >7 | | 3.62 (2.19 to 5.96) | < 0.001 | | 2.26 (1.29 to 3.94) | 0.004 |
| **Coronary artery calcium score** | | | | | | |
| 0-100 (Reference) | | | | | | |
| 101-300 | | 2.00 (1.19 to 3.36) | 0.009 | | 1.55 (0.92 to 2.63) | 0.103 |
| >300 | | 3.21 (2.13 to 4.84) | < 0.001 | | 1.93 (1.20 to 3.10) | 0.006 |
| **CAD-RADS** | | | | | | |
| 0-1 (Reference) | | | | | | |
| 2-3 | | 3.02 (1.88 to 4.86) | < 0.001 | | 2.24 (1.36 to 3.69) | 0.002 |
| 4-5 | | 5.80 (3.56 to 9.46) | < 0.001 | | 4.66 (2.73 to 7.94) | < 0.001 |


Univariable and multivariable Cox regression of different clinical characteristics, artificial intelligence-guided quantitative coronary computed tomography angiography analysis (AI-QCT) plaque parameters, coronary artery calcium scoring, and Coronary Artery Disease Reporting and Data System (CAD-RADS) for the primary outcome. Multivariable Cox regression was adjusted for clinical risk characteristics: age, sex, hypertension, hypercholesterolemia, diabetes, body mass index (BMI), active smoking, and family history of coronary artery disease (CAD).

**LONG-TERM SURVIVAL ACCORDING TO QUANTITATIVE PLAQUE STAGES.** Patients were stratified into plaque stages based on their PAV at baseline. There were 15 patients without plaque (CAD stage 0), 257 patients with a PAV between 0% and 5% (CAD stage 1), 149 patients with a PAV between 5% and 15% (CAD stage 2), and 115 patients with ≥15% PAV (CAD stage 3). Additionally, patients were stratified based on their NCPV: 15 patients without NCPV (NCPV stage 0), 212 patients with a NCPV volume between 0% and 2.5%, 160 patients with NCPV between 2.5% and 7.5%, and 149 patients with >7.5% NCPV. Patients with higher PAV stages showed worse survival for both the primary outcome ($P < 0.001$) (Figure 1A) and the secondary outcome ($P < 0.001$) (Figure 1B). Similarly, patients with higher NCPV stages showed worse survival for both outcomes ($P < 0.001$) (Figures 1C and 1D). Patients with no plaque volume (PAV stage 0/NCPV stage 0) did not experience events during follow-up.

**PROGNOSTIC VALUE OF DIFFERENT CT CHARACTERISTICS.** The plaque volume stages defined by AI-QCT analysis were associated with the primary outcome in both the

**TABLE 2 Performance of Different Models for MACE During Follow-up**

| Model | Reference | 2 Years AUC (95% CI) | 2 Years AUC *P* Value | 2 Years NRI (95% CI) | 5 Years AUC (95% CI) | 5 Years AUC *P* Value | 5 Years NRI (95% CI) | 10 Years AUC (95% CI) | 10 Years AUC *P* Value | 10 Years NRI (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| Clinical | | 0.66 (0.56-0.76) | Ref. | Ref. | 0.67 (0.61-0.74) | Ref. | Ref. | 0.69 (0.63-0.75) | Ref. | Ref. |
| Clinical + CACS | Clinical | 0.69 (0.61-0.77) | 0.224 | 0.07 (−0.17 to 0.35) | 0.70 (0.63-0.76) | 0.203 | 0.04 (−0.06 to 0.28) | 0.73 (0.68-0.79) | 0.019 | 0.11 (−0.02 to 0.25) |
| Clinical + CACS + CAD-RADS 2.0 | Clinical + CACS | 0.74 (0.67-0.81) | 0.206 | 0.13 (−0.17 to 0.42) | 0.75 (0.70-0.80) | 0.052 | 0.21 (−0.05 to 0.30) | 0.78 (0.73-0.83) | 0.039 | 0.12 (−0.05 to 0.27) |
| Clinical + CACS + manual QCT | Clinical + CACS | 0.74 (0.67-0.80) | 0.054 | 0.13 (−0.12 to 0.36) | 0.75 (0.70-0.80) | 0.023 | 0.22 (−0.02 to 0.30) | 0.78 (0.73-0.83) | 0.005 | 0.15 (0.00-0.30) |
| Clinical + CACS + AI-QCT | Clinical + CACS | 0.81 (0.74-0.87) | <0.001 | 0.50 (0.10-0.60) | 0.79 (0.74-0.85) | <0.001 | 0.37 (0.10-0.49) | 0.82 (0.78-0.87) | <0.001 | 0.21 (0.09-0.38) |
| | Clinical + CACS + CAD-RADS 2.0 | | 0.036 | 0.32 (−0.03 to 0.50) | | 0.111 | 0.19 (−0.05 to 0.36) | | 0.032 | 0.09 (−0.02 to 0.29) |
| | Clinical + CACS + manual QCT | | 0.022 | 0.34 (0.00-0.51) | | 0.070 | 0.19 (−0.02 to 0.36) | | 0.040 | 0.04 (−0.05 to 0.27) |

Shown is the discriminatory value of different risk models for the primary outcome during follow-up.

AUC = area under the curve; NRI = net reclassification improvement; QCT = quantitative computed tomography; Ref. = reference; other abbreviations as in Table 1.

univariable analysis and the multivariable analysis adjusted for clinical risk factors (Figure 2). The clinical risk factors that associated with the primary outcome were age (adjusted HR [aHR] per 10 years: 1.68; 95% CI: 1.36-2.07; $P < 0.001$), male sex (aHR: 1.82; 95% CI: 1.23-2.69; $P = 0.003$), and presence of hypertension (aHR: 1.67; 95% CI: 1.12-2.48; $P = 0.012$). PAV (stage 2: aHR: 1.77; 95% CI: 1.08-2.90; $P = 0.023$; stage 3: aHR: 3.57; 95% CI: 2.12-6.00; $P < 0.001$) and NCPV (stage 2: aHR: 2.13; 95% CI: 1.22-3.71; $P = 0.008$; stage 3: aHR: 4.37; 95% CI: 2.51-7.62; $P < 0.001$) showed a strong association with the primary outcome. When using the CAD-RADS classification, there was a strong association with the primary outcome (CAD-RADS 2-3: aHR: 2.24; 95% CI: 1.36-3.69; $P = 0.002$; CAD-RADS 4-5: aHR: 4.66; 95% CI: 2.73-7.94; $P < 0.001$; reference CAD-RADS 0-1). When examining other models, CPV (stage 2: aHR: 1.70; 95% CI: 1.06-2.72; $P = 0.027$; stage 3: aHR: 2.42; 95% CI: 1.46-4.01; $P = 0.001$) and the presence of 2 high-risk plaque characteristics (low-attenuation plaque and positive remodeling; aHR: 1.58; 95% CI: 1.05-2.36; $P = 0.027$) were moderately associated with outcomes. When stratified by CACS, only the highest CACS group was significantly associated with the primary outcome (CACS 101-300: aHR: 1.55; 95% CI: 0.92-2.63; $P = 0.103$; CACS >300: aHR: 1.93; 95% CI: 1.20-3.10; $P = 0.006$; reference CACS 0-100).

**ADDITIONAL DISCRIMINATORY VALUE OF AI-QCT DURING FOLLOW-UP.** The addition of AI-QCT to a risk model with clinical risk factors and CACS improved risk discrimination for MACE at 2, 5, and 10 years of follow-up (10-year AUC: 0.82 [95% CI: 0.78-0.87] vs 0.73 [95% CI: 0.68-0.79]; $P < 0.001$; NRI: 0.21 [95% CI: 0.09-0.38]) (Table 2). AI-QCT modestly outperformed a model based on the CAD-RADS 2.0 guidelines (manual stenosis grading and segment involvement score [SIS]) in prediction of MACE at 10 years (AUC: 0.82 [95% CI: 0.78-0.87] vs 0.78 [95% CI: 0.73-0.83]; $P = 0.032$; NRI: 0.09 [95% CI: −0.02 to 0.29]) (Table 2). Finally, the AI-QCT model was also superior compared to manual QCT (Supplemental Figure 1) in prediction of MACE at 10 years (AUC: 0.82 [95% CI: 0.78-0.87] vs 0.78 [95% CI: 0.73-0.83]; $P = 0.040$; NRI: 0.04 [95% CI: −0.05 to 0.27]) (Table 2).

**IMPACT OF PLAQUE BURDEN ON 10-YEAR ASCVD RISK AND ACROSS PATIENT SUBGROUPS BASED ON STENOSIS GRADE.** Survival probability estimates from a Cox proportional hazards model with PAV as continuous variable were used to evaluate the 10-year risk of ASCVD events (nonfatal myocardial infarction, nonfatal stroke, and death) in this study population (Figure 3). Patients in stage 1 had an estimated 10-year risk between 8.2% and 10.0%, patients in stage 2 had a 10-year risk between 10.1% and 15.4%, and patients in stage 3 had a 10-year ASCVD risk ≥15.4%. A Cox proportional hazard model was constructed with an interaction between plaque burden (PAV/NCPV stage) and stenosis grade (CAD-RADS categories). Survival probability estimates from this model were used to evaluate the 10-year cardiovascular event risk associated with PAV and NCPV across different CAD-RADS categories (Figures 4A and 4B). The effect of the PAV

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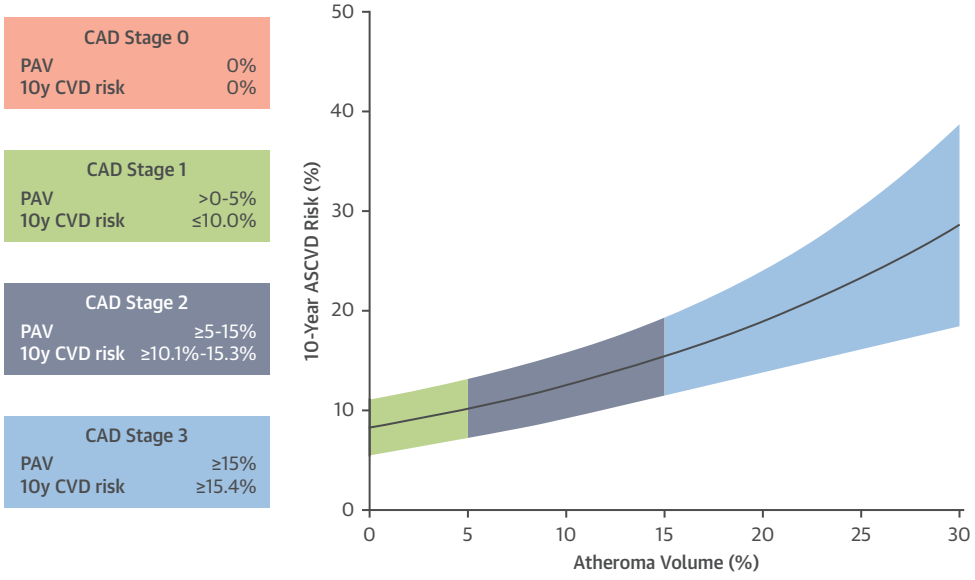
**FIGURE 3 Estimated 10-Year ASCVD Risk for Different CAD Stages**




Shown is 10-year atherosclerotic cardiovascular disease (ASCVD) risk associated with PAVs for the secondary outcome (ASCVD defined as all-cause mortality, nonfatal myocardial infarction, nonfatal stroke). Data shown are predicted absolute risks with 95% CI from an univariable Cox regression model at 10 years of follow-up with the secondary outcome as dependent variable. 95% CI is colored based on CAD stages. CVD = cardiovascular disease; other abbreviations as in Figures 1 and 2.

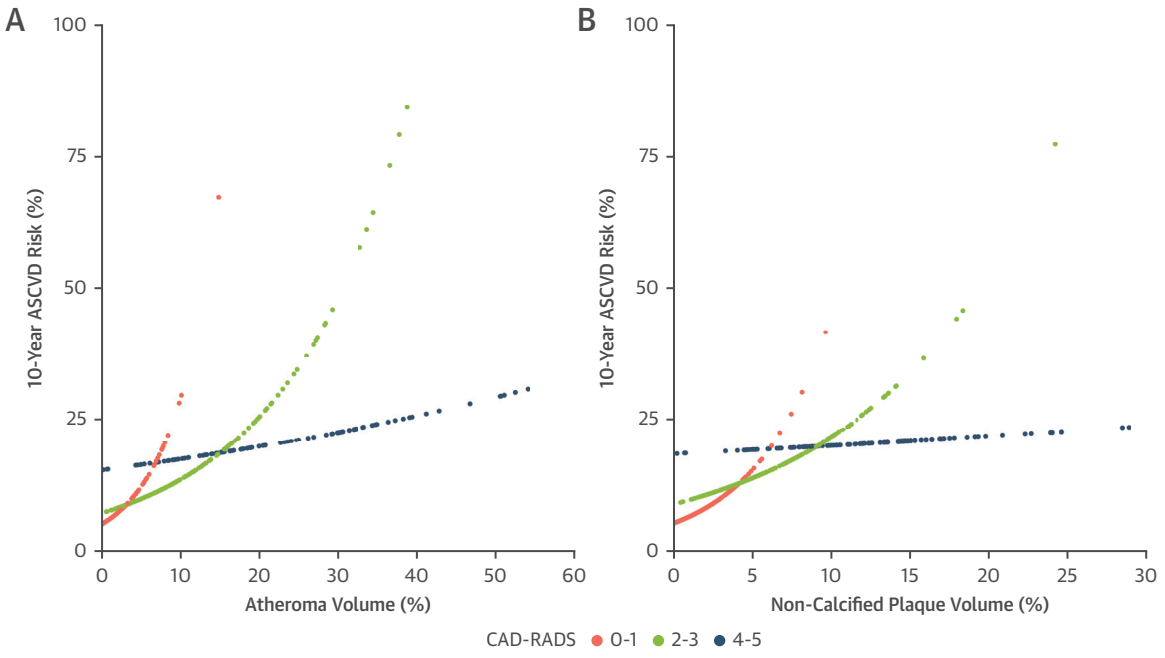
or NCPV on 10-year ASCVD risk was most important in patients with lower CAD-RADS scores. In patients with high CAD-RADS scores, PAV or NCPV only minimally had an impact on ASCVD risk.

## DISCUSSION

Here, we show that a quantitative coronary plaque staging system can effectively stratify patients to estimate 10-year ASCVD risk in a cohort of patients with suspected CAD (Central Illustration). Compared to clinical risk factors, CACS and manual guideline-recommended CCTA assessment of stenosis and plaque, AI-QCT assessment provided additive discriminatory value for prediction of future MACE. Especially in patients with nonobstructive stenosis, plaque volume largely determined 10-year ASCVD risk. Collectively, these data show that evaluation of quantitative plaque analysis through AI-QCT in clinical risk assessment in patients suspected of CAD may improve risk stratification for long-term MACE.

This is the first study to investigate the 10-year prognostic value of quantified atherosclerosis through AI-QCT and a recently proposed staging system.[13,25] Previous studies found associations between qualitative plaque characteristics and low-attenuation noncalcified plaque as predictor of future MACE. Motoyama et al[8] found that high-risk plaques (positive remodeling and low attenuation) were associated with acute coronary syndromes during a 4-year follow-up. Chang et al[11] showed that high-risk plaque characteristics at the lesion level were associated with acute coronary syndromes. In a substudy from the PROMISE trial, Ferencik et al[10] found that high-risk plaque (positive remodeling, low attenuation, or napkin ring sign) was predictive of future MACE. In addition, at 4.7 years of follow-up, a post hoc analysis from SCOT-HEART identified low-attenuation NCPV as the best predictor of the primary outcome of fatal or nonfatal myocardial infarction (aHR: 1.60; 95% CI: 1.10-2.34).[12] In contrast, the present study identified total NCPV and PAV as the strongest predictor of events rather than low-attenuation NCPV alone. Despite having a comparable European study population of chest pain patients when compared to SCOT-HEART, an important difference between the study by Williams et al[12] and this

**FIGURE 4** Survival Estimates According to PAV and CAD-RADS Stenosis Grades

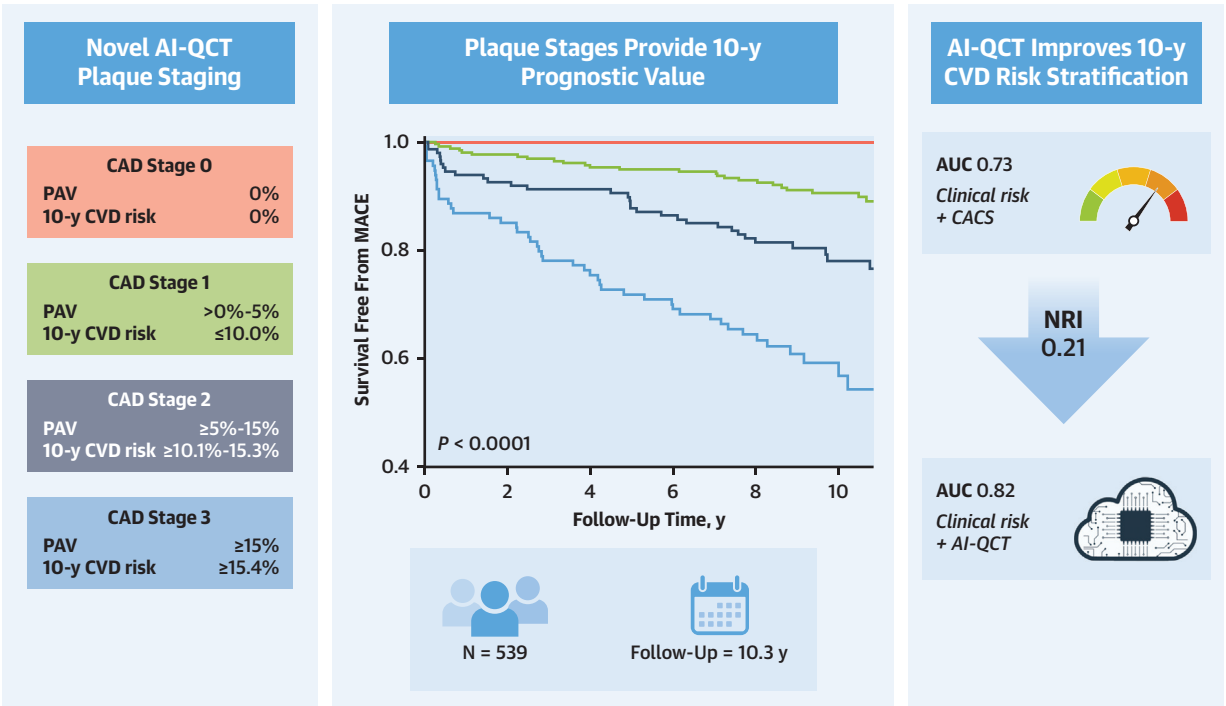



Ten-year survival estimates from Cox regression model with PAV (A) or noncalcified plaque volume (B) and CAD-RADS categories for the secondary outcome (all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke). The Cox regression model consisted of the respective plaque volume and CAD-RADS category as independent variable, and the secondary outcome as dependent variable. Data shown are predicted survival probabilities per individual patient in study population and shown in plot categorized by their CAD-RADS category. Abbreviations as in Figures 1 to 3.

study is the superior prognostication of total NCPV rather than low-attenuation NCPV alone. The SCOT-HEART analysis used on a primary outcome restricted to myocardial infarction rather than MACE in the current study. In terms of imaging, the observed LD-NCP and NCPV were significantly lower in the current study, which may have had greater impact on the discrepancy than the difference in outcomes. There are a few potential reasons for this difference in plaque quantification. First, this may be because different scanning platforms were used. Second, the approach to calculation of noncalcified and LD plaque differed between the 2 studies: a standardized semiautomatic software vs AI-guided plaque quantification. In the absence of a head-to-head comparison of software platforms and a unified societal guideline regarding plaque quantification, it remains to be determined whether our findings will be affirmed in other long-term follow-up cohorts when assessing both LD-NCP and NCPV. Nevertheless, both SCOT-HEART and the current analysis underline the opportunities, through multiple emerging approaches to quantitative CCTA analysis, for MACE risk stratification with further study required to evaluate the differing outputs.[26]

It is valuable to discuss the role of CACS vs NCPV or PAV in risk prognostication. Although CACS had important prognostic value for MACE in the Cox regression and area under the curve analysis, the addition of both CAD-RADS 2.0 and AI-QCT parameters further improved the discriminatory value for MACE. Despite the fact that CACS provides a valuable estimate of overall plaque burden, it is an absolute measure of a solely calcified and stable subset of coronary atherosclerosis as opposed to noncalcified plaques, which have been more strongly associated with plaque rupture.[11,12] In addition, multiple studies have shown that 15%-20% of acute coronary syndrome patients previously had a zero CACS from primarily noncalcified coronary artery pathology.[11,27] As demonstrated by the discrimination and NRI, the addition of AI-QCT characteristics improved MACE risk stratification at 2, 5, and 10 years of follow-up. Hence, the routine addition of reliably estimated plaque burden to CACS may further enhance the prediction of MACE in clinical practice.

**CENTRAL ILLUSTRATION** **AI-QCT Plaque Staging Improves Long-Term CVD Risk Stratification**

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Through 10-year follow-up, artificial intelligence-guided coronary computed tomography angiography (AI-QCT)-guided plaque staging based on percentage atheroma volume (PAV) (left) showed important prognostic value for atherosclerotic cardiovascular disease (CVD) (middle) and provided important reclassification benefit compared to clinical risk characteristics and coronary artery calcium scoring (CACS) (right). AUC = area under the curve; CAD = coronary artery disease; MACE = major adverse cardiac events; NRI = net reclassification improvement.

The current data underline that the superiority of CCTA for prognostication lies beyond the visual grading of coronary artery stenosis to encompass determination of atherosclerosis.[5] In ICONIC, >75% of the culprit lesions prior to myocardial infarction were nonobstructive.[11] In the current study, we found that plaque volumes were a greater determinant of 10-year ASCVD risk in patients with low CAD-RADS stenosis score compared to patients with a high CAD-RADS score. These data suggest that patients with high plaque burden—despite having no obstructive CAD—are at relatively high risk and thus may require more intensive treatment. A practical problem in assessment of coronary plaque on CCTA has been how to score atherosclerotic features for use in clinical reporting and prognosis estimation models. The recently published CAD-RADS 2.0 guideline has incorporated a measure of plaque burden or diffusivity that encompasses CACS, visual estimate, or SIS and is an important step forward.[22] Bittencourt et al[28] showed that among patients with nonobstructive CAD, those with extensive plaque (defined by SIS >4) experienced a higher rate of cardiovascular death or myocardial infarction than those with nonextensive plaque. Min et al[29] demonstrated that a SIS >5 predicted a 5% higher absolute rate of all-cause mortality among 1,127 stable chest pain patients followed up for a mean of 15 months. However, SIS is not routinely measured clinically and may be prone to interobserver variability. The current analysis shows modest, but significant additional value of an AI-QCT analysis with plaque burden over the CAD-RADS 2.0 approach including SIS. As CAD-RADS 2.0 left open the opportunity to incorporate plaque quantification to refining plaque categorization, the present study may underline future guideline refinement.

For clinical implementation and application, the current findings may be placed in light of recent pharmacologic developments. The successful introductions of novel agents, comprising proprotein convertase subtilisin/kexin type 9 inhibitors, low-dose oral anticoagulants, sodium-glucose transport

protein 2 inhibitors, glucagon-like peptide 1 agonists, and anti-inflammatory agents such as colchicine and icosapent ethyl, offer an unique opportunity to target therapies based on the risk prognostication offered by plaque quantification, especially in those with non-obstructive CAD. Given the high cost of these agents, an AI-QCT approach enables improved identification of high-risk patients for cost-effective implementation. In addition, select subgroups of younger patients with low or absent CACS, or those in whom clinical risk scores have less validity (eg, systemic inflammatory disease, strong family history of ASCVD) may benefit from an understanding of quantified NCPV and PAV. A multiparametric model including rapid AI-guided quantitative CCTA analysis with (noncalcified) plaque volume and high-risk plaque characteristics may enable individualized patient management with the goal of ultimately improving ASCVD outcomes.

**STUDY LIMITATIONS.** This study had a relatively small sample size, which was partially compensated by the long follow-up duration, >10 years. Given the single-center nature of the study, CCTA scans were obtained using a single vendor. Because this was a clinical cohort, a significant number of the patients underwent early revascularization on findings of severe obstructive disease, which had to be excluded from the revascularization component of the primary outcome. In the AI-QCT analysis and subsequent quality assurance adjustment, several segments had to be excluded because of poor image quality, which may affect findings in future cohorts. Furthermore, 5% of patients had no full follow-up available and were censored at the time of last contact for the previous follow-up study. Importantly, as the current analysis used a single novel AI-guided approach to quantitative plaque analysis, the specific plaque volume thresholds may require recalibration when used with different software platforms. Finally, although this study has unique 10-year follow-up, the field will benefit from large prospective multicenter studies with long-term follow-up to further validate these findings and assessment of the benefit of treatment.

## CONCLUSIONS

Through 10-year follow-up, AI-QCT-guided plaque staging showed important prognostic value for ASCVD and provided reclassification benefit compared to clinical risk characteristics, CACS, as well as manual guideline-recommended CCTA assessment of stenosis and plaque. These data suggest that current clinical risk assessment in patients suspected of CAD could benefit from implementation of quantitative atherosclerosis assessment that includes plaque burden.

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Nurmohamed is co-founder of Lipid Tools. Dr Stroes has received lecturing/advisory board fees from Amgen, Novartis, Esperion, Sanofi-Regeneron, and Akcea. Drs Min and Earls are employees of and hold equity in Cleerly Inc. Dr Choi has received grant support from GW Heart and Vascular Institute; holds equity in Cleerly, Inc; and has provided consulting services to Siemens Healthineers. Dr Knaapen has received research grants from HeartFlow, Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** In patients with suspected CAD, AI-QCT-guided plaque staging can provide superior risk stratification compared to standard clinical risk scoring, CACS, and manual guideline-recommended CCTA assessment of stenosis and plaque.

**TRANSLATIONAL OUTLOOK:** Prospective studies are needed to evaluate the whether implementation of AI-guided CCTA assessment can improve ASCVD outcomes.

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**KEY WORDS** atherosclerosis, AI-QCT, ASCVD, CAD, CCTA, MACE

**APPENDIX** For an expanded Methods section as well as a supplemental figure and references, please see the online version of this paper.