Interaction of AI-enabled quantitative coronary plaque volumes on coronary CT angiography, FFRCT, and clinical outcomes: a retrospective analysis of the ADVANCE registry

Dundas, J.; Leipsic, J.; Fairbairn, T.; Ng, N.; Sussman, V.; Guez, I.; ... ; Tzimas, G.

Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

Interaction of AI-Enabled Quantitative Coronary Plaque Volumes on Coronary CT Angiography, FFR_{CT}, and Clinical Outcomes: A Retrospective Analysis of the ADVANCE Registry

James Dundas, MBBS; Jonathon Leipsic, MD; Timothy Fairbairn, PhD; Nicholas Ng, BS; Vida Sussman; Ilana Guez; Rachael Rosenblatt; Lynne M. Hurwitz Koweek, MD; Pamela S. Douglas, MD; Mark Rabbat, MD; Gianluca Pontone, MD, PhD; Kavitha Chinnaiyan, MD; Bernard de Bruyne, MD, PhD; Jeroen J. Bax, MD; Tetsuya Amano, MD, PhD; Koen Nieman, MD; Campbell Rogers, MD; Hironori Kitabata, MD; Niels P.R. Sand, MD, PhD; Tomohiro Kawasaki, MD; Sarah Mullen, MBT; Whitney Huey, CCRP; Hitoshi Matsuo, MD, PhD; Manesh R. Patel, MD; Bjarne L. Norgaard, MD, PhD; Amir Ahmadi, MD; Georgios Tzimas, MD

BACKGROUND: Luminal stenosis, computed tomography–derived fractional-flow reserve (FFR_{CT}), and high-risk plaque features on coronary computed tomography angiography are all known to be associated with adverse clinical outcomes. The interactions between these variables, patient outcomes, and quantitative plaque volumes have not been previously described.

METHODS: Patients with coronary computed tomography angiography (n=4430) and one-year outcome data from the international ADVANCE (Assessing Diagnostic Value of Noninvasive FFR_{CT} in Coronary Care) registry underwent artificial intelligence–enabled quantitative coronary plaque analysis. Optimal cutoffs for coronary total plaque volume and each plaque subtype were derived using receiver-operator characteristic curve analysis. The resulting plaque volumes were adjusted for age, sex, hypertension, smoking status, type 2 diabetes, hyperlipidemia, luminal stenosis, distal FFR_{CT}, and translesional delta-FFR_{CT}. Median plaque volumes and optimal cutoffs for these adjusted variables were compared with major adverse cardiac events, late revascularization, a composite of the two, and cardiovascular death and myocardial infarction.

RESULTS: At one year, 55 patients (1.2%) had experienced major adverse cardiac events, and 123 (2.8%) had undergone late revascularization (>90 days). Following adjustment for age, sex, risk factors, stenosis, and FFR_{CT}, total plaque volume above the receiver-operator characteristic curve–derived optimal cutoff (total plaque volume >564 mm^3) was associated with the major adverse cardiac event/late revascularization composite (adjusted hazard ratio, 1.515 [95% CI, 1.093–2.099]; P=0.0126), and both components. Total percent atheroma volume greater than the optimal cutoff was associated with both major adverse cardiac event/late revascularization (total percent atheroma volume >24.4%; hazard ratio, 2.046 [95% CI, 1.474–2.839]; P<0.0001) and cardiovascular death/myocardial infarction (total percent atheroma volume >37.17%, hazard ratio, 4.53 [95% CI, 1.943–10.576]; P=0.0005). Calcified, noncalcified, and low-attenuation percentage atheroma volumes above the optimal cutoff were associated with all adverse outcomes, although this relationship was not maintained for cardiovascular death/myocardial infarction in analyses stratified by median plaque volumes.

CONCLUSIONS: Analysis of the ADVANCE registry using artificial intelligence–enabled quantitative plaque analysis shows that total plaque volume is associated with one-year adverse clinical events, with incremental predictive value over luminal stenosis or abnormal physiology by FFR_{CT}.

Correspondence to: James Dundas, MBBS, Department of Cardiology, University Hospital of N Tees, Stockton-on-Tees, TS19 8PE, United Kingdom.
Email james.dundas@nhs.net
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCIMAGING.123.016143.
For Sources of Funding and Disclosures, see page 212.

Circulation: Cardiovascular Imaging is available at www.ahajournals.org/journal/circimaging

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02499679.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: artificial intelligence ■ atherosclerotic plaque ■ cardiac death ■ computed tomography angiography ■ coronary artery disease ■ major adverse cardiac events ■ myocardial infarction

See Editorial by Bittencourt

CLINICAL PERSPECTIVE

It is already known that lesion-specific features on coronary computed tomography angiography, including stenosis severity, obstructive noninvasive physiology by fractional flow reserve (computed tomography–derived fractional-flow reserve), and high-risk plaque features are all associated with risk of adverse outcomes. Using artificial intelligence–enabled plaque analysis, we found that the same is true of patient-level quantitative total plaque volumes, even after adjusting for patient age, sex, cardiac risk factors, stenosis severity, and computed tomography–derived fractional-flow reserve. This suggests that a higher plaque burden is an independent predictor of events, which in our study were particularly driven by late revascularization. This implies high plaque volumes could identify those likely to have persistent symptoms, a finding that merits further investigation. Importantly, our analysis revealed that plaque burden provides incremental predictive value beyond noninvasive physiology assessment using computed tomography–derived fractional-flow reserve, underscoring the potential of quantitative plaque analysis to enhance risk assessment and refine clinical decision-making in patients with suspected coronary artery disease. Further research is needed to confirm and expand upon these findings, particularly in the context of long-term outcomes and symptom management.

Nonstandard Abbreviations and Acronyms

ADVANCE	Assessing Diagnostic Value of Noninvasive FFR_{CT} in Coronary Care
AI-QCPA	artificial intelligence–enabled quantitative coronary plaque analysis
CCTA	coronary computed tomography angiography
CPAV	calcified percent atheroma volume
FFR_{CT}	computed tomography–derived fractional-flow reserve
HR	hazard ratio
LAP	low-attenuation plaque
LAPPAV	low-attenuation percent atheroma volume
LAPV	low-attenuation plaque volume
MACE	major adverse cardiac event
MI	myocardial infarction
NCPAV	noncalcified percent atheroma volume
ROC	receiver-operator characteristic curve
TPAV	total percent atheroma volume
TPV	total plaque volume

Coronary computed tomography angiography (CCTA) is an established test for the assessment of coronary artery disease and carries a class IA recommendation for the investigation of stable chest pain in patients at intermediate-high risk of coronary artery disease by the American College of Cardiology/American Heart Association,[1] with similar recommendations from the European Society of Cardiology[2] and UK NICE.[3] Existing guidelines for the analysis of CCTA[4] describe a framework for reporting both severity of coronary stenosis and burden of atheromatous plaque, leveraging the ability of CCTA to image coronary atheroma, unlike invasive coronary angiography or noninvasive ischemia imaging. Plaque burden[5] and certain high-risk plaque characteristics[6] have been shown to predict adverse patient outcomes independent of coronary stenosis.[7] However, in routine clinical practice, these factors are usually reported qualitatively or semiquantitatively, using segment-involvement score or surrogates such as coronary calcium score.

Quantitative plaque analysis using semiautomated or artificial intelligence (AI)–assisted automated tools has been shown to be feasible,[8] and multiple quantitative plaque characteristics have been associated with major adverse cardiac effects (MACEs),[9] with quantitative low-attenuation plaque (LAP) burden identified as a predictor of future myocardial infarction (MI).[10] However, the interaction between these measures and functional assessment of physiology across stenotic lesions with computed tomography–derived fractional-flow reserve (FFR_{CT}) is less well understood and has been identified as an area for further investigation.[8]

The 1-year outcomes from the ADVANCE (Assessing Diagnostic Value of Noninvasive FFR_{CT} in Coronary Care) registry have been previously reported,[11] demonstrating an association between abnormal noninvasive coronary physiology by $FFR_{CT} \leq 0.80$ and increased risk

of cardiovascular death or MI. This large international cohort of 4737 patients with suitable image quality for FFR_{CT} analysis provides the potential for further insight into the potential benefits of quantitative assessment of coronary plaque. We evaluated the relationship between AI-enabled quantitative coronary plaque analysis (AI-QCPA) of CCTAs from the ADVANCE registry with clinical outcomes, adjusting for anatomic stenosis and noninvasive physiology derived by FFR_{CT}.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. The design[12] and 1-year outcomes[11] of the ADVANCE registry have been previously described. This was an international observational registry from 38 centers, designed to evaluate real-world clinical impact of FFR_{CT}, which from 2015 to 2017 recruited 5083 patients with at least 30% coronary stenosis after undergoing CCTA for suspected coronary artery disease. All patients provided written informed consent following Institutional Review Board review and approval. Clinical outcomes were assessed at 90 days and 1 year and were adjudicated by a blinded independent clinical events committee at the Duke Clinical Research Institute (Durham, NC).

Studies previously analyzed for FFR_{CT} underwent AI-QCPA at a single center (HeartFlow Inc, Mountain View, CA) by personnel blinded to clinical characteristics and FFR_{CT} results. Of the 5083 patients recruited to the original registry, 190 were not submitted for FFR_{CT}, and 156 were deemed not analyzable for FFR_{CT}, leaving 4734 with adequate image quality for assessment. A further 307 previously processed cases (6.5%) could not undergo AI-QCPA, leaving 4430 cases with plaque volumes generated to be included in this study (Figure 1, Consortium diagram).

The AI methodology, training, and validation of this AI-QCPA tool have been previously described in detail in the Supplemental Methods of Tzimas et al[13] study of nomographic quantitative plaque data. The tool, which has been validated against intravascular ultrasound,[14,15] assessed total plaque volume (TPV, expressed in mm^3) and stratified this by computed tomography attenuation into calcified plaque volume, noncalcified plaque volume, and LAP volume (LAPV).[13] LAP was defined as voxels with attenuation of <30 Hounsfield Units (HU). Calcified plaque was derived using a process of adaptive thresholding based on aortic luminal contrast to generate a scan-specific HU threshold for calcium.[16] Noncalcified plaque was then defined as voxels with attenuation between 30 HU and the calcified plaque threshold. These 4 categories were further stratified by vessel volume (defined as plaque volume/vessel volume×100), which has been suggested as an optimal method for normalizing plaque volume for vessel size,[17] giving indices of total percent atheroma volume (TPAV, expressed as %), calcified percent atheroma volume (CPAV), noncalcified percent atheroma volume (NCPAV), and low-attenuation percent atheroma volume (LAPPAV), respectively.

Prespecified outcomes of interest were MACE (defined as all-cause mortality, nonfatal MI, or acute coronary syndrome leading to unplanned hospitalization with urgent revascularization), late revascularization (defined as being coronary revascularization >90 days), a composite of the 2, and cardiovascular death and MI during 12 months of follow-up.

Statistical Analysis

Continuous variables are presented as median (interquartile range) and categorical variables are presented as number (percentage). Receiver-operator characteristic curve (ROC) analysis using the Youden *J* statistic was used to derive optimum cutoffs for each of the 8 plaque volume variables (TPV and TPAV, calcified plaque volume, and CPAV, noncalcified plaque volume, and NCPAV, LAPV, and LAPPAV) for the specified outcomes. Each variable was dichotomized at this cutoff, and outcomes compared as an unadjusted hazard ratio (HR). This was then adjusted in a multivariable model for both patient demographic and clinical variables (age, sex, hypertension, type 2 diabetes, smoking status, and hyperlipidemia); and CCTA variables (stenosis severity, per-patient nadir FFR_{CT}, and translesional FFR_{CT} across the most severe lesion [delta-FFR_{CT}]). Comparison with each outcome was also made with the cohort dichotomized by the median plaque volume for each variable. Survival curves for time-to-event analysis were constructed based on all available follow-up data at 1 year with the use of Kaplan-Meier estimates, and were compared with the use of a log-rank test. Each plaque characteristic was also analyzed as a continuous variable within the adjusted multivariable models for each outcome. A 2-sided $P<0.05$ was considered significant for all tests. All statistical analyses (frequency, means, logistic regression, PHREG, and LIFETEST) were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

Of 4430 subjects from the ADVANCE registry with CCTA studied for AI-QCPA, 2918 (65.9%) were males. Type 2 diabetes was present in 958 (21.8%), hypertension in 2635 (59.9%), and current smoking in 2251 (54.9%) subjects. Obstructive coronary artery disease (at least one anatomic stenosis ≥50%) was present in 3156 (71.2%), with 2919 (65.9%) demonstrating obstructive coronary physiology (FFR_{CT}≤0.8). Baseline demographics, stratified by presence or absence of MACE, are summarized in Table 1. Details of patient enrollment including breakdown by region, country, and institution can be found in Table S1.

After AI-QCPA analysis, the median TPV was 390 mm^3 (IQR, 163–760 mm^3), median calcified plaque volume, 59 mm^3 (IQR, 16–145 mm^3), median noncalcified plaque volume, 323 mm^3 (IQR, 141–615 mm^3), and median LAAPV, 9 mm^3 (IQR, 3–19 mm^3). The ROC-derived optimum cutoffs for the outcome of MACE or late revascularization were 564 mm^3 for TPV, 85 mm^3 for calcified plaque volume, 323 mm^3 for noncalcified plaque volume, 10 mm^3 for LAPV, 24.3% for TPAV, 3.2% for CPAV, 18.9% for NCPAV, and 0.3% for LAPPAV, respectively. Further details of the median plaque volume for each variable, and the ROC-derived optimal cutoffs for each of the study outcomes (MACE or late revascularization, combination of cardiovascular death and MI and MACE and late revascularization separately) are

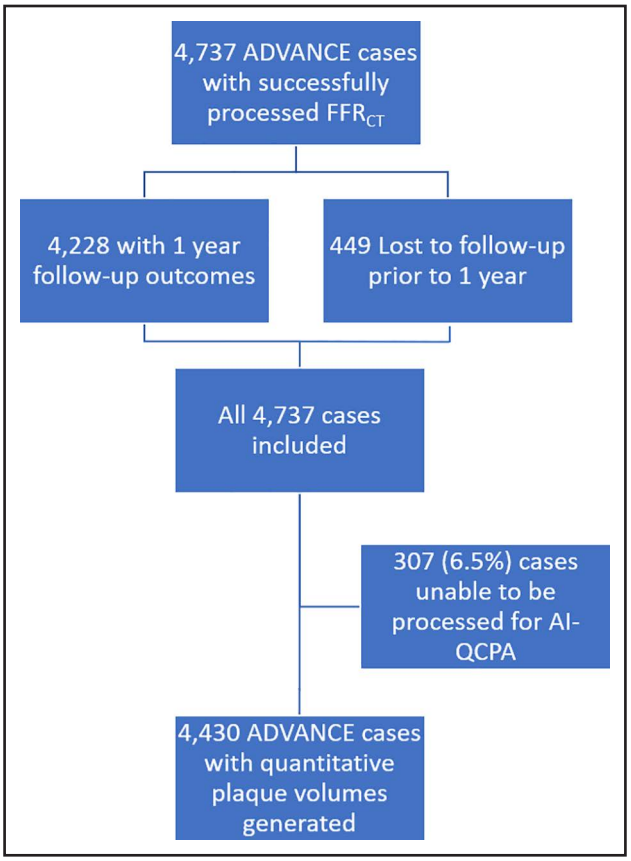

Figure 1. Enrollment consortium diagram.
In 6.5% of patients, reduced image quality including motion artifact and image noise precluded automated artificial intelligence–enabled quantitative coronary plaque analysis (AI-QCPA) analysis. ADVANCE indicates Assessing Diagnostic Value of Noninvasive FFR$_{CT}$ in Coronary Care; and FFR$_{CT}$, fractional-flow reserve derived from coronary computed tomography angiography.

presented in Table 2. The area under the ROC for each optimum cutoff is detailed in Table S2.

At 1 year, 55 patients (1.2%) had experienced a MACE. A total of 1190 patients (26.9%) had undergone coronary revascularization, of which 1035 (87.0%) were by percutaneous coronary intervention and 155 (13.0%) by coronary artery bypass grafting. Among the total population, 123 patients (2.8%) were classified as late revascularization (>90 days after enrollment). The combination outcome of MACE or late revascularization was met in 170 patients (3.8%). Twenty-seven patients experienced either cardiovascular death (15 patients, 0.3%) or MI (12 patients, 0.27%). The 1-year clinical outcomes are presented in Table 3. Further comparison of the demographics, risk factors, CCTA, and FFR$_{CT}$ results of patients undergoing percutaneous coronary intervention, coronary artery bypass grafting, or no revascularization can be found in Table S3.

One-Year Outcomes by Plaque Component

Unadjusted plaque volume or percentage atheroma volume greater than the ROC-derived optimum cut for all 8 plaque characteristics was associated with all 4 adverse clinical outcomes (MACE, late revascularization, combination of MACE and late revascularization, and cardiovascular death/MI) at 1 year. However, this association did not remain for all plaque characteristics and outcomes once adjusted for age, sex, cardiac risk factors, stenosis severity, nadir FFR$_{CT}$, and delta-FFR$_{CT}$. The unadjusted and adjusted HRs for each plaque characteristic are presented in Table 4 for the composite outcome of MACE or late revascularization, and in Table 5 for cardiovascular death and MI. HRs for the individual outcomes of MACE (Table S4) and late revascularization

Table 1. Patient Demographics, Symptom Status at Enrollment, CCTA and FFR$_{CT}$ Findings

Demographics	All patients (n=4430)	Patients with MACE (n=55)	Patients without MACE (n=4375)
Median age	67 (59–73)	72 (62–77.5)	67 (59–73)
Men	2918/4430 (65.9%)	40/55 (72.7%)	2878/4375 (65.8%)
Type II diabetes	958/4394 (21.8%)	18/55 (32.7%)	940/4339 (21.7%)
Hypertension	2635/4400 (59.9%)	32/55 (58.2%)	2603/4345 (59.9%)
Current smoker	2251/4102 (54.9%)	30/52 (57.7%)	2221/4050 (54.8%)
Symptom status			
None	1079/4430 (24.4%)	11/55 (20.0%)	1068/4375 (24.4%)
Typical angina	967/4430 (21.8%)	13/55 (23.6%)	954/4375 (21.8%)
Atypical angina	1621/4430 (36.6%)	13/55 (23.6%)	1608/4375 (36.8%)
Noncardiac chest pain	277/4430 (6.3%)	4/55 (7.3%)	273/4375 (6.2%)
Dyspnea	438/4430 (9.9%)	12/55 (21.8%)	426/4375 (9.7%)
Unknown	48/4430 (1.1%)	2/55 (3.6%)	46/4375 (1.1%)
CCTA findings			
Stenosis <50%	1265/4430 (28.6%)	8/55 (14.5%)	1257/4375 (28.7%)
Stenosis ≥50%	3156/4430 (71.2%)	46/55 (83.6%)	3110/4375 (71.1%)
Stenosis not evaluable	9/4430 (0.2%)	1/55 (1.8%)	8/4375 (0.2%)
FFR$_{CT}$ findings			
FFR$_{CT}$>0.8	1511/4430 (34.1%)	12/55 (21.8%)	1499/4375 (34.3%)
FFR$_{CT}$≤0.8	2919/4430 (65.9%)	43/55 (78.2%)	2876/4375 (65.7%)

Values are expressed as median (IQR) or n (%). Denominators vary for patient demographics, due to missing registry data for type II diabetes (n=36 missing), hypertension (n=30 missing), and smoking status (n=328 missing). In 9/4430 patients suitable for AI-QCPA analysis, coronary stenosis grading was not available. AI-QCPA indicates artificial intelligence–enabled quantitative coronary plaque analysis; CCTA, coronary computed tomography angiography; FFR$_{CT}$, fractional-flow reserve derived from coronary computed tomography angiography; and MACE, major adverse cardiac event.

Table 2. Median Plaque Volume Variables and Youden *J* Statistic ROC-Derived Optimum Cutoffs by Study Outcome

	Median (IQR) (min–max)	ROC-derived optimal cutoffs by outcome			
		MACE or late revascularization	MACE	Late revascularization	CV death or MI
Absolute plaque volumes					
TPV, mm³	390 (163–760) (0–4187)	64.42	473.88	570.04	473.84
CPV, mm³	59 (16–145) (0–1777)	85.14	61.00	85.22	63.89
NCPV, mm³	323 (141–615) (0–3163)	323.08	522.60	246.82	574.07
LAPV, mm³	9 (3–19) (0–191)	10.00	24.00	9.99	21.02
Percent atheroma volumes					
TPAV, %	15.1 (6.8–26.6) (0–75.1)	24.39	32.57	24.53	37.17
CPAV, %	2.3 (0.7–5.1) (0–33.5)	3.18	5.99	3.18	5.99
NCPAV, %	12.5 (5.9–21.4) (0–56.9)	18.86	25.30	18.88	31.14
LAPPAV, %	0.3 (0.1–0.7) (0–3.9)	0.34	0.76	0.24	0.76

CPAV indicates calcified percent atheroma volume; CPV, calcified plaque volume; CV, cardiovascular; IQR, interquartile range; LAPPAV, low-attenuation percent atheroma volume; LAPV, low-attenuation plaque volume; MACE, major adverse cardiac event; MI, myocardial infarction; NCPAV, noncalcified percent atheroma volume; NCPV, noncalcified plaque volume; ROC, receiver-operator curve; TPAV, total percent atheroma volume; and TPV, total plaque volume.

(Table S5) separately can be found in the supplementary appendix. Adjusted HRs for plaque characteristics analyzed as continuous variables are presented for composite MACE/late revascularization and CV death/MI outcomes in Table 6 and for the separate outcomes of MACE and late revascularization in Table S6.

Further analyses of each plaque variable, stratified instead by median plaque volume, are available for each outcome in the Supplemental Material (composite of MACE or late revascularization in Table S7, cardiovascular death and MI in Table S8, MACE alone in Table S9, and late revascularization in Table S10). HRs for the effect of the demographic, clinical, and CCTA variables on each outcome are also found in the Supplemental Material; for multivariable models dichotomized by optimal TPV cutoff in Table S11, and for models dichotomized by median TPV in Table S12.

Total plaque volume greater than cutoff remained associated with composite of MACE and late revascularization at 1 year following adjustment for age/sex/risk factors/stenosis/FFR_{CT}/delta-FFR_{CT} (HR, 1.52 [95% CI, 1.09–2.10]; *P*=0.0126) as well as both components (MACE HR, 1.86 [95% CI, 1.02–3.39]; *P*=0.0425; late revascularization HR, 1.68 [95% CI, 1.15–2.47]; *P*=0.0075). There was an increased risk of cardiovascular death and MI associated with adjusted TPV, though this did not reach statistical significance (HR, 1.87 [95% CI, 0.79–4.43]; *P*=0.1534). Adjusted TPAV greater than optimal cutoff was also associated with increased risk of MACE/late revascularization (HR, 2.05 [95% CI, 1.47–2.84]; *P*<0.0001); as well as MACE (HR, 3.37 [95% CI, 1.87–6.07]; *P*<0.0001) and late revascularization (HR, 2.47 [95% CI, 1.68–3.61]; *P*<0.0001) individually. Adjusted TPAV was also associated with cardiovascular death/MI (HR, 4.53 [95% CI, 1.94–10.58]; *P*=0.0005), unlike adjusted TPV. The relationship between adjusted TPV/TPAV and MACE/late revascularization was maintained when dichotomized by median plaque volume (Table S7). TPAV remained associated with all 4 outcomes when analyzed as a continuous variable (Table 6; Table S6). An illustration of the AI-QCPA technique, with Kaplan-Meier curves demonstrating the relationship of TPV and TPAV with MACE/late revascularization can be found in Figure 2.

Calcified plaque volume greater than cutoff was associated with 1-year MACE/late revascularization (HR, 1.74 [95% CI, 1.26–2.41]; *P*=0.0009), and both MACE and late revascularization individually, following adjustment for age/sex/risk factors/stenosis/FFR_{CT}/delta-FFR_{CT}, but not with cardiovascular death/MI (HR, 1.90 [95% CI, 0.79–4.53]; *P*=0.15). Once corrected for vessel volume, CPAV greater than cutoff was associated with all 4 study outcomes including CV death/MI (HR, 3.12 [95% CI, 1.39–7.03]; *P*=0.006), and this was also true when CPAV was evaluated as a continuous variable.

Adjusted noncalcified plaque volume greater than cutoff was also associated with MACE/late revascularization (HR, 1.53 [95% CI, 1.08–2.16]; *P*=0.0164), driven primarily by late revascularization (HR for MACE, 1.76 [0.99–3.14]; *P*=0.054; HR for late revascularization 1.79 [95% CI, 1.15–2.80]; *P*=0.0103), but the association with CV death/MI was not statistically

Table 3. Outcome Events at 1-Year Follow-Up

Outcomes	No. of events (frequency)
MACE	55 (1.2%)
MACE components	
Cardiovascular death	15/55 (27.3%)
Noncardiovascular death	20/55 (36.4%)
Myocardial infarction	12/55 (21.8%)
ACS leading to urgent revascularization	8/55 (14.5%)
Cardiovascular death and MI	27 (0.6%)
All revascularization	1190 (26.9%)
Revascularization modality	
Percutaneous coronary intervention	1035/1190 (87%)
Coronary artery bypass graft	155/1190 (13%)
Early revascularization (<90 d)	1067 (24.1%)
Revascularization modality	
Percutaneous coronary intervention	936/1067 (87.7%)
Coronary artery bypass graft	131/1067 (12.3%)
Late revascularization (≥90 d)	123 (2.8%)
Revascularization modality	
Percutaneous coronary intervention	99/123 (80.5%)
Coronary artery bypass graft	24/123 (19.5%)
MACE or all revascularization	1217 (27.5%)
MACE or early revascularization	1102 (24.9%)
MACE or late revascularization	170 (3.8%)

ACS indicates acute coronary syndrome; MACE, major adverse cardiac event; and MI, myocardial infarction.

significant (HR, 1.73 [95% CI, 0.77–3.88]; *P*=0.1816). However, adjusted noncalcified percent atheroma volume greater than cutoff was associated with all 4 outcomes, including cardiovascular death/MI (adjusted HR, 6.48 [95% CI, 2.75–15.26]; *P*<0.0001), which remained the case when analyzed as a continuous variable.

LAPV greater than optimal cutoff was associated with all 4 outcomes following adjustment for age/sex/risk factors/stenosis/FFR_{CT}/delta-FFR_{CT} (HR for MACE/late revascularization, 1.54 [95% CI, 1.09–2.18]; *P*=0.0141; HR for cardiovascular death/MI, 3.12 [95% CI, 1.39–7.00]; *P*=0.0058). This relationship was maintained for all 4 outcomes with adjusted low-attenuation percent atheroma volume greater than cutoff (HR for MACE/late revascularization, 1.48 [95% CI, 1.05–2.09]; *P*=0.0253; HR for cardiovascular death/MI, 2.79 [95% CI, 1.24–6.26]; *P*=0.0132). When analyzed dichotomized by median plaque volume, both LAPV and LAPPAV greater than the median were associated with late revascularization (see Table S10), but not the other outcomes.

Kaplan-Meier curves stratified by both optimal cutoffs and median plaque, demonstrating the relationship between all 3 adjusted percent atheroma volume subtypes with MACE/late revascularization are shown in Figure 3. The relationships between TPAV and all 3 plaque subtypes to the outcome of CV death/MI, similarly stratified, are illustrated in Figure 4.

DISCUSSION

In keeping with previous studies,[5,6,8,9,18] our study found that quantitative TPV generated by an AI-assisted tool is associated with adverse patient outcomes. This relationship is maintained following adjustment for patient age and sex, despite the association of male sex and increasing age with increased plaque volumes,[13] and for confounding factors that have previously been shown to predict adverse outcomes themselves, namely anatomic stenosis. Importantly, our analysis is the first to assess the incremental prognostic utility of quantitative plaque measures from CCTA beyond noninvasive physiology. Our data suggest that TPV and TPAV provide incremental prediction of risk beyond flow-limiting coronary physiology, as assessed by nadir FFR_{CT} and translesional delta-FFR_{CT} across the most severe stenosis in a vessel, driven primarily by greater discrimination of late revascularization.

There is growing interest in machine learned quantitative plaque analyses for computed tomography to provide measures of total atherosclerotic burden and to help inform medical management and risk. Recently, Nurmohammed[18] and colleagues explored the prognostic utility of AI-QCPA for event prediction beyond traditional measures of visual stenosis grading in 536 subjects followed for a median of 10 years. They found that noncalcified percent atheroma volume of >7.5% had a >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. Similarly, Lin[19] and colleagues explored a deep learning-based plaque tool and found that a total plaque volume of 238.5 mm^3 or higher was associated with an increased risk of MI (HR, 5.36 [95% CI, 1.70–16.86]; *P*=0.0042) after adjustment for the presence of deep learning-based obstructive stenosis (HR, 2.49 [1.07–5.50]; *P*=0.0089) and the ASSIGN clinical risk score (HR, 1.01 [, 0.99-1.04; *P*=0.35).

Our study however represents the first observational data that examine the interaction between noninvasive coronary physiology by FFR_{CT} and overall plaque burden. While it is unsurprising that plaque burden is predictive of events, the fact that this is additional to FFR_{CT} is a new finding that may provide further granularity in predicting patient prognosis. Importantly the events in our study are largely related to late revascularization, owing the modest number of death and MI. Therefore, our findings may provide new insight into mechanisms of residual angina beyond the focality of the anatomic stenosis and lesion-specific physiology. If a higher plaque burden is a predictor of persisting symptoms beyond these more traditional focal measures, this may prove helpful in prospectively identifying patients who may have persisting symptoms and angina, which could inform more thoughtful upfront

Table 4. HRs for MACE or Late Revascularization by Plaque Characteristic Greater Than ROC-Derived Optimum Cutoff vs Below Cutoff

	Unadjusted HR (95% CI)	*P* value	HR adjusted for patient sex, age, cardiac risk factors,* stenosis, FFR_{CT}, and delta-FFR_{CT} (HR [95% CI])	*P* value
Plaque volume greater than ROC-derived optimum cutoff, mm^3				
TPV>564.42 mm^3	2.011 (1.488–2.719)	<0.0001	1.515 (1.093–2.099)	0.0126
CPV>85.14 mm^3	2.189 (1.613–2.971)	<0.0001	1.739 (1.255–2.408)	0.0009
NCPV>323.08 mm^3	2.070 (1.503–2.849)	<0.0001	1.527 (1.081–2.158)	0.0164
LAPV>10 mm^3	2.231 (1.620–3.072)	<0.0001	1.542 (1.091–2.179)	0.0141
Percent atheroma volume greater than ROC-derived optimum cutoff, %				
TPAV>24.39%	2.706 (2.003–3.657)	<0.0001	2.046 (1.474–2.839)	<0.0001
CPAV>3.18%	2.372 (1.744–3.226)	<0.0001	1.876 (1.352–2.601)	0.0002
NCPAV>18.86%	2.752 (2.034–3.724)	<0.0001	2.057 (1.478–2.862)	<0.0001
LAPPAV>0.34%	2.193 (1.590–3.024)	<0.0001	1.483 (1.050–2.094)	0.0253

CPAV indicates calcified percent atheroma volume; CPV, calcified plaque volume; FFR_{CT}, computed tomography–derived fractional-flow reserve; HR, hazard ratio; LAPPAV, low-attenuation percent atheroma volume; LAPV, low-attenuation plaque volume; MACE, major adverse cardiac event; NCPAV, noncalcified percent atheroma volume; NCPV, noncalcified plaque volume; TPAV, total percent atheroma volume; and TPV, total plaque volume.

*Cardiac risk factors adjusted for in the multivariable model; hypertension, smoking, type 2 diabetes, hyperlipidemia.

clinical decision-making. Expert consensus[8] has already identified that future studies should evaluate the clinical outcomes using plaque imaging to guide management including plaque-guided medical therapy. Our findings would support TPV (and TPAV) on a per-patient basis being considered as a variable in those studies, as distinct from lesion-level or vessel-level variables such as stenosis severity or FFR_{CT} to complement overall risk assessment and perhaps refine which patients may have outstanding angina in the absence of abnormal physiology.

Furthermore, if the late revascularization events reported most likely represent elective intervention for ongoing angina symptoms despite medical therapy, then this may suggest that total coronary plaque burden could be predictive of persisting symptom presence. Overall plaque burden would be expected to proportionately reduce coronary luminal volume even in absence of focal stenosis.[20] This perhaps may help identify those patients with a more diffuse pattern of atherosclerosis, with poor vasoreactivity and worse overall vascular health, who then experience refractory angina despite medical therapy. Unfortunately, ADVANCE did not assess anginal symptom status at the 90-day and 1-year follow-up visits, so this relationship between plaque burden and residual symptoms remains speculative. Further studies should evaluate the interaction between total plaque burden and symptoms, independent of obstructive stenosis or physiology. The question of whether coronary revascularization assists with symptom relief,[21] and how this may interact with total plaque burden and distribution, also remains unanswered.

All 3 percentage atheroma volume plaque subtypes (CPAV, NCPAV, and LAPPAV) were predictive not just

Table 5. HRs for Cardiovascular Death and MI by Plaque Characteristic Greater Than ROC-Derived Optimum Cutoff vs Below Cutoff

	Unadjusted HR (95% CI)	*P* value	HR adjusted for patient sex, age, cardiac risk factors,* stenosis, FFR_{CT}, and delta-FFR_{CT} (HR [95% CI])	*P* value
Plaque volume greater than ROC-derived optimum cutoff, mm^3				
TPV>473.84 mm^3	2.697 (1.212–6.004)	0.0151	1.873 (0.791–4.433)	0.1534
CPV>63.89 mm^3	2.609 (1.142–5.960)	0.0229	1.896 (0.794–4.529)	0.15
NCPV>574.07 mm^3	2.431 (1.143–5.171)	0.0211	1.732 (0.774–3.876)	0.1816
LAPV>21.02 mm^3	3.965 (1.864–8.435)	0.0003	3.119 (1.390–7.000)	0.0058
Percent atheroma volume greater than ROC-derived optimum cutoff, %				
TPAV>37.17%	5.661 (2.627–12.199)	<0.0001	4.533 (1.943–10.576)	0.0005
CPAV>5.99%	3.856 (1.813–8.204)	0.0005	3.122 (1.387–7.027)	0.0060
NCPAV>31.14%	7.679 (3.564–16.547)	<0.0001	6.480 (2.752–15.262)	<0.0001
LAPPAV>0.76%	3.519 (1.654–7.486)	0.0011	2.786 (1.239–6.262)	0.0132

CPAV indicates calcified percent atheroma volume; CPV, calcified plaque volume; FFR_{CT}, computed tomography–derived fractional-flow reserve; HR, hazard ratio; LAPPAV, low-attenuation percent atheroma volume; LAPV, low-attenuation plaque volume; MI, myocardial infarction; NCPAV, non-calcified percent atheroma volume; NCPV, non-calcified plaque volume; TPAV, total percent atheroma volume; and TPV, total plaque volume.

*Cardiac risk factors adjusted for in the multivariable model; hypertension, smoking, type 2 diabetes, hyperlipidemia.

Table 6. HRs for the Outcomes of MACE/Late Revascularization (Upper) and Cardiovascular Death and MI (Lower), for Plaque Characteristics Expressed As Continuous Variables

	HR adjusted for patient sex, age, cardiac risk factors,* stenosis, FFR_{CT}, and delta-FFR_{CT} (HR per mm^3 plaque volume [95% CI])	*P* value
Outcome: MACE or late revascularization		
Plaque volume characteristic		
TPV	1.000 (1.000–1.001)	0.0170
CPV	1.001 (1.000–1.002)	0.0033
NCPV	1.000 (1.000–1.001)	0.0438
LAPV	1.003 (0.994–1.013)	0.5109
Percent atheroma volume characteristic		
TPAV	1.026 (1.016–1.038)	<0.0001
CPAV	1.077 (1.047–1.109)	<0.0001
NCPAV	1.032 (1.017–1.048)	<0.0001
LAPPAV	1.286 (0.974–1.699)	0.0763
Outcome: cardiovascular death and myocardial infarction		
Plaque volume characteristic		
TPV	1.001 (1.000–1.001)	0.0330
CPV	1.002 (1.001–1.003)	0.0020
NCPV	1.001 (1.000–1.001)	0.1126
LAPV	1.013 (0.992–1.033)	0.2282
Percent atheroma volume characteristic		
TPAV	1.041 (1.014–1.069)	0.0024
CPAV	1.120 (1.053–1.192)	0.0003
NCPAV	1.048 (1.010–1.087)	0.0120
LAPPAV	1.710 (0.920–3.180)	0.0901

CPAV indicates calcified percent atheroma volume; CPV, calcified plaque volume; FFR_{CT}, computed tomography–derived fractional-flow reserve; HR, hazard ratio; LAPPAV, low-attenuation percent atheroma volume; LAPV, low-attenuation plaque volume; MACE, major adverse cardiac event; MI, myocardial infarction; NCPAV, noncalcified percent atheroma volume; NCPV, noncalcified plaque volume; TPAV, total percent atheroma volume; and TPV, total plaque volume.

*Cardiac risk factors adjusted for in the multivariable model; hypertension, smoking, type 2 diabetes, hyperlipidemia.

of late revascularization, but of the more definitive hard end points of MACE and cardiovascular death/MI. This is in line with the findings of prior studies, including large datasets specifically associating LAP with MI.[10] However, this finding was not maintained in analyses dichotomized by median plaque volumes, rather than optimal cutoffs. In these analyses, NCPAV and LAPPAV remained associated with late revascularization, but not with CV death/MI (Table S8) or MACE (Table S9). This is unsurprising for several reasons. First, any effect from LAP would have to be very strong to outweigh the absolute effect of total plaque, and it may be that given the relatively low number of MIs at 1 year, our study was insufficiently powered to detect this.

Furthermore, the optimal cutoffs were derived from this same study sample, which may therefore overestimate their discriminatory ability. We do not propose these specific optimal cutoffs as representing binary values that can be immediately applied to other populations. Rather, they represent potential cut points for validation in future studies. The association of all 4 percentage atheroma volumes with late revascularization, even when the cohort is divided by the median values, serves to illustrate that higher plaque burden may incrementally be related to ongoing symptoms beyond physiology and stenosis severity. These findings are also in line with a recent analysis from Sakai and colleagues[22] highlighting plaque differences driving different physiological phenotypes. Focal noncalcified plaque results in sudden pressure loss, whereas more diffuse disease is associated with gradual pressure loss, which may serve as a driver of residual angina.

Last, there is growing awareness that LAP is more relevant on a per-lesion basis rather than a measure of overall coronary atherosclerosis. The pathology typically attributed to LAP is plaque rupture, leading to MI. However, MI constitutes only a small portion of the events in our cohort. Our analysis aggregates plaque volumes across the entire coronary vasculature on a per-patient basis. If LAP represents necrotic plaque core that is at higher risk of plaque rupture events, we might expect LAPV to be predictive on a per-lesion or per-vessel analysis, which indeed it was in the ICONIC[7] and other studies.[23] The interaction between noninvasive coronary physiology and high-risk plaque features for predicting acute coronary syndromes was explored

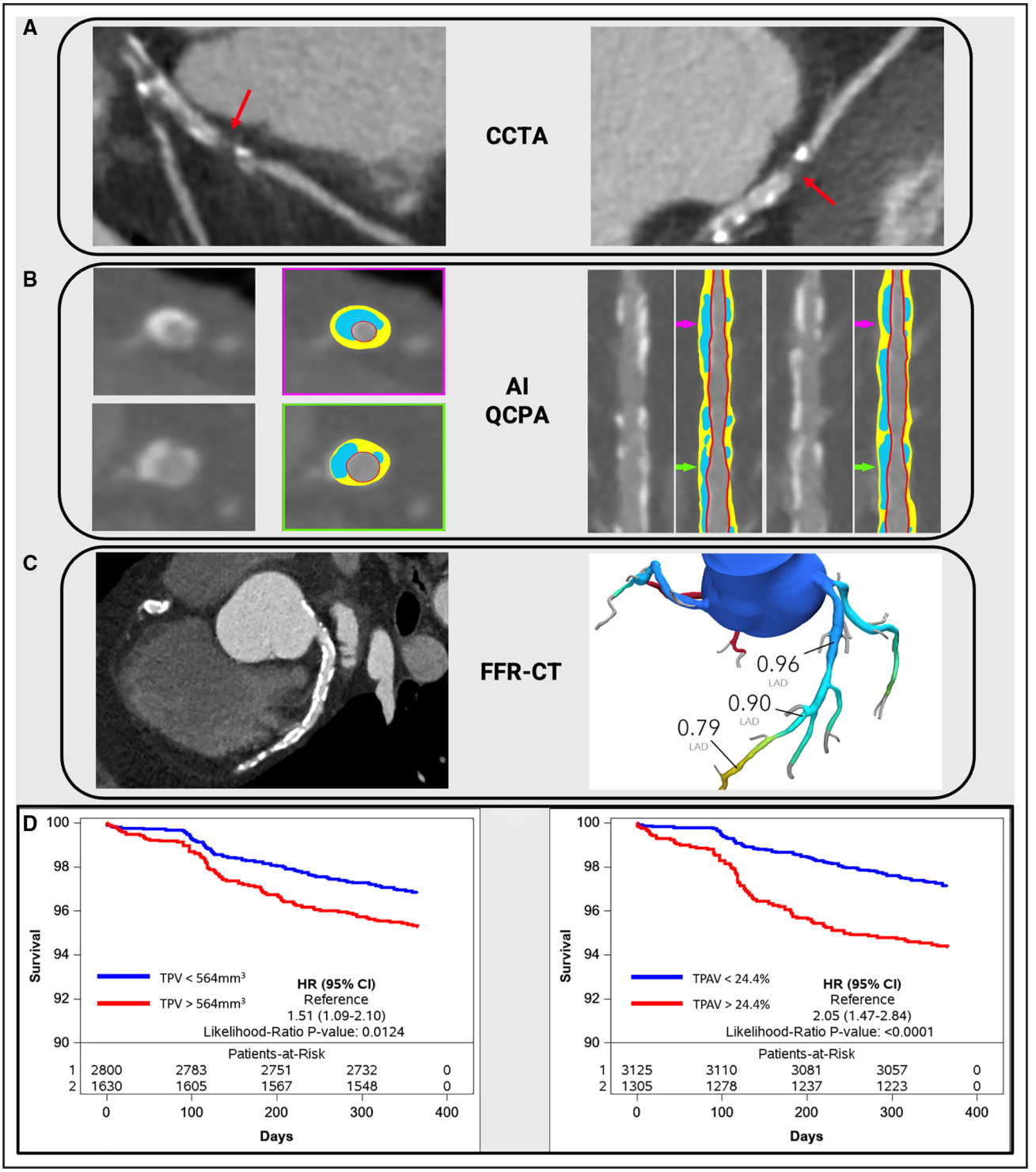

Figure 2. Central illustration of artificial intelligence–enabled quantitative coronary plaque analysis (AI-QCPA).
A, Coronary computed tomography angiography (CCTA) images showing a sub-total occlusion of the mid left anterior descending (LAD) coronary artery. **B**, AI-QCPA on CCTA. Blue-colored areas are calcified plaque, and yellow-colored areas are noncalcified plaque. The pink and green arrows of the longitudinal view (**right**) correspond to the specific corresponding cross-sectional view (**left**). **C**, CCTA image demonstrating a stenosis in the LAD coronary artery (**left**) and fractional-flow reserve derived from coronary computed tomography angiography (FFR_{CT}) 3-dimensional model (**right**) showing the FFR_{CT} values across the LAD coronary artery. **D**, Kaplan-Meier curves for the association of total plaque volume (**bottom left**) and total percent atheroma volume (**bottom right**) greater than optimum cutoff (total plaque volume [TPV]>564 mm^3, total percent atheroma volume [TPAV]>24.4%), with composite of major adverse cardiac event (MACE) or late revascularization, adjusted for age, sex, hypertension, smoking status, type 2 diabetes, hyperlipidemia, stenosis severity, FFR_{CT}, and delta-FFR_{CT}.

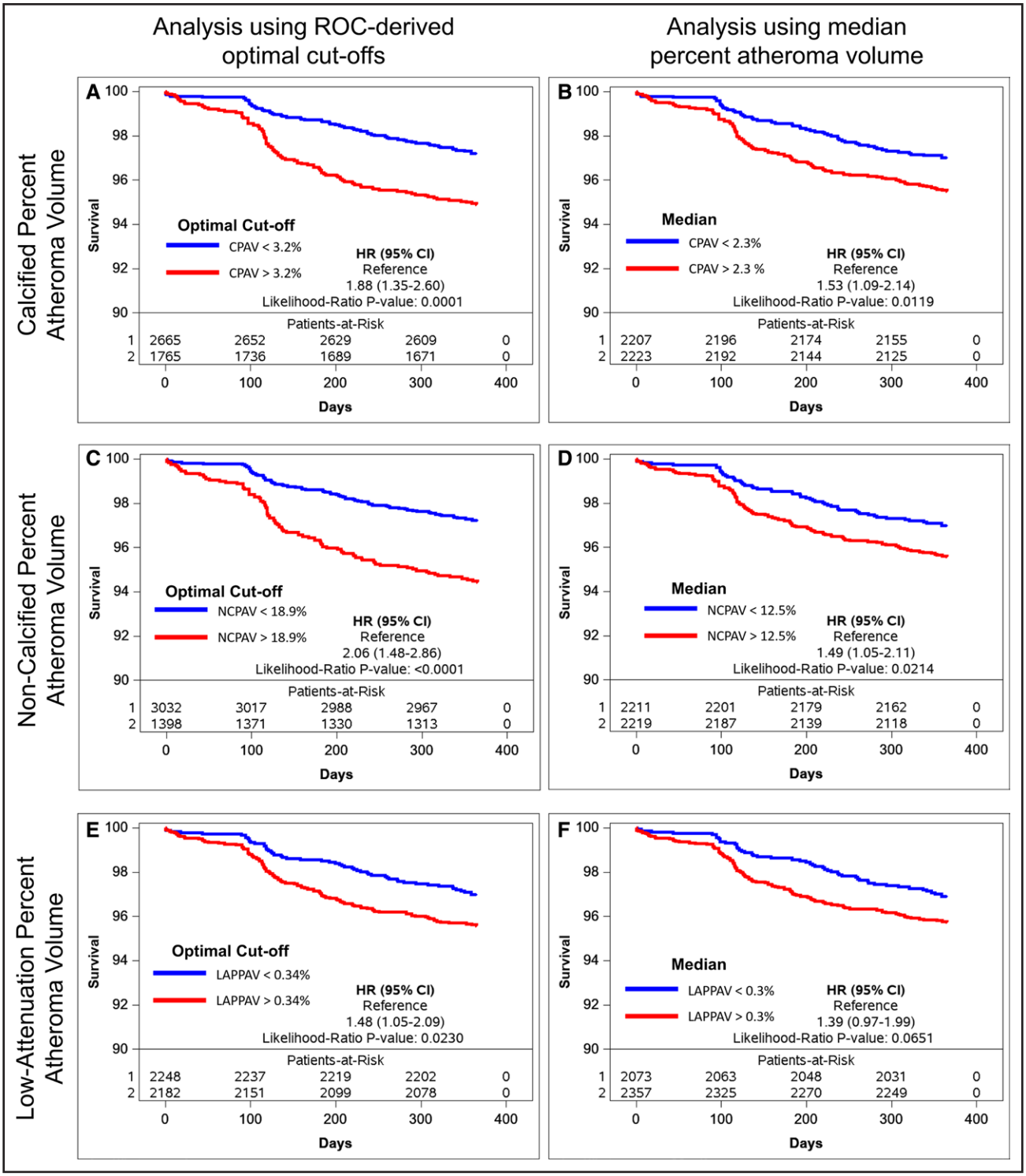

Figure 3. Kaplan-Meier curves for the association of adjusted percent atheroma volume subtypes (calcified percent atheroma volume [CPAV] A and B, non-calcified plaque volume [NCPAV] C and D, and low-attenuation percent atheroma volume [LAPPAV] E and F) with composite of major adverse cardiac event (MACE) and late revascularization, adjusted for age, sex, hypertension, smoking status, type 2 diabetes, hyperlipidemia, stenosis, fractional-flow reserve derived from coronary computed tomography angiography (FFR_{CT}), and delta-FFR_{CT}.

Analyses using receiver-operator characteristic (ROC)-derived optimal cutoffs on the left (**A**, CPAV>3.2%; **C**, NCPAV>18.9%; and **E** LAPPAV>0.34%); and analyses stratified by median plaque on the right (**B**, CPAV>2.3%; **D**, NCPAV>12.5%; **F**, LAPPAV>0.3%).

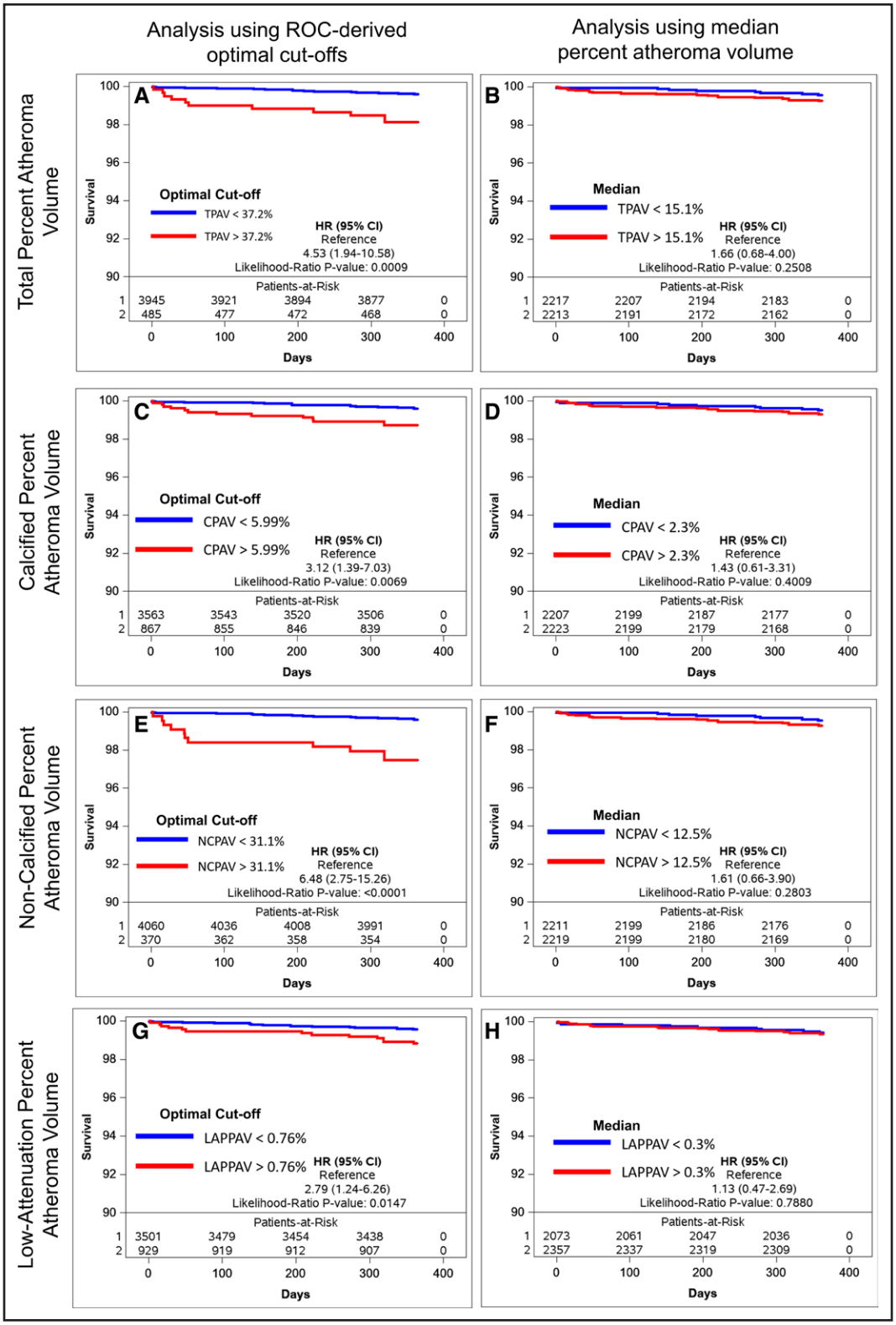

Figure 4. Kaplan-Meier curves for the association of adjusted percent atheroma volume subtypes (total percent atheroma volume [TPAV] A and B, calcified percent atheroma volume [CPAV] C and D, noncalcified plaque volume [NCPAV] E and F, and low-attenuation percent atheroma volume [LAPPAV] G and H) with cardiovascular death and myocardial infarction, adjusted for age, sex, hypertension, smoking status, type 2 diabetes, hyperlipidemia, stenosis, fractional-flow reserve derived from coronary computed tomography angiography (FFR_{CT}), and delta-FFR_{CT}.

Analyses using receiver-operator characteristic (ROC)-derived optimal cutoffs on the left (**A**, TPAV>37.2%; **C**, CPAV>5.99%; **E**, NCPAV>31.1%, and **G**, LAPPAV>0.76%); and analyses stratified by median plaque on the right (**B**, TPAV>15.1%; **D**, CPAV>2.3%; **F**, NCPAV>12.5%; and **F**, LAPPAV>0.3%).

in the EMERALD study,[24] and the relationship between quantitative plaque analysis, noninvasive physiology, and acute coronary syndromes will be further investigated in the forthcoming EMERALD II study.[25] Our findings suggest that overall aggregate plaque volumes may predict residual angina and symptoms on a patient level but are unlikely to provide practical guidance on lesion-specific management such as revascularization decision-making.

Limitations

All of the limitations previously reported for the ADVANCE study[11] remain pertinent to our analysis; namely, that as a nonrandomized registry evaluating real-world practice, it is prone to potential bias both in enrollment and in local nonrandomized treatment decisions, and conclusions regarding treatment strategy cannot be drawn from this data. Some demographic variables were not collected by the ADVANCE registry, including baseline medication use and ethnicity, meaning that any differences between groups in those respects could be a source of unrecognized bias. Future studies are needed to explore the potential influence of ethnicity on the study's outcomes and provide a more comprehensive analysis.

Furthermore, the ROC-derived optimal cutoffs were developed from the same cohort that we analyzed for outcomes, optimizing their performance in this population, and these values may not be appropriate in a different population. That said, our analysis is meant to explore the interplay between the focality and the burden of coronary atherosclerosis in predicting late revascularization. It should be noted that nomographic values for quantitative plaque analysis have been recently published using this AI-QCPA tool.[13]

As discussed above, the relatively short follow-up (12 months) and low number of absolute events, particularly cardiovascular death and MI, means that associations are driven mainly by late revascularization. This may limit the power for exploration of individual plaque subtypes, particularly LAPV. Moreover, identification of LAP on CCTA may have changed management during follow-up, such as the initiation, intensification, or improved patient concordance with disease-modifying medication, which would tend to confound our analysis and reduce the apparent effect of LAP.

Late revascularization has uncertain prognostic implications, given the lack of improvement in prognosis from revascularization in large randomized trials in stable chronic coronary syndromes.[26] It is also an outcome vulnerable to bias, as treating clinicians were aware of the CCTA result when offering revascularization. Larger studies with longer follow-up are needed to enhance statistical power and provide more robust insights into the observed outcomes.

The lack of per-vessel or per-lesion level data precludes drawing conclusions on the effects of quantitative plaque features on acute coronary syndrome culprit lesions. Moreover, lack of data on both symptom burden and anti-anginal medication use during follow-up reduces the ability to assess our proposed interaction between total plaque burden and future symptom status.

It is important to acknowledge that our study population predominantly consists of patients referred for FFR_{CT}, which typically includes a higher proportion of individuals with obstructive CAD. We recognize that this might limit the generalizability of our findings to a broader population of patients, such as all-comers undergoing CCTA evaluation.

Last, our analysis does not account for multiple hypothesis testing in the interaction of the 8 plaque variables and 4 outcomes being assessed, increasing the probability of a type I error.

Conclusions

Analysis of the ADVANCE registry using AI-enabled quantitative plaque analysis shows an association between TPV and 1-year adverse clinical outcomes, predominantly late revascularization, beyond that predicted by luminal stenosis or abnormal physiology by noninvasive FFR_{CT}.

ARTICLE INFORMATION

Received September 20, 2023; accepted December 12, 2023.

Affiliations

Department of Cardiology, North Tees and Hartlepool NHS Foundation Trust, Stockton-on-Tees, United Kingdom (J.D.). Department of Radiology, University of British Columbia, Vancouver, Canada (J.D., J.L., V.S., I.G., R.R., G.T.). Liverpool Heart and Chest Hospital, United Kingdom (T.F.). HeartFlow Inc, Mountain View, CA (N.N., C.R., S.M., W.H.). Duke Clinical Research Institute, Duke University, Durham, NC (L.M.H.K., P.S.D., M.R.P.). Loyola University Medical Center, Maywood, IL (M.R.). Centro Cardiologico Monzino, Milan, Italy (G.P.). Beaumont Hospital, Royal Oak, MI (K.C.). Cardiovascular Centre Aalst OLV Clinic, Belgium (B.d.B.). Leiden University Medical Centre, the Netherlands (J.J.B.). Aichi Medical University, Nagakute, Japan (T.A.). Stanford University Medical Centre, CA (K.N.). Wakayama Medical University, Japan (H.K.). Hospital of South West Jutland, Denmark (N.P.R.S.). Shin-Koga Hospital, Fukuoka, Japan (T.K.). Gifu Heart Center, Japan (H.M.). Aarhus University Hospital, Denmark (B.L.N.). Mount Sinai Heart, New York City (A.A.). Division of Cardiology, Lausanne University Hospital and University of Lausanne, Switzerland (G.T.).

Sources of Funding

The ADVANCE (Assessing Diagnostic Value of Noninvasive FFR_{CT} in Coronary Care) registry was funded by HeartFlow, Inc.

Disclosures

Dr Patel has received research grants from HeartFlow, Bayer, Janssen, and the National Heart, Lung, and Blood Institute; and has served on the advisory board for HeartFlow, Bayer, and Janssen. Dr Nørgaard has received unrestricted institutional research grants from Siemens and HeartFlow. Dr Fairbairn has served on the Speakers Bureau for HeartFlow. Dr Nieman has received institutional research support from Siemens Healthineers, HeartFlow, GE Healthcare, and Bayer Healthcare. Dr Hurwitz Koweek has received research support and speaking fees from HeartFlow and Siemens. Dr Pontone has received institutional research grant and honorarium as consultant/speaker from GE Healthcare, Bracco, Medtronic, Bayer, and HeartFlow. Dr Rabbat has served as a consultant for HeartFlow. Ms Mullen is an employee of and owns equity in HeartFlow. Dr De

Bruyne has an institutional consulting relationship with Boston Scientific, Abbott Vascular, CathWorks, Siemens, GE Healthcare, and Coroventis Research; has received institutional research grants from Abbott Vascular, Coroventis Research, CathWorks, and Boston Scientific; and holds equities in Philips, Siemens, GE Healthcare, Edwards Lifesciences, HeartFlow, Opsens, and Celiad. Dr Rogers is employee of and owns equity in HeartFlow. Dr Leipsic has received an unrestricted research grant from GE Healthcare, has stock options and received consulting fees from HeartFlow and Circle CVI, and speaking fees from GE and Philips. Dr Ng is an employee of HeartFlow. The other authors report no conflicts.

Supplemental Material

Tables S1–S12

REFERENCES

1. Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, Blankstein R, Boyd J, Bullock-Palmer RP, Conejo T, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *Circulation*. 2021;144:e368–e454. doi: 10.1161/CIR.0000000000001030
2. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes: the task force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J*. 2019;3:407–477. doi: 10.1093/eurheartj/ehz425
3. National Institute of Health and Clinical Excellence. Overview | Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis | Guidance | NICE. 2010. Accessed September 16, 2023. https://www.nice.org.uk/guidance/cg95
4. Cury RC, Leipsic J, Abbara S, Achenbach S, Berman D, Bittencourt M, Budoff M, Chinnaiyan K, Choi AD, Ghoshhajra B, et al. CAD-RADS™ 2.0 - 2022 coronary artery disease-reporting and data system: an expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Cardiology (ACC), the American College of Radiology (ACR), and the North America Society of Cardiovascular Imaging (NASCI). *J Cardiovasc Comput Tomogr*. 2022;16:536–557. doi: 10.1016/j.jcct.2022.07.002
5. Mortensen MB, Dzaye O, Steffensen FH, Bøtker HE, Jensen JM, Rønnow Sand NP, Kragholm KH, Sørensen HT, Leipsic J, Mæng M, et al. Impact of plaque burden versus stenosis on ischemic events in patients with coronary atherosclerosis. *J Am Coll Cardiol*. 2020;76:2803–2813. doi: 10.1016/j.jacc.2020.10.021
6. Williams MC, Moss AJ, Dweck M, Adamson PD, Alam S, Hunter A, Shah ASV, Pawade T, Weir-McCall JR, Roditi G, et al. Coronary artery plaque characteristics associated with adverse outcomes in the SCOT-HEART study. *J Am Coll Cardiol*. 2019;3:291–301. doi: 10.1016/j.jacc.2018.10.066
7. Chang H-J, Lin FY, Lee S-E, Andreini D, Bax J, Cademartiri F, Chinnaiyan K, Chow BJW, Conte E, Cury RC, et al. Coronary atherosclerotic precursors of acute coronary syndromes (ICONIC). *J Am Coll Cardiol*. 2018;22:2511–2522. doi: 10.1016/j.jacc.2018.02.079
8. Shaw L, Narula J, Blankstein R. Society of cardiovascular computed tomography/ north American society of cardiovascular imaging – expert consensus document on coronary CT imaging of atherosclerotic plaque. *J Cardiovascular Computed Tomography*. 2021;2:93–109. doi: 10.1016/j.jcct.2020.11.002
9. Nadjiri J, Hausleiter J, Jahnichen C, Will A, Hendrich E, Martinoff S, Hadamitzky M. Incremental prognostic value of quantitative plaque assessment in coronary CT angiography during 5 years of follow up. *J Cardiovascular Computed Tomography*. 2016;10:97–104. doi: 10.1016/j.jcct.2016.01.007
10. Williams MC, Kwiecinski J, Doris M, McElhinney P, D'Souza MS, Cadet S, Adamson PD, Moss AJ, Alam S, Hunter A, et al. Low-attenuation noncalcified plaque on coronary computed tomography angiography predicts myocardial infarction: results from the multicenter SCOT-HEART trial. *Circulation*. 1452;141:1452–1462. doi: 10.1161/CIRCULATIONAHA.119.044720
11. Patel M, Nørgaard B, Fairbairn T. 1-year impact on medical practice and clinical outcomes of FFRCT. *J Am Coll Cardiol Img*. 2020;1:97–105. doi: 10.1016/j.jcmg.2019.03.003
12. Chinnaiyan KM, Akasaka T, Amano T. Rationale, design and goals of the HeartFlow assessing diagnostic value of non-invasive FFR CT in coronary care (ADVANCE) registry. *J Cardiovasc Comput Tomogr*. 2017;1:62–67. doi: 10.1016/j.jcct.2016.12.002
13. Tzimas G, Gulsin GS, Everett RJ, Akodad M, Meier D, Sewnarain K, Ally Z, Alnamasy R, Ng N, Mullen S, et al. Age- and sex-specific nomographic CT quantitative plaque data from a large international cohort. *JACC Cardiovasc Imaging*. 2023:S1936-878X(23)00234-6. doi: 10.1016/j.jcmg.2023.05.011.
14. Narula J, Stuckey T, Nakazawa G, Maehara A, Matsumura M, Petersen K, Mirza S, Ng N, Mullen S, Schaap M, et al. Primary results of the REVEAL-PLAQUE study: a prospective quantitative assessment of AI-based CCTA plaque volume compared with IVUS. *J Cardiovasc Comput Tomogr*. 2023;17:S39. doi: 10.1016/j.jcct.2023.05.096
15. Petersen K, Schaap M, Mirza S, Ng N, Maehara A, Matsumura M, Safian R. 452 quantitative assessment of AI-based CCTA plaque volume compared with IVUS. *J Cardiovasc Comput Tomogr*. 2022;16:S24. doi: 10.1016/j.jcct.2022.06.057
16. Schuhbaeck A, Otaki Y, Achenbach S, Schneider C, Slomka P, Berman DS, Dey D. Coronary calcium scoring from contrast coronary CT angiography using a semiautomated standardized method. *J Cardiovasc Comput Tomogr*. 2015;9:446–453. doi: 10.1016/j.jcct.2015.06.001
17. Rosendael A, Lin F, Ma X, Hoogen I, Chang H-J. Percent atheroma volume: optimal variable to report whole-heart atherosclerotic plaque burden with coronary CTA, the PARADIGM study. R. *J Cardiovasc Comput Tomogr*. 2020;5:400–406. doi: 10.1016/j.jcct.2020.01.012
18. Nurmohamed NS, Bom MJ, Jukema RA, de Groot RJ, Driessen RS, van Diemen PA, de Winter RW, Gaillard EL, Sprengers RW, Stroes ESG, et al. AI-guided quantitative plaque staging predicts long-term cardiovascular outcomes in patients at risk for atherosclerotic CVD. *JACC Cardiovasc Imaging*. 2023: S1936-878X(23)00277-2 . doi: 10.1016/j.jcmg.2023.05.020.
19. Lin A, Manral N, McElhinney P, Killekar A, Matsumoto H, Kwiecinski J, Pieszko K, Razipour A, Grodecki K, Park C, et al. Deep learning-enabled coronary CT angiography for plaque and stenosis quantification and cardiac risk prediction: an international multicentre study. *Lancet Digit Health*. 2022;4:e256–e265. doi: 10.1016/S2589-7500(22)00022-X
20. Ihdayhid AR, Fairbairn TA, Gulsin GS, Tzimas G, Danehy E, Updegrove A, Jensen JM, Taylor CA, Bax JJ, Sellers SL, et al. Cardiac computed tomography-derived coronary artery volume to myocardial mass. *J Cardiovasc Comput Tomogr*. 2022;16:198–206. doi: 10.1016/j.jcct.2021.10.007
21. Al-Lamee R, Francis D. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet*. 2017;10115:31–40. doi: 10.1016/S0140-6736(17)32714-9
22. Sakai K, Mizukami T, Leipsic J, Belmonte M, Sonck J, Nørgaard BL, Otake H, Ko B, Koo B, Maeng M, et al. Coronary atherosclerosis phenotypes in focal and diffuse disease. *JACC Cardiovasc Imaging*. 2023;16:1452. doi: 10.1016/j.jcmg.2023.05.018
23. Yang S, Lee J, Hoshino M. Prognostic implications of comprehensive whole vessel plaque quantification using coronary computed tomography angiography. *JACC: Asia*. 2021;1:37–48. doi: 10.1016/j.jacasi.2021.05.003
24. Lee J, Choi G, Koo B. Identification of high-risk plaques destined to cause acute coronary syndrome using coronary computed tomographic angiography and computational fluid dynamics. *JACC Cardiovasc Imaging*. 1032;12:1032–1043. doi: 10.1016/j.jcmg.2018.01.023
25. Koo B-K. Seoul national university hospital. exploring the mechanism of plaque rupture in acute coronary syndrome using coronary CT angiography and computational fluid dynamics II. Accessed September 16, 2023. https://clinicaltrials.gov/study/NCT03591328
26. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, Chaitman BR, Senior R, López-Sendón J, Alexander KP, et al; ISCHEMIA Research Group. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382:1395–1407. doi: 10.1056/NEJMoa1915922