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Feature article

Coronary CTA plaque volume severity stages according to invasive coronary angiography and FFR

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A B S T R A C T

Background: Atherosclerotic plaque characterization by coronary computed tomography angiography (CCTA) enables quantification of coronary artery disease (CAD) burden and type, which has been demonstrated as the strongest discriminant of future risk of major adverse cardiac events (MACE). To date, there are no clinically useful thresholds to assist with understanding a patient's disease burden and guide diagnosis and management, as there exists with coronary artery calcium (CAC) scoring. The purpose of this manuscript is to establish clinically relevant plaque stages and thresholds based on evidence from invasive angiographic stenosis (ICA) and fractional flow reserve (FFR) data.

Methods: 303 patients underwent CCTA prior to ICA and FFR for an AHA/ACC clinical indication. Quantitative computed tomography (QCT) was performed for total plaque volume (TPV, mm^3) and percent atheroma volume (PAV, %). We segmented atherosclerosis by composition for low-density non-calcified plaque (LD-NCP), non-calcified plaque (NCP), and calcified plaque (CP). ICAs were evaluated by quantitative coronary angiography (QCA) for all coronary segments for % diameter stenosis. The relationship of atherosclerotic plaque burden and composition by QCT to ICA stenosis extent and severity by QCA and presence of ischemia by FFR was assessed to develop 4 distinct disease stages.

Results: The mean age of the patients was 64.4 ± 10.2 years; 71% male. At the 50% QCA stenosis threshold, QCT revealed a mean PAV of 9.7 (±8.2)% and TPV of 436 (±444.9)mm^3 for those with non-obstructive CAD; PAV of 11.7 (±8.0)% and TPV of 549.3 (±408.3) mm^3 for 1 vessel disease (1VD), PAV of 17.8 (±9.8)% and TPV of 838.9 (±550.7) mm^3 for 2VD, and PAV of 19.2 (±8.2)% and TPV of 799.9 (±357.4) mm^3 for 3VD/left main disease (LMD). Non-ischemic patients (FFR >0.8) had a mean PAV of 9.2 (±7.3) % and TPV of 422.9 (±387.9 mm^3) while patients with at least one vessel ischemia (FFR ≤0.8) had a PAV of 15.2 (±9.5)% and TPV of 694.6 (±485.1). Definition of plaque stage thresholds of 0, 250, 750 mm^3 and 0, 5, and 15% PAV resulted in 4 clinically distinct stages in which patients with no, non-obstructive, single VD and multi-vessel disease were optimally distributed.

Conclusion: Atherosclerotic plaque burden by QCT is related to stenosis severity and extent as well as ischemia. We propose staging of CAD atherosclerotic plaque burden using the following definitions: Stage 0 (Normal, 0% PAV, 0 mm^3 TPV), Stage 1 (Mild, >0–5% PAV or >0–250 mm^3 TPV), Stage 2 (Moderate, >5–15% PAV or >250–750 mm^3 TPV) and Stage 3 (Severe, >15% PAV or >750 mm3 TPV).

1. Introduction

Coronary CT angiography (CCTA) has demonstrated high diagnostic performance for evaluation of coronary artery disease (CAD) stenosis.[1–3] Prior multicenter studies have demonstrated CCTA diagnostic sensitivity for angiographically severe stenosis to be 94–99% and specificity to be 64–83%, when compared to a quantitative coronary angiographic (QCA) reference standard. CCTA has also been evaluated for its ability to quantify and characterize coronary atherosclerosis. In a recent meta-analysis of 42 studies including 1360 patients, the sensitivity and

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specificity of CCTA for identification and exclusion of any atherosclerotic plaque was 93% and 92%, respectively, with an area under the receiver operating characteristics curve of 0.97.[4]

Both angiographic stenosis and qualitative atherosclerotic assessment by CCTA impart significant clinical utility beyond conventional risk factors of CAD.[5] In the CONFIRM study of 23,854 patients undergoing CCTA, presence of angiographically obstructive CAD conferred increased hazards of 2.60 for mortality ($p < 0.0001$) at 2.3 years.[6] For major adverse cardiac events (MACE)—including death, myocardial infarction and late revascularization—the presence of stenosis was associated with an 11-fold higher rate of MACE during 2.4 ± 1.2 years follow-up.[7] In CONFIRM, the predictive ability for MACE was further augmented by combining angiographic stenosis with atherosclerosis extent by qualitative estimates.[8]

Recently, quantitative computed tomography (QCT) has been introduced for determining atherosclerotic plaque burden and composition in all epicardial coronary arteries and their branches, findings that have proven to provide robust prognostic value.[9–14] In the ICONIC study, the strongest discriminants of future acute coronary syndromes were presence of LD-NCP volumes as well as the presence of high risk plaques (HRP) with >75% of culprit lesions exhibiting <50% stenosis by CCTA.[12] Similarly, in the SCOT-HEART and PROMISE trials, LD-NCP was the strongest predictor of future myocardial infarction.[13,14] Collectively, these findings provide an additive and independent value of severe stenosis and atherosclerosis for risk prediction.

To date, there is no staging system for atherosclerotic plaque burden as exists for coronary artery calcium scoring (CACS). The CACS system is a widely used for prediction of adverse clinical events, including mortality, nonfatal myocardial infarction, and other major adverse events, with improved prognostic and risk reclassification value above and beyond clinical risk factors alone.[15–21] CACS categories have been incorporated into guidelines.[22–24] Because quantitative coronary plaque analysis takes all of the plaque into account, not just the calcified plaque reported with CACS, a plaque volume staging system may prove to be even more prognostic of clinical events and useful for selection of optimal medical therapy.

This study articulates a potentially useful staging system based upon coronary atherosclerotic plaque volume, the categories are guided by the relationship of atherosclerotic plaque burden by QCT to stenosis extent and severity by invasive QCA and ischemia by invasive FFR.

2. Methods

2.1. Study population

The study population is a consecutively enrolled derivation cohort of CREDENCE (clinicaltrials.gov NCT02173275), a prospective, multicenter clinical trial recruiting stable patients with suspected CAD.[25,26] Eligibility criteria included referral to non-emergent invasive angiography based on a class II indication from the ACC/AHA clinical practice guidelines for stable ischemic heart disease. All index tests were interpreted in blinded fashion by core laboratories. The institutional review board of each enrolling site approved the study protocol and all patients provided written informed consent. Patient demographics and cardiovascular risk factors were prospectively collected and recorded.

2.2. CCTA imaging protocols

CCTA was performed using single or dual source CT scanners of ≥64-detector rows. Sites performed CCTA in accordance with the guidelines established by the Society of Cardiovascular Computed Tomography (SCCT).[27] Patients received nitroglycerin immediately prior to CCTA acquisition to improve image quality. Beta-blockers were administered to patients who required heart rate control.

2.3. QCT analysis

Quantitative coronary atherosclerosis evaluation by CCTA was performed for all CCTAs. Coronary segments with a diameter ≥1.5 mm were included in the analysis using the modified 18-segment SCCT model. 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.

Quantitative atherosclerosis characterization was performed for every coronary artery and its branches using an automated artificial intelligence (AI)-enabled web-based software platform (Cleerly Labs, Cleerly Inc., Denver CO) (9,10). Plaque volumes (mm^3) were calculated for each coronary lesion and then summated to compute the total plaque volume at the patient level. Plaque volume was categorized using Hounsfield unit (HU) ranges, with LD-NCP defined as plaques <30 HU, NCP defined as HU between −30 and + 350, and CP defined as >350 HU.[28,29] Coronary plaque burden was normalized to vessel volume to account for variation in coronary artery volume. Plaque burden was reported as percent atheroma volume (PAV), which was calculated as Plaque Volume/Vessel Volume x 100%, the Vessel Volume is defined as the volume of all coronary segments with a diameter of >1.5 mm regardless of whether they contain plaque or not. This is different from other QCT software which will include only the vessel volume of segments containing plaque.

When impaired image quality was present due to motion, poor opacification, beam hardening or other artifacts, only the portion of the coronary artery with poor quality was excluded from the analysis, this step was performed by the QA technologists. Amongst the 171,195 mm of vessel length evaluated, a total of 1861 mm (1.09%) of vessel length was excluded with an average exclusion measuring 14.1 (±13.9) mm.

2.4. Quantitative coronary angiography

Patients underwent diagnostic ICA by board-certified interventional cardiologists in accordance with usual clinical indications and by imaging standards set forth by the American College of Cardiology/Society for Cardiac Angiography and Interventions. ICA images were transmitted to independent masked readers at the Angiographic Core Laboratory. QCA was performed by a blinded core laboratory using an automated edge-detection algorithm by standard approaches for any lesion that appeared >30% stenosis, as previously reported.[30] Angiographic percent diameter stenosis, and lumen diameters of the proximal and distal reference segments were measured and reported in a continuous fashion. Similar to CCTA images, an 18-segmental model of the coronary tree was used for coronary evaluation. ICA was analyzed by validated quantitative coronary angiography software, employing the use of automated edge-detection algorithms. Employing the outer diameter of the coronary injection catheter as a standard for calibration, a minimum lumen diameter and percentage stenosis was measured from the view that demonstrates the greatest reduction in luminal diameter with the least amount of foreshortening of the segment at a motion-free state during the cardiac cycle (typically during diastole). The stenosis represented a relative reduction in comparison to the most normal appearing region proximal and distal to the stenosis. All vessels ≥1.5 mm in diameter were measured. All lesions with a diameter stenosis of at least 30% were measured with quantitative coronary angiography in a continuous fashion and recorded as 30–100% diameter stenosis. If a total occlusion was observed, all segments distal to that occlusion was not assessed.

2.5. Fractional flow reserve

All major coronary arteries or branches (≥2.0 mm) containing a lesion between 40% and 90% were interrogated by FFR during

intracoronary (150 μg) or intravenous (140 μg × kg1 × min−1) adenosine infusion to achieve maximal hyperemia.[25,26] For the invasive FFR, ischemia was defined as an FFR value of <0.8.

2.6. Plaque stage definition

Using volume and PAV cut-offs, we evaluated multiple stage cut-off values were evaluated to define four distinct plaque stages. The plaque stages are defined as Stage 0 (no plaque), Stage 1 (Mild Plaque), Stage 2 (Moderate Plaque) and Stage 3 (Severe plaque). Plaque volume cut-off levels in 50 mm^3 increments and PAV cut-off values in 1% increments were evaluated, with a goal of maximizing nonobstructive disease in stage 1, multivessel disease and ischemia in stage 3, and to use easy to remember values.

2.7. Statistical analysis

All statistical analyses were performed using SAS version 9.4 (SAS, Cary, NC). Continuous data are reported as mean ± standard deviation, and categorical variables are presented as absolute numbers with corresponding frequencies. Demographics were compared across subgroups using Student's t-test for continuous variables and chi-square and Fisher exact tests were used to compare categorical variables. The Jonckheere-Terpstra test was used to test the ordered alternative hypothesis that plaque volumes and percent atheroma volumes are associated with more significant disease (non-obstructive stenosis, 1VD, 2VD or 3VD/LM). The non-parametric Wilcoxon Rank Sum test was used to compare per-patient plaque volumes and percent atheroma volumes across dichotomized subgroups groups (<50% stenosis vs. ≥50% stenosis, <70% vs. ≥70% stenosis, age <65 vs. age ≥65, and males vs. females). Generalized estimating equations method was used for the corresponding per lesion comparisons to account for the correlation of multiple measures included per patient, using a log transform to normalize the data.

The upper threshold of TPV and PAV used to define Stage 1 was calculated as the TPV or PAV value that maximized diagnostic accuracy for predicting non-obstructive disease. The lower threshold for Stage 3 was determined by calculating the threshold for TPV or PAV that maximized diagnostic accuracy for predicting 2-3VD/LM. Stage 2 was then defined as the TPV or PAV ranges between stage 1 and stage 3.

3. Results

3.1. Study population

The study cohort was comprised of 303 patients. The cohort was 29% female, had a mean age of 64.4 ± 10.2 years, and a high prevalence of CAD risk factors; 64.4% had hypertension, 44.6% had dyslipidemia, 31.4% had diabetes, 19.5% had a family history of CAD and 48.2% had a history of smoking (Table 1). Because eligibility criteria for the CREDENCE Trial included referral to non-emergent ICA, prevalence of stenosis ≥50% was high and was observed in 67% (202/303) of patients and 36% (308/848) of vessels. A ≥50% stenosis was observed in 1, 2 and 3 coronary vessel territories in 32% (96/303), 21% (105/303) and 13% (38/303) subjects, respectively; 21% (64/303) had non-obstructive disease.

Table 1
Baseline demographics of the study population.

Variable	All (N = 303)
Age, mean (SD), y	64.4 (10.2)
Female	88 (29.0%)
Hypertension (%)	195 (64.4%)
Dyslipidemia (%)	135 (44.6%)
Diabetes (%)	95 (31.4%)
Family history (%)	59 (19.5%)
Tobacco use, ever (%)	146 (48.2%)

3.2. Plaque burden and ICA stenosis extent and severity

When considering increasing ICA stenosis extent and severity, there was an upward trend of mean TPV and PAV for patients with ICA non-obstructive, 1VD, 2VD and 3VD/LMD ($p < 0.001$ for both TPV and PAV at the 50% stenosis threshold) (Table 2). Stepwise increases were similar for average TPV and PAV by median (Fig. 1). TPV and PAV were higher for those with ≥50% stenosis compared to <50% stenosis, respectively, with higher TPV and PAV for total, LD-NCP, NCP and CP ($p < 0.0001$ for all) (Appendix A).

3.3. Plaque burden and FFR

Patients with ischemia demonstrated increased PAV and plaque volume. Non-ischemic patients (FFR >0.8) had a mean PAV of 13.7 (±10.3)% and TPV of 422.3 mm^3 (±387.9 mm^3) while patients with at least one vessel ischemia (FFR ≤0.8) had a mean PAV of 22.2 (±13.0)% and TPV of 694.6 mm^3 (±485.1 mm^3), differences p-value <0.0001 respectively (Table 2).

3.4. Age, plaque and ICA stenosis

The relationship of age and plaque volumes differed in those with and without obstructive disease (Fig. 2, Appendix B). In patients with non-obstructive CAD (<50%) there was sequential increase with age group (34–60 vs 61–69 vs 70–89 years) in TPV and CP volumes and PAV but not LD-NCP or NCP volumes or PAV. In patients with obstructive CAD (≥50%) there was significant sequential increase with age group (34–60 vs 61–69 vs 70–89 years) in TPV, NCP, and CP volumes and PAV, while the LD-NCP volume and PAV decreased sequentially.

3.4.1. Sex, plaque and ICA stenosis

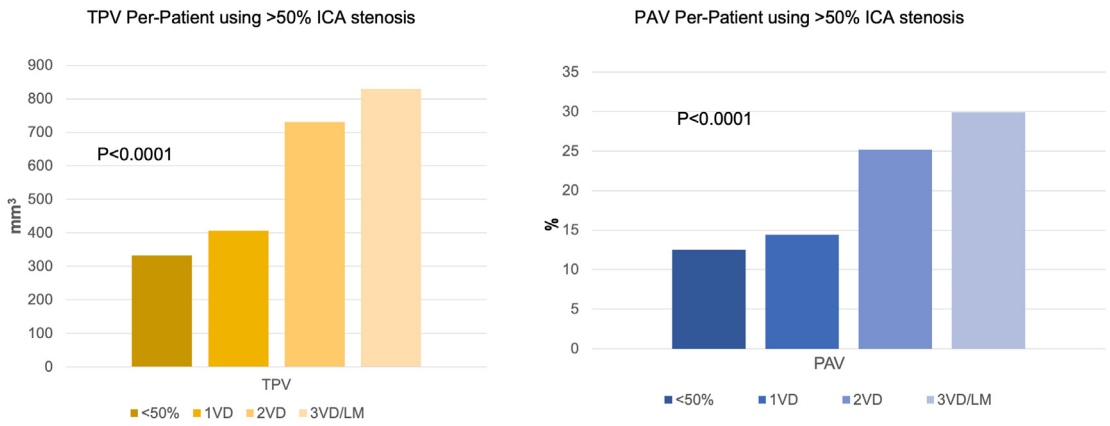
The relationship of sex and plaque volumes differed in those with and without obstructive disease (Appendix C). Men with non-obstructive CAD <50% exhibited higher TPV and NCP than women, with no differences in LD-NCP or CP. When normalized for vessel volume through PAV, men still had higher NCP but not TPV PAV. In contrast, for patients with obstructive CAD ≥50% stenosis, men had more LD-NCP and NCP than women. When normalized for vessel volume through PAV, men possessed higher LD-NCP and CP than women.

Table 2
Atherosclerotic plaque burden and ICA stenosis extent and FFR ischemia.

Variable	TPV (mm^3)	P Value	PAV (%)	P Value
ICA Stenosis Threshold: 50%				
0–50% stenosis (n = 126)	438.2 (444.9) [332.4]	**<0.001**	14.1 (10.7) [12.5]	**<0.001**
1VD (n = 106)	549.3 (408.3) [406.0]		17.6 (11.5) [14.4]	
2VD (n = 47)	838.9 (520.7) [731.2]		26.0 (14.1) [25.2]	
3VD/LMD (n = 24)	799.9 (357.4) [829.6]		27.8 (11.3) [29.9]	

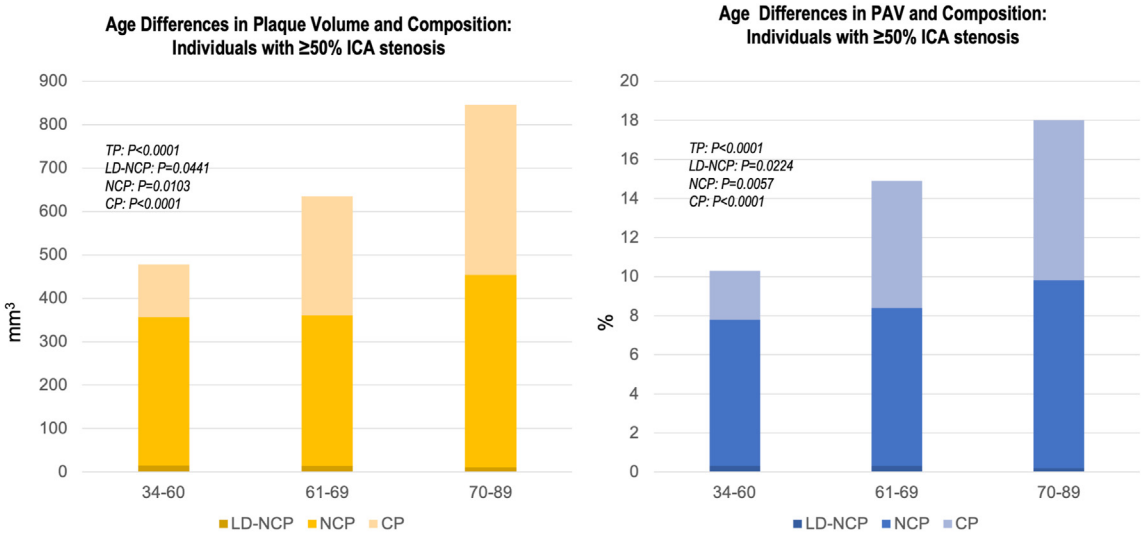
Variable	Non-Ischemic (FFR>0.80)	Ischemic (FFR≤0.80)	P-Value
	N = 141	N = 162	
TPV (mm^3)	422.3 (387.9) [322.2]	694.6 (485.1) [582.6]	<0.0001
PAV (%)	13.7 (10.3) [11.9]	22.2 (13.0) [19.6]	<0.0001

Abbreviations: TPV = total plaque volume; **PAV** = percent atheroma volume; **1VD** = 1-vessel disease; **2VD** = 2-vessel disease; **3VD** = 3-vessel disease; **LMD** = left main disease.
Results are mean (SD) [median].



Abbreviations: TPV = total plaque volume; **PAV** = percent atheroma volume; **1VD** = 1-vessel disease; **2VD** = 2-vessel disease; **3VD** = 3-vessel disease; **LMD** = left main disease

Fig. 1. Per-patient atherosclerotic plaque burden and ICA stenosis extent and severity.



Abbreviations: TPV = total plaque volume; **PAV** = percent atheroma volume; **1VD** = 1-vessel disease; **2VD** = 2-vessel disease; **3VD** = 3-vessel disease; **LMD** = left main disease

Fig. 2. Relationship of age, per-patient severe stenosis, and atherosclerotic plaque burden by plaque composition.

3.5. Proposed plaque stage definition and composition

We determined that PAV based stage definitions of 0%, >0-5%, >5-15%, and >15% and volume-based stages of 0, >0-250, >250-750, and >750 mm^3 best met the 3 criteria of maximizing nonobstructive disease in stage 1, multivessel disease and ischemia in stage 3, and to be easy to remember values (Table 3). The distribution of CREDENCE patients based on ICA stenoses and ischemia into these plaque-based stages is presented (Fig. 3).

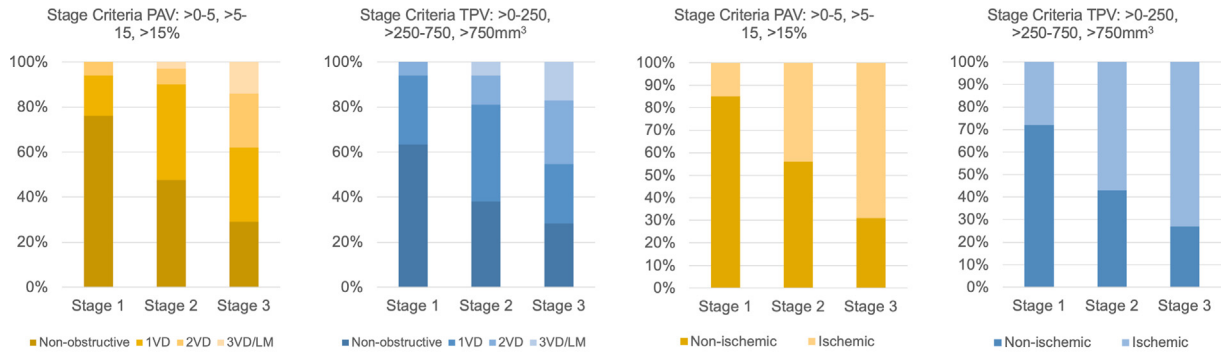
Using plaque volume criteria, stages included stage 0 (0% - no CREDENCE patients met the criteria), stage 1 (76% non-obstructive, 18% 1VD, 6% 2VD, 0% 3VD/LM), stage 2 (48% non-obstructive, 43% 1 VD, 7% 2 VD, 4% 3VD/LM), stage 3 (29% non-obstructive, 33% 1VD, 24% 2VD, 14% 3VD/LM). Using PAV criteria, the stages included stage 0 (0%), stage 1 (62% non-obstructive, 30% 1VD, 6% 2VD, 0% 3VD/LM), stage 2 (38% non-obstructive, 43% 1 VD, 13% 2 VD, 6% 3VD/LM), stage 3 (28% non-obstructive, 26% 1VD, 28% 2VD, 17% 3VD/LM).

Distribution of ischemic patients was also analyzed; using PAV thresholds included stage 0 (0% - no CREDENCE patients met the criteria), stage 1 (85% non-ischemic, 15% ischemic), stage 2 (56% non-ischemic, 44% ischemic), stage 3 (31% non-ischemic, 69% ischemic). Using plaque volume (mm^3), the stages included stage 0 (0%), stage 1 (72% non-ischemic, 28% ischemic), stage 2 (43% non-ischemic, 57% ischemic), stage 3 (27% non-ischemic, 73% ischemic).

Clinical Examples of disease stages are presented in Fig. 4.

4. Discussion

In this analysis we defined a novel 4-stage system of staging patients based upon their coronary atherosclerotic plaque burden. The system thresholds are derived from the relationship of atherosclerosis plaque volume to ICA stenosis and ischemia in a large group of patients from a prospective multicenter clinical trial in which CCTA, ICA and FFR data was available. Beyond simple measures of presence versus absence, we determined the association of atherosclerotic plaque burden to ICA stenosis extent and severity and FFR ischemia. We observed a strong relationship of increasing atherosclerotic plaque burden to increasing ICA stenosis extent and severity, as measured by 1VD, 2VD and 3VD/LMD, and a significant association of ischemia with increasing plaque burden. Based upon this analysis, we propose a system to stage atherosclerotic plaque burden which may be clinically useful for CAD diagnosis, management and prognosis.



Abbreviations: TPV = total plaque volume; **PAV** = percent atheroma volume; **1VD** = 1-vessel disease; **2VD** = 2-vessel disease; **3VD** = 3-vessel disease; **LMD** = left main disease

Fig. 3. Disease stages: Composition of Patient's extent of ICA derived angiographic stenosis and ischemia.

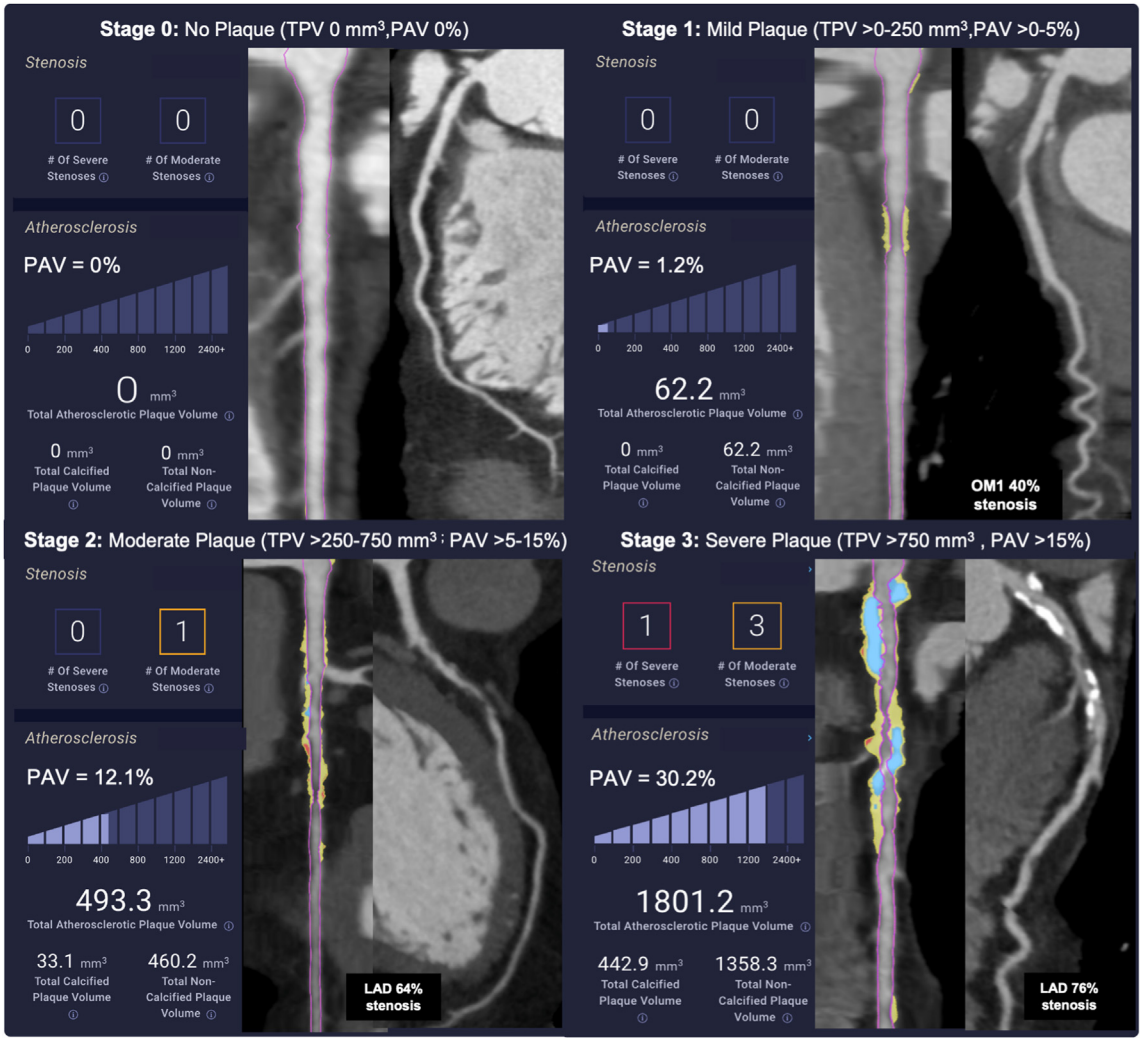


Fig. 4. Clinical examples of plaque disease stages.

A system of categorization of atherosclerotic plaque burden should be both based upon important landmarks of clinical disease, such as significant coronary stenosis and myocardial ischemia and be easy to remember for clinical utility. The well described CACS categories have proven useful for both determination of prognosis and description of disease extent; a similar system based upon CAD plaque volumes may

also be useful. The CACS system is divided into easy to remember categories of normal (0), minimal (1–9), mild (10–99), moderate (100–399), severe (>400).[31] The recently described Coronary Artery Calcium Data and Reporting System (CAC-DRS) and the SCCT indications for use of CACS use slightly different categories: very low (0), mildly increased (1−99), moderately increased (100–299), and moderately to severely increased (>300).[32,33]

To our knowledge, these findings represent the first to relate atherosclerosis, stenosis, and ischemia on a per-patient basis in a large-scale multisite study. As angiographic stenosis is a secondary anatomic consequence of encroachment of atherosclerosis on the coronary lumen, it seems intuitive that more atherosclerosis may cause greater stenosis severity[34]; we found this to be generally true. However, important differences were noted for plaque type, age and sex, which may help to explain prognostic findings in prior studies that have found NCP to be a strong predictor of future major adverse cardiovascular events and differentially observed for age and gender.[12–14]

To date, the relationship of atherosclerosis and stenosis has been inadequately described. While traditional CAD assessment has relied strongly on the identification and exclusion of severe stenoses, it is well-known that the majority of coronary lesions causing future MI do not cause severe angiographic stenosis.[35] Prior studies have observed an additive effect of both stenosis and atherosclerosis for prediction of future MACE, with specific atherosclerotic phenotypes representing the strongest predictors of future MACE.[8,12–14] An important question remains unanswered as to whether this is because the patients without severe stenosis have different plaque makeup or whether the severe stenosis independently serves as a prognostic harbinger for future MACE events. As an example, in the ICONIC study, NCP volume and, in particular, LD-NCP, was the strongest discriminator of future acute coronary syndromes (ACS) even as the future culprit lesions averaged only 44% stenosis, and with nearly 2/3 culprit lesions measuring <50% diameter stenosis.[10] Conversely, in ICONIC, increasingly dense calcified plaques were associated with lower rates of ACS, suggesting the importance of atherosclerotic plaque type and future MI risk.[36]

The present study findings are in accord with the ICONIC study, where age and sex were strong discriminants of ACS risk for older patients (more CP) and male patients (higher NCP). This study offers important insights to help explain the findings that relate ICA stenosis to clinical outcomes and may serve as phenotypic markers of CAD that can guide therapy selection and longitudinal therapeutic success. Future studies examining stenosis, atherosclerosis and outcomes are needed to further explore the relationship of these findings to precision diagnostic and therapeutic approaches to care.

Clinically useful stages of coronary atherosclerosis severity could be defined as (1) population-based ranges of atherosclerosis based upon age, gender and ethnicity; (2) average plaque volumes for stable individuals who will experience future ACS; and (3) average plaque volumes according to angiographic stenosis severity by invasive quantitative coronary angiography (QCA). We chose to use the latter, given the widespread use of these cut points in clinical cardiology care for non-obstructive and obstructive 1-vessel, 2-vessel or 3-vessel/Left main angiographic stenosis >50% diameter stenosis. We acknowledge that volumes may be affected by sex and age differences, however for simplicity (and therefore to promote clinical usefulness) we propose a system that does not specifically take sex or age into account, as the CACS stages have also ignored sex and age considerations.

The proposed four-stage system is based on atherosclerotic plaque volume measured using either absolute volume (mm^3) or PAV (%). While stenosis and/or ischemia can occur with even small amounts of plaque, we found a strong correlation between increasing plaque volume and increasing stenosis severity and extent as well as ischemia. We selected plaque cut points for the proposed stages to generate clinically distinct grouping of patients based on plaque volumes as well as grouping of expected stenoses. This system includes Stage 0 - no plaque; Stage 1 - mild plaque (majority non-obstructive disease), Stage 2 – moderate plaque (mixture of non-obstructive disease and 1VD), and Stage 3 – severe plaque (majority ischemic/multivessel disease) (Table 3). Ischemic patients were less optimally distributed as stenoses, but a large majority of Stage 1 patients were non-ischemic, and a large majority of Stage 3 patients were ischemic (Fig. 3).

The CREDENCE study was useful for purposes of this study because all patients had CCTA, QCT, IA and FFR available for analysis. However, because the eligibility criteria included referral to non-emergent invasive angiography based on a class II indication from the ACC/AHA clinical practice guidelines for stable ischemic heart disease, the patients had a very high disease prevalence with 1, 2 and 3 coronary vessel territories in 32%, 21% and 13% subjects, respectively; only 21% had non-obstructive disease. In order to evaluate how a routine group of typically imaged CCTA patients would distribute within the new stages, analysis of a separate sequential group of clinical CCTA patients with lower disease prevalence reveals that approximately 10–20% of patients will likely fall into Stage 0, 40–50% Stage 1, 20% Stage 2 and 10% Stage 3 (unpublished data JPE).

Using these stages of atherosclerotic plaque, we believe further analysis will show that they will likely will be prognostic for future events, as prior studies have independently shown that increasing TPV as well as NCP and LD-NCP are prognostic for future MACE. Given this, these stages may also be useful for designing clinical medical treatment algorithms which may account for the increased risk inherent in increased plaque volumes, independent of other commonly used clinical variables such as age, cholesterol and other risk factors.

4.1. Limitations

In this study of QCT, we examined the relationship of angiographic stenosis to plaque burden, in order to help define clinically useful categories of atherosclerotic plaque burden. While we aimed to report findings in manner consistent with clinical practice (i.e., TPV, PAV and 50% stenosis thresholds), this study is nevertheless not without limitations. In the study eligibility criteria, patients were enrolled only after a clinical referral for invasive coronary angiography was made based upon an AHA/ACC class II indications; most patients manifested symptoms suspicious of CAD or abnormal stress test findings prior to enrollment. Thus, widespread applicability to asymptomatic patients warrants research. Further, while we stratified our study findings by age and gender, we did not incorporate age or gender considerations into the plaque stages. The interaction of age and gender together may influence atherosclerosis and stenosis findings and age and sex dependent stages may be both more clinically useful and prognostic. Future studies should examine this issue. We elected to define the disease stages based upon angiographic stenosis and FFR; however, these categories might be better defined in the context of events, therefore these stage thresholds should be considered preliminary or pilot data and future investigations based on events and not angiographic stenosis or FFR may lead to modifications of the stage thresholds. In addition, the cohort was predominately (71%) male and we did not account for prior statin and other medication usage. Also, we assessed clinical risk factors but did not uniformly account for risk factor duration, severity, and treatment. Each of these factors may have influenced the phenotypic appearance of atherosclerosis in any individual; ongoing studies are assessing how risk factor duration, severity and treatment influences the natural history of atherosclerosis and stenosis. We elected to use a 50% angiographic threshold to define stenosis, this

Table 3
Coronary Atherosclerotic Plaque Burden Stage Definition.

CAD Stage Description	TPV (mm^3)	PAV (%)
Stage 0: No Plaque	0	0
Stage 1: Mild Plaque	>0–250 mm^3	>0–5%
Stage 2: Moderate Plaque	>250–750 mm^3	>5–15%
Stage 3: Severe Plaque	>750 mm^3	>15%

could have also been 70%. Finally, we leveraged a latest-generation AI-enabled software platform that allows for highly accurate measures of CAD, as evidenced in prior multicenter clinical trials compared expert level III readers, QCA, FFR and IVUS,[9–11] additional validation trials are underway.

4.2. Conclusions

Atherosclerotic plaque burden and composition by QCT is related to angiographic stenosis extent and severity and myocardial ischemia. We propose a system for staging of atherosclerotic plaque volume using easy to remember absolute volume and PAV based upon the complex relationship between plaque volume, stenosis and ischemia. These findings may better inform future studies regarding the precise relationship amongst atherosclerosis, vascular morphology, and adverse cardiovascular events.

Funding

Statistical support provided by Cleerly, Inc.

Declaration of competing interest

JKM, TC, JPE are employees and retain equity interest in Cleerly.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2022.03.001.

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