

ORIGINAL RESEARCH

Atherosclerotic Plaque Characteristics by CT Angiography Identify Coronary Lesions That Cause Ischemia



A Direct Comparison to Fractional Flow Reserve

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ABSTRACT

OBJECTIVES This study evaluated the association between atherosclerotic plaque characteristics (APCs) by coronary computed tomographic angiography (CTA), and lesion ischemia by fractional flow reserve (FFR).

BACKGROUND FFR is the gold standard for determining lesion ischemia. Although APCs by CTA—including aggregate plaque volume % (%APV), positive remodeling (PR), low attenuation plaque (LAP), and spotty calcification (SC)—are associated with future coronary syndromes, their relationship to lesion ischemia is unclear.

METHODS 252 patients (17 centers, 5 countries; mean age 63 years; 71% males) underwent coronary CTA, with FFR performed for 407 coronary lesions. Coronary CTA was interpreted for <50% and ≥50% stenosis, with the latter considered obstructive. APCs by coronary CTA were defined as: 1) PR, lesion diameter/reference diameter >1.10; 2) LAP, any voxel <30 Hounsfield units; and 3) SC, nodular calcified plaque <3 mm. Odds ratios (OR) and net reclassification improvement of APCs for lesion ischemia, defined by FFR ≤0.8, were analyzed.

RESULTS By FFR, ischemia was present in 151 lesions (37%). %APV was associated with a 50% increased risk of ischemia per 5% additional APV. PR, LAP, and SC were associated with ischemia, with a 3 to 5 times higher prevalence than in nonischemic lesions. In multivariable analyses, a stepwise increased risk of ischemia was observed for 1 (OR: 4.0, $p < 0.001$) and ≥2 (OR: 12.1, $p < 0.001$) APCs. These findings were APC dependent, with PR (OR: 5.3, $p < 0.001$) and LAP (OR: 2.1, $p = 0.038$) associated with ischemia, but not SC. When examined by stenosis severity, PR remained a predictor of ischemia for all lesions, whereas %APV and LAP were associated with ischemia for only ≥50%, but not for <50% stenosis.

CONCLUSIONS %APV and APCs by coronary CTA improve identification of coronary lesions that cause ischemia. PR is associated with all ischemia-causing lesions, whereas %APV and LAP are only associated with ischemia-causing lesions ≥50%. (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography; [NCT01233518](https://clinicaltrials.gov/ct2/show/study/NCT01233518)) (J Am Coll Cardiol Img 2015;8:1-10) © 2015 by the American College of Cardiology Foundation.

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**ABBREVIATIONS
AND ACRONYMS****ACS** = acute coronary syndrome**APC** = atherosclerotic plaque characteristic**APV** = aggregate plaque volume**AS** = area stenosis**CI** = confidence interval**FFR** = fractional flow reserve**ICA** = invasive coronary angiography**LAP** = low attenuation plaque**LCX** = left circumflex coronary artery**NRI** = net reclassification improvement**OR** = odds ratio**PR** = positive arterial remodeling**QCA** = quantitative coronary angiography/angiographic**RCA** = right coronary artery**SC** = spotty intraplaque calcification**TCFA** = thin-cap fibroatheroma

Fractional flow reserve (FFR) enables physiological assessment of coronary lesions at the time of invasive coronary angiography (ICA), and is the gold standard for identification of lesions that cause ischemia (1). Prior studies have demonstrated the importance of FFR, with identification of ischemia-causing lesions associated with worsened survival, and with FFR-guided revascularization enhancing event-free survival (2). Use of FFR has established stenosis severity as an unreliable indicator of ischemia, with approximately one-half of high-grade stenoses manifesting no ischemia. Conversely, a significant proportion of nonobstructive lesions cause ischemia by FFR (3), emphasizing the importance of other factors beyond stenosis as critical to lesion-specific ischemia.

By invasive and pathological studies, high-risk anatomic plaque features have been established as fundamental to the processes of acute coronary syndromes (ACS) and sudden cardiac death (4). For these lesions, several common characteristics are shared, including plaque burden, thin-cap fibroatheroma (TCFA), positive arterial remodeling (PR), necrotic cores, spotty calcifications (SC), and macrophage infiltration (5). Prior invasive data have observed the majority of plaques implicated in ACS to be nonobstructive in anatomic stenosis severity—with high-grade stenoses comprising less than one-third of culprit lesions—and have emphasized the need for improved methods beyond stenosis for identification of high-risk plaques (6). To date, the precise relationship of these plaque features to coronary lesion-specific ischemia remains unstudied.

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Recently, coronary computed tomographic angiography (CTA) has emerged as a noninvasive method for accurate detection and exclusion of high-grade coronary stenoses, when compared with an ICA reference standard. In addition to luminal diameter narrowing, coronary CTA also enables assessment of several

coronary atherosclerotic plaque characteristics (APCs) with high accuracy; including aggregate plaque volume (APV), PR; low attenuation plaque (LAP) as a marker for necrotic lipid-laden intraplaque core; and intraplaque SC (7). Similar to invasive studies by intravascular ultrasound, these coronary CTA characteristics have been associated with culprit lesions in retrospective and prospective cohorts (8,9).

Yet, the physiologic mechanisms underlying these findings remain ill-defined. To this end, whether APCs by coronary CTA are associated with specific coronary lesions that cause ischemia remains unknown. In a prospective international multicenter study, we thus examined the relationship between APCs by coronary CTA and lesion-specific ischemia by FFR.

METHODS

STUDY POPULATION. We studied 252 consecutive stable patients (178 men and 74 women, mean age: 62.9 ± 8.7 years) and 407 coronary lesions from the DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography) study (NCT01233518), which was performed prospectively at 17 centers in 5 countries (Belgium [n = 1], Canada [n = 1], Latvia [n = 1], South Korea [n = 2], and United States [n = 12]) (10). Enrolled patients were adults with suspected coronary artery disease who underwent clinically indicated invasive coronary angiography after coronary CTA within 60 days with no intervening coronary event. Exclusion criteria included: prior coronary artery bypass graft surgery; prior percutaneous coronary intervention with suspected in-stent restenosis based upon coronary CTA findings; contraindication to adenosine; suspicion of or recent ACS; complex congenital heart disease; prior pacemaker or defibrillator; prosthetic heart valve; significant arrhythmia; serum creatinine level >1.5 mg/dl; allergy to iodinated contrast; pregnant state; body mass index >35 kg/m²; evidence of active clinical instability or life-threatening disease; or inability to adhere to study procedures. In this study, 33 patients were excluded (non-evaluable coronary CTA scans, n = 31; unresolvable integration of FFR wire

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transducer location by ICA to corresponding location on coronary CTA, $n = 2$).

ICA AND FFR MEASUREMENTS. Selective ICA was performed by standard protocol in accordance with societal guidelines, with a minimum of 2 projections obtained per vessel distribution and with angles of projection optimized based on the cardiac position. ICAs were evaluated by quantitative coronary angiographic (QCA) stenosis severity using a blinded angiographic core laboratory (University of British Columbia, Vancouver, BC, Canada) using commercially available software (Discovery; Quinton Inc., Bothell, Washington). FFR was performed at the time of ICA (PressureWire Certus, St. Jude Medical Systems, St. Paul, Minnesota; ComboWire, Volcano Corp, San Diego, California). Investigators performed FFR in vessels deemed clinically indicated for evaluation, demonstrating an ICA stenosis between 30% and 90%. After administration of nitroglycerin, a pressure-monitoring guidewire was advanced distal to a stenosis. Hyperemia was induced by administration of intravenous or intracoronary adenosine at a rate of 140 $\mu\text{g}/\text{kg}/\text{min}$. FFR was calculated by dividing the mean distal coronary pressure by the mean aortic pressure during hyperemia. FFR at a threshold of 0.80 or less was considered hemodynamically significant and causal of ischemia.

CORONARY CTA PERFORMANCE, IMAGE RECONSTRUCTION, AND EVALUATION. Coronary CTA was performed using 64-detector row or higher scanners with prospective or retrospective electrocardiographic gating in accordance with the Society of Cardiovascular Computed Tomography guidelines. Approximately 80 to 100 ml of intravenous contrast, followed by 50 to 80 ml of saline, was administered at a rate of 5 ml/s via a power injector through an antecubital vein. Scanning parameters included heart-rate-dependent pitch (0.20 to 0.45), 330 ms gantry rotation time, 100 kVp or 120 kVp tube voltage, and 350 to 800 mA tube current. Estimated radiation dose for CTs ranged between 2 and 10 mSv.

CTs were reconstructed using the following parameters: 0.5- to 0.75-mm slice thickness, 0.3-mm slice increment, 160- to 250-mm field of view, 512×512 matrix, and a standard kernel. Optimal phase reconstruction was assessed by comparison of different phases, if available, and the phase with the least amount of coronary artery motion was chosen for analysis. Multiple phases were utilized for image interpretation if minimal coronary artery motion differed among the various arteries. All CTs were interpreted in an intention-to-diagnose fashion.

Independent level III-experienced readers blinded to clinical, ICA, and FFR results analyzed all of the CTs. Coronary CTA analysis was performed on dedicated 3-dimensional workstations (Ziosoft, Redwood City, California; Advantage AW Workstation, GE Healthcare, Milwaukee, Wisconsin). CTs were evaluated by an array of post-processing techniques, including axial, multiplanar reformat, maximum-intensity projection, and short-axis cross-sectional views. In each coronary artery segment, coronary atherosclerosis was defined as tissue structures $\geq 1 \text{ mm}^2$ that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself.

Coronary arteries and branches were categorized into 1 of 4 vascular territories: left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery (LCX), and right coronary artery (RCA); diagonal branches, obtuse marginal branches, and posterolateral branches were considered as part of the left anterior descending coronary artery, LCX, and RCA systems, respectively. The posterior descending artery was considered as part of the RCA or LCX system, depending upon the coronary artery dominance.

Qualitative coronary APCs—including PR, LAP, and SC—were evaluated for coronary lesions directly interrogated by FFR. Stenosis severity was graded in accordance with societal guidelines, and categorized as 0%, 1% to 29%, 30% to 49%, 50% to 69%, and $\geq 70\%$. A remodeling index was defined as a maximal lesion vessel diameter divided by proximal reference vessel diameter, with PR defined as a remodeling index ≥ 1.1 . LAP was defined as any voxel < 30 Hounsfield units within a coronary plaque. SC was defined by an intralumen calcific plaque < 3 mm in length that comprised $< 90^\circ$ of the lesion circumference.

Quantitative coronary atherosclerotic plaque analysis was performed using semiautomated plaque analysis software (QAngio CT Research Edition v2.02, Medis Medical Imaging Systems, Leiden, the Netherlands), which has been previously validated for accuracy. Lesion length, lumen area stenosis (AS), plaque volume, and percent aggregate plaque volume (%APV) were measured. As we have previously described, APV was measured from the coronary artery ostium to the distal end of the lesion. %APV was defined as the aggregate plaque volume divided by the total vessel volume (11).

Direct comparison of FFR to APCs was performed at the precise location of the wire transducer at the time of FFR. To maintain blinding, an Integration Core Laboratory (Minneapolis Heart Institute,

Age, yrs	62.9 ± 8.7
Male	178 (71)
BMI	26.8 ± 3.8
Race	
Caucasian	169 (67)
Other	83 (33)
Diabetes mellitus	53 (21)
Hypertension	179 (71)
Hyperlipidemia	201 (80)
Family history of coronary artery disease	50 (20)
Current smoker	44 (18)
Prior myocardial infarction	15 (6)
Prior PCI	16 (6)

Values are mean ± SD or n (%).
BMI = body mass index; PCI = percutaneous coronary intervention.

Minneapolis, Minnesota) was used. The Integration Core Laboratory identified the location on coronary CTA that corresponded to the point where the FFR was measured. The location was communicated to the coronary CTA imagers by an arrow on a 3-dimensional volume-rendered coronary CTA image of the coronary arteries.

STATISTICAL METHODS. Continuous variables were compared by use of a Student unpaired *t* test for normally distributed variables or by the Mann-Whitney *U* test for non-normally distributed

variables. Categorical variables were examined by Pearson chi-square or Fisher exact test, as appropriate. Demographics of the study sample are reported as mean ± SD for continuous variables, and by counts with proportions for categorical variables. FFR measurements were recorded on a continuous scale and dichotomized at a threshold of 0.80, with values ≤0.80 considered hemodynamically significant and causal of ischemia. High-grade stenosis by coronary CTA was dichotomized at the 50% threshold, with a stenosis ≥50% considered obstructive.

Global chi-square analyses utilized logistic regression and a likelihood ratios test. In order to account for the correlation of coronary artery segments within patients in an unbalanced design, a random effects model using a maximum likelihood logit model for panel data was applied, wherein the binary outcome value of FFR ≤0.80 was modeled using a binomial distribution and a logit link function, with the individual patient serving as the random component. Univariable and multivariable odds ratio (OR) estimates with 95% confidence intervals (CI) utilizing a random effects model were employed to evaluate predictors of ischemia. Further, a category-free net reclassification improvement (NRI) of APCs was obtained using the resultant predicted probabilities of the random effects logit models predicting ischemia where Model 1 consisted of coronary CTA stenosis ≥50% or <50%, and Model 2 comprised

	Overall			Obstructive Coronary CTA Stenosis (≥50%) (n = 215)			Nonobstructive Coronary CTA Stenosis (<50%) (n = 192)		
	FFR ≤0.8 Ischemic Group (n = 151)	FFR >0.8 Nonischemic Group (n = 256)	p Value	FFR ≤0.8 Ischemic Group (n = 119)	FFR >0.8 Nonischemic Group (n = 96)	p Value	FFR ≤0.8 Ischemic Group (n = 32)	FFR >0.8 Nonischemic Group (n = 160)	p Value
FFR	0.69 ± 0.11	0.90 ± 0.05	<0.0001	0.68 ± 0.11	0.88 ± 0.05	<0.0001	0.74 ± 0.10	0.91 ± 0.05	<0.0001
QCA stenosis, %	57.1 ± 12.4	40.8 ± 13.8	<0.001	59.2 ± 11.2	48.1 ± 12.3	<0.001	49.4 ± 13.6	36.5 ± 12.9	<0.0001
Lesion length, mm	30.1 ± 12.3	22.0 ± 10.8	<0.001	30.8 ± 12.9	24.4 ± 11.8	<0.001	27.3 ± 9.7	20.5 ± 9.9	<0.001
Plaque volume, mm ³	324.7 ± 210.4	206.0 ± 147.7	<0.001	344.1 ± 220.1	244.7 ± 158.0	<0.001	252.3 ± 151.5	182.7 ± 136.4	0.005
%APV	59.7 ± 7.6	52.2 ± 8.2	<0.001	60.3 ± 7.5	54.0 ± 7.1	<0.001	57.1 ± 7.6	51.1 ± 8.7	<0.001
Reference vessel diameter, mm	3.1 ± 0.9	3.1 ± 0.6	0.9	3.2 ± 0.9	3.1 ± 0.6	0.50	2.9 ± 0.5	3.0 ± 0.6	0.12
PR	121 (80)	72 (28)	<0.001	97 (82)	39 (41)	<0.001	24 (75)	33 (21)	<0.001
LAP	66 (44)	24 (9)	<0.001	58 (49)	16 (17)	<0.001	8 (25)	8 (5)	<0.001
SC	42 (28)	26 (10)	<0.001	33 (28)	13 (14)	0.01	9 (28)	13 (8)	0.001
0 APCs	25 (17)	173 (68)	<0.001	18 (15)	50 (52)	<0.001	7 (22)	123 (77)	<0.001
1 APC	48 (32)	52 (20)	0.009	37 (31)	29 (30)	0.89	11 (34)	23 (14)	0.007
2 APCs	53 (35)	23 (9)	<0.001	41 (35)	12 (13)	<0.001	12 (38)	11 (7)	<0.001
3 APCs (overall p)	25 (17)	8 (3)	<0.001 (<0.001)	23 (19)	5 (5)	0.002 (<0.001)	2 (6)	3 (2)	0.16 (<0.001)

Values are mean ± SD or n (%).
%APV = percent aggregate plaque volume; APC = atherosclerotic plaque characteristic; CTA = computed tomographic angiography; FFR = fractional flow reserve; LAP = low attenuation plaque; PR = positive remodeling; QCA = quantitative coronary angiographic; SC = spotty calcification.

Model 1 plus any individual APC (e.g., PR, LAP, or SC) or number of APCs. Ten-fold cross-validated estimates of the area under the receiver-operating characteristic curve models were employed to evaluate the discrimination of ischemia and compared using the method proposed by Kennedy et al. (12) Category-free NRIs were calculated using a SAS macro (SAS Institute, Cary, North Carolina). Statistical tests were 2-tailed, with a significance level set at $p < 0.05$. Statistical analyses were performed using STATA software, version 11 (StataCorp, College Station, Texas).

RESULTS

Baseline characteristics of the study population are listed in Table 1. Of 407 lesions, the mean FFR value was 0.82 ± 0.13 . Overall, 215 (53%) lesions were found to be obstructive (coronary CTA stenosis $\geq 50\%$), whereas 192 (47%) lesions were nonobstructive.

RELATIONSHIP OF APCs BY CORONARY CTA TO LESION-SPECIFIC ISCHEMIA BY FFR. As compared to non-ischemia-causing lesions, coronary artery lesions that caused ischemia consisted of a higher stenosis; longer lesion length; larger plaque volume; higher %APV; and higher rates of PR, LAP, and SC (Table 2). These findings were observed for both $\geq 50\%$ and $< 50\%$ stenosis. As compared with lesions that did not cause ischemia, those that did were associated with a 11-, 13-, and 4-fold higher prevalence of PR, LAP, and SC, respectively (Table 3). Likewise, increasing numbers of APCs were observed within ischemic lesions compared with nonischemic lesions, with 1 and ≥ 2 APCs associated with a 7- and 20-fold higher odds of lesion ischemia. Other quantitative measures of plaque burden—including lumen area stenosis, lesion length, plaque volume, and %APV—were also associated with lesion ischemia.

In multivariable analyses, obstructive stenosis, lesion length, PR, and LAP were associated with ischemia, but SC was not (Table 3 [Model 1]). Independent of lumen area stenosis and lesion length, the presence of 2 or more 2 APCs was associated with 13-fold increased odds of ischemia (Table 3 [Model 2]). When considering either specific APCs or number of APCs, %APV was an independent predictor of lesion-specific ischemia independent of obstructive stenosis severity, and provided incremental discriminatory power when added to APCs and coronary CTA stenosis (Table 3 [Models 3 and 4], Figure 1).

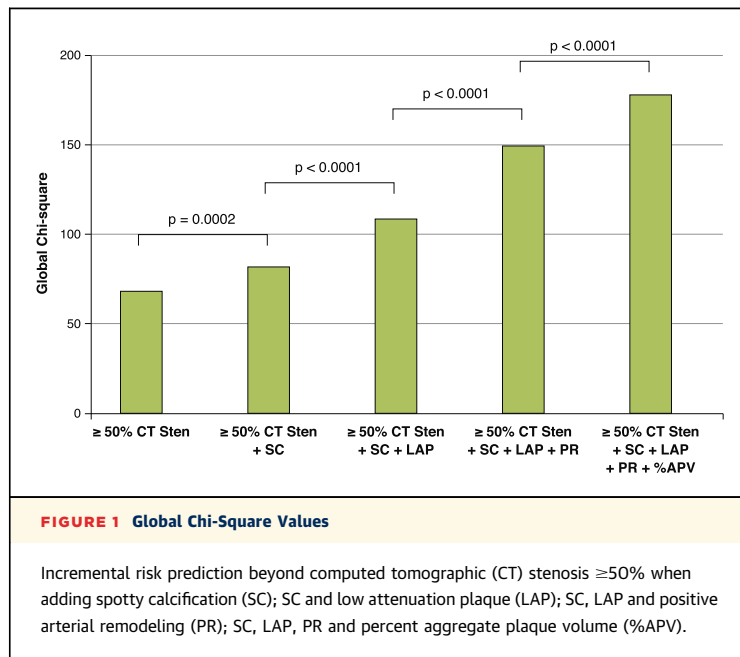
RELATIONSHIP OF APCs TO LESION-SPECIFIC ISCHEMIA STRATIFIED BY CORONARY ARTERY STENOSIS SEVERITY. Table 2 describes FFR and APC prevalence for ischemic versus nonischemic lesions,

TABLE 3 Univariable and Multivariable Analysis of APCs for Ischemia Detection

	OR (95% CI)	p Value
Univariable		
Coronary CTA stenosis $\geq 50\%$	8.7 (4.2-18.1)	<0.001
Lumen area stenosis, per 5%	1.4 (1.2-1.5)	<0.001
Lesion length, mm	1.1 (1.04-1.09)	<0.001
Plaque volume, per 10 mm ³	1.04 (0.03-1.06)	<0.001
% APV, per 5%	2.0 (1.6-2.5)	<0.001
PR	10.5 (5.9-18.8)	<0.001
LAP	12.9 (5.4-30.9)	<0.001
SC	3.9 (2.0-7.4)	<0.001
0 APCs	1.0 (reference)	—
1 APC	6.9 (3.6-13.3)	<0.001
≥ 2 APCs	19.7 (9.1-42.5)	<0.001
Multivariable		
Model 1		
Lumen area stenosis, per 5%	1.2 (1.1-1.4)	<0.001
Lesion length	1.03 (1.01-1.06)	0.008
PR	5.4 (3.0-10.0)	<0.001
LAP	2.2 (1.1-4.5)	0.028
SC	1.6 (0.8-3.1)	0.177
Model 2		
Lumen area stenosis, per 5%	1.2 (1.1-1.4)	<0.001
Lesion length	1.03 (1.01-1.06)	0.004
0 APCs	1.0 (reference)	—
1 APC	4.5 (2.3-8.8)	<0.001
≥ 2 APCs	13.2 (6.1-28.7)	<0.001
Model 3		
Lumen area stenosis, per 5%	1.3 (1.1-1.4)	<0.001
% APV, per 5%	1.5 (1.3-1.9)	<0.001
PR	5.3 (2.9-10.0)	<0.001
LAP	2.1 (1.04-4.3)	0.038
SC	1.4 (0.7-2.9)	0.32
Model 4		
Lumen area stenosis, per 5%	1.2 (1.1-1.4)	<0.001
%APV, per 5%	1.5 (1.3-1.9)	<0.001
0 APCs	1.0 (reference)	—
1 APC	4.0 (2.8-8.1)	<0.001
≥ 2 APCs	12.1 (5.4-26.8)	<0.001

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 2.

stratified by obstructive versus nonobstructive stenoses. For $\geq 50\%$ and $< 50\%$ stenoses, ischemia was observed in 119 of 215 (55%) and 32 of 192 (17%) lesions, respectively. PR, LAP, SC, and increasing numbers of intraplaque APCs were associated with ischemia for both $\geq 50\%$ and $< 50\%$ stenotic coronary lesions. In multivariable analyses, PR, 1 APC, ≥ 2 APCs were associated with ischemia for both $\geq 50\%$ and $< 50\%$ stenotic lesions, whereas lesion length, LAP, and %APV (per 5%) were associated with ischemia only for lesions $\geq 50\%$ stenosis; and lumen area stenosis (per 5%) was only associated with ischemia for lesions $< 50\%$ stenosis. SC was not associated with ischemia for both $\geq 50\%$ and $< 50\%$



stenotic lesions (Table 4). Compared with the base model of lumen area stenosis alone, the area under the receiver-operating characteristic curve displayed further discriminatory value towards prediction of ischemia by invasive FFR when %APV and, subsequently, APCs were added (Figure 2).

NRI OF ISCHEMIC LESIONS. Individual APCs were associated with improved reclassification of lesions that cause ischemia for PR (NRI: 0.97, 95% CI: 0.80 to 1.15, $p < 0.001$), LAP (NRI: 0.92, 95% CI: 0.74 to 1.09, $p < 0.001$), and SC (NRI: 0.35, 95% CI: 0.19 to 0.51, $p = 0.0006$). Similarly, an increasing number of APCs enabled effective reclassification of ischemic lesions

for coronary CTA stenoses $\geq 50\%$ for ≥ 1 APC (NRI: 1.02, 95% CI: 0.86 to 1.19, $p < 0.001$) or ≥ 2 APCs (NRI: 0.79, 95% CI: 0.61 to 0.97, $p < 0.001$). These findings remained robust when QCA substituted coronary CTA for determining stenosis severity. An example of a nonobstructive, yet ischemia-causing, coronary artery lesion possessing PR, LAP, and SC is depicted in Figure 3. An example of an obstructive non-ischemia-causing coronary artery lesion that does not possess PR, LAP, or SC is depicted in Figure 4.

DISCUSSION

We identified an independent association between quantitative and qualitative measures of atherosclerosis—by %APV and APCs—and ischemia-causing coronary lesions confirmed by FFR. We observed higher %APV, longer lesion length, and increasing prevalence of APCs within ischemic lesions of higher stenosis severity, a finding that was more pronounced for lesions of higher angiographic stenosis. Furthermore, we observed a strong relationship between APC number and type—particularly for PR—and lesion-specific ischemia even amongst non-obstructive lesions that do not meet conventional thresholds of angiographically severe. Importantly, the absence of APCs identified lesions with a considerably lower prevalence of ischemia, even for highly stenotic coronary lesions. To our knowledge, these data represent the first to examine the quantitative as well as qualitative relationship of APCs by coronary CTA for precise identification of coronary lesions that do versus do not cause ischemia.

The relationship observed between stenosis and ischemia in the present study is in accordance with prior published reports. In the multicenter FAME

TABLE 4 Multivariable Analysis of APCs in Obstructive Lesions ($\geq 50\%$) and Nonobstructive Lesions ($< 50\%$) for Ischemia Detection

	Obstructive Lesions ($\geq 50\%$)		Nonobstructive Lesions ($< 50\%$)		
	OR (95% CI)	p Value	OR (95% CI)	p Value	
Model 1			Model 3		
Lumen area stenosis (per 5%)	1.1 (0.99-1.3)	0.07	Lumen area stenosis (per 5%)	1.3 (1.06-1.6)	0.01
Lesion length	1.03 (1.01-1.06)	0.01	Lesion length	1.02 (0.97-1.07)	0.44
PR	3.6 (1.8-7.2)	< 0.001	PR	10.5 (3.1-36.4)	< 0.001
LAP	2.5 (1.2-5.3)	0.018	LAP	1.3 (0.3-5.6)	0.74
SC	1.4 (0.6-3.2)	0.42	SC	1.8 (0.5-7.3)	0.40
Model 2			Model 4		
Lumen area stenosis (per 5%)	1.1 (0.97-1.3)	0.12	Lumen area stenosis (per 5%)	1.3 (1.02-1.6)	0.03
% APV (per 5%)	1.8 (1.4-2.2)	< 0.001	%APV (per 5%)	1.3 (0.9-1.9)	0.24
0 APC	1.0 (reference)	—	0 APC	1.0 (reference)	—
1 APC	2.3 (1.1-5.1)	0.037	1 APC	7.8 (1.9-31.6)	0.004
> 2 APCs	8.6 (3.8-19.3)	< 0.001	≥ 2 APCs	25.2 (3.1-207.4)	0.003

Abbreviations as in Table 2.

(Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial, 20% of lesions $\geq 70\%$ did not cause ischemia, a rate that is paralleled in the present study (1). Distinct from the FAME study, we also interrogated lesions that were $< 50\%$ stenosis, and observed a 17% rate of ischemia (3). Given the relationship of ischemic lesions by FFR to future adverse events and the improved event-free survival for revascularization based upon FFR guidance, these data suggest the need for alternative factors beyond stenosis alone for enhancing the diagnosis of ischemic lesions (1,13,14).

We identified a distinct relationship between specific APCs and ischemia, independent of stenosis severity. Specifically, PR was associated with higher rates of ischemic lesions in both obstructive and nonobstructive stenoses. It is that this finding represents a point in the development of an atheroma wherein the lesion-specific burden exceeds a certain threshold that results in compensatory remodeling. Yet prior post-mortem studies (15-17), where PR has demonstrated a correlation to luminal stenosis than plaque size, and our study both corroborate as well as advances these findings. Indeed, PR was a better predictor of ischemia in lesions of $\geq 50\%$ and $< 50\%$ stenosis, whereas plaque size (as measured by %APV and lesion length) were only predictive of ischemia in $\geq 50\%$ stenosis. Interestingly, both in our study as well as the prior post-mortem study (17), the relationships between luminal stenosis and PR in the arterial system were highly heterogeneous, suggesting a mechanism that cannot be fully deciphered by morphological evaluation alone.

We also identified a relationship between LAP—a coronary CTA surrogate for necrotic lipid core—and lesion-specific ischemia (18). This relationship—similar to %APV and lesion length—was present only for lesions $\geq 50\%$. Although it is tempting to conjecture that these lesions represent atheromas in a more advanced stage of their development, only future serial evaluation studies will be able to determine this. However, the presence of necrotic core has been related to endothelial dysfunction, which depresses coronary vasodilation and accentuates myocardial hypoperfusion (19-21). At the phenotypic level, the size of lipid cores by intravascular methods has been associated with reduced myocardial blood flow, and our study results reinforce these findings.

We observed SC to allow reclassification, but not prediction, of ischemic lesions. These findings may be considered discordant with prior studies (22), which observed SC to be associated with ACS. This lack of prediction of ischemia by SC may be explained by a multitude of reasons. First, although these

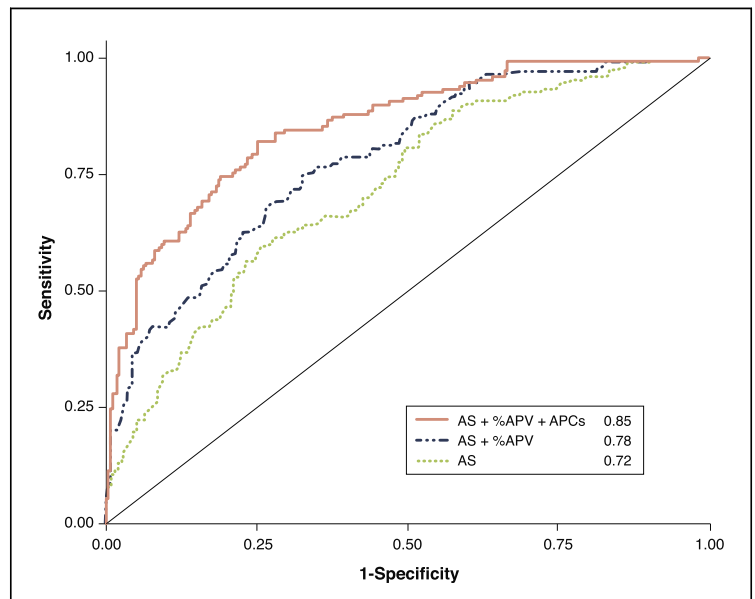
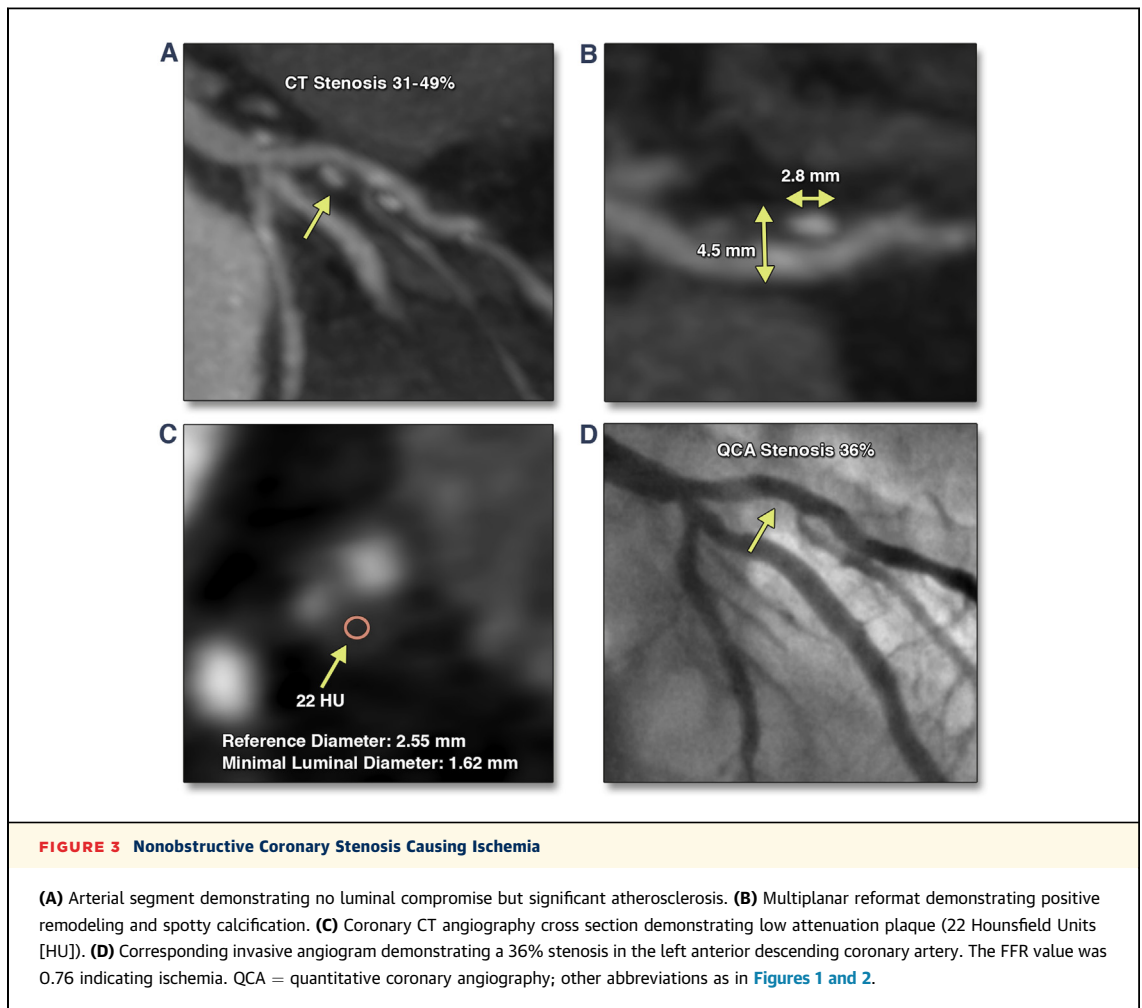


FIGURE 2 AUC for Detecting FFR

Area under the receiver-operating characteristic curve (AUC) values gradually improving up to 0.79 (AS + %APV, $p < 0.001$) and 0.86 (AS + %APV + APCs, $p < 0.001$), respectively, when %APV and APCs combined serially into AS. %APV = percent aggregate plaque volume; APC = atherosclerotic plaque characteristic; AS = lumen area stenosis (%); FFR = fractional flow reserve.

calcifications are small, the microcalcifications associated with pathologically confirmed high-risk plaque are beyond the detection of coronary CTA imaging. Thus, SC may represent a later stage in the evolution of an atheroma that precedes ischemia production. Also, the presence of SC may reflect a form of “pseudodisease,” wherein this plaque feature may track with other morphological characteristics (such as PR or LAP) but does not cause ischemia.

In our study, quantitative metrics of atherosclerotic burden—using lesion length and %APV—were useful to discriminate lesions that caused ischemia, albeit restricted to lesions $\geq 50\%$. These findings confirm prior FFR and coronary CTA studies (23,24) that have documented the importance of diffuse disease identification for diagnosis of ischemia. De Bruyne (25) related abnormal coronary resistance and reduced hyperemic in arteries with diffuse atherosclerosis, a finding corroborated by our group in nonstenotic lesions. It is notable to mention that APCs embedded within any specific plaque represent that lesion alone, without consideration of the amount of myocardium that is subtended by this vessel. Future studies addressing the relationship between APCs and perfusion may be helpful to further elucidate the clinical utility of APCs.



Finally, the relationship of plaque burden and APCs is dose dependent. And although it remains possible that collinearity exists amongst some of these variables, the coexistence of these features together likely represent an atheroma that is at higher risk of producing ischemia, and potentially of future events.

To date, the preponderance of studies evaluating APCs by coronary CTA have been related to ACS rather than to ischemia (8,9,26,27). These studies suggest a correlation between APCs and ACS, with APCs by coronary CTA—particularly PR and LAP—associated with future short-term rather than stable events. In a prospective evaluation of 1,059 patients undergoing coronary CTA, Motoyama et al. (9) associated plaques with PR and LAP with future ACS. The incremental value of APCs beyond stenosis was further confirmed by Kristensen et al. (28), who observed in 312 patients presenting with ACS that increased noncalcified plaque within nonobstructive

lesions was associated with an increased risk of recurrent adverse cardiac events, although the degree of PR or LAP was not specifically examined.

At present, interpretation of coronary CTA is based primarily on stenosis, a method advocated by societal guidance documents (29). Our study results reinforce a notion that stenosis is insufficient for the identification of specific coronary lesions that are implicated in the cause of ischemia (3) and, given the ability of %APV and APCs to independently improve discrimination of ischemia-causing coronary lesions—coupled with their association with incident ACS risk—consideration should be given to include these features in clinical reporting. Recently, other physiological measures of coronary artery disease by coronary CTA have emerged, including FFR derived from coronary CTA (FFR_{CT}) (30). Whether APCs augment the prediction of lesion-specific ischemia in a manner incremental to FFR_{CT} remains unknown, but future study of this concept is needed.

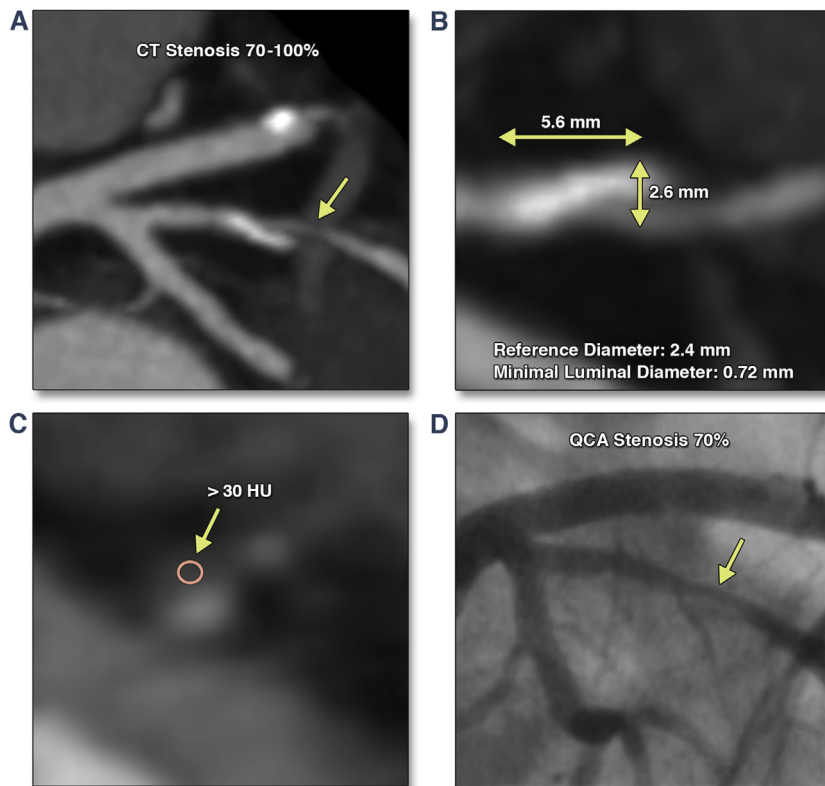


FIGURE 4 Obstructive Coronary Stenosis Does Not Cause Ischemia

(A) Arterial segment demonstrating significant luminal compromise. (B) Multiplanar reformat demonstrating no positive remodeling (remodeling index 1.08) and no spotty calcification. (C) Coronary CT angiography cross section demonstrating no low attenuation plaque (>30 HU). (D) Corresponding invasive angiogram demonstrating a 70% stenosis in obtuse marginal branch of the circumflex coronary artery. The FFR value was 0.89, indicating no ischemia. Abbreviations as in Figures 1 to 3.

STUDY LIMITATIONS. This study is not without limitations. Although prior studies have observed coronary CTA APCs to be concordant with intravascular ultrasound for measures of arterial remodeling, necrotic cores, and SC, coronary CTA is limited in resolution, and the accuracy of coronary CTA measures may have affected study results. Because of spatial resolution, coronary CTA cannot identify TCFA, a feature vital to the coronary disease process. Although it is unknown whether TCFA is directly associated with lesion ischemia, APCs by coronary CTA in this study are associated with TCFA when compared with optical coherence tomography, and may help explain our study findings (31). Further, the vessels interrogated by FFR were limited to those deemed clinically indicated. Thus, a potential bias of selection cannot be disencumbered from the present study, and all results presented herein should be

considered hypothesis-generating. In addition, it is possible that the presence of atherosclerosis in other coronary vessels may have influenced the presence of ischemia in the FFR-interrogated vessel, and this premise could not be adequately tested.

CONCLUSIONS

Independent and incremental to stenosis severity, plaque burden and APCs by coronary CTA improve identification, discrimination, and reclassification of coronary artery lesions that cause ischemia.

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