JAMA Cardiology | Original Investigation

Stress Myocardial Perfusion Imaging vs Coronary Computed Tomographic Angiography for Diagnosis of Invasive Vessel-Specific Coronary Physiology

Predictive Modeling Results From the Computed Tomographic Evaluation of Atherosclerotic Determinants of Myocardial Ischemia (CREDENCE) Trial

Wijnand J. Stuijfzand, MD; Alexander R. van Rosendael, MD; Fay Y. Lin, MD; Hyuk-Jae Chang, MD, PhD; Inge J. van den Hoogen, MD; Umberto Gianni, MD; Jung Hyun Choi, MD, PhD; Joon-Hyung Doh, MD; Ae-Young Her, MD; Bon-Kwon Koo, MD, PhD; Chang-Wook Nam, MD, PhD; Hyung-Bok Park, MD; Sang-Hoon Shin, MD; Jason Cole, MD; Alessia Gimelli, MD; Muhammad Akram Khan, MD; Bin Lu, MD; Yang Gao, MD; Faisal Nabi, MD; Ryo Nakazato, MD; U. Joseph Schoepf, MD; Roel S. Driessen, MD; Michiel J. Bom, MD; Randall Thompson, MD; James J. Jang, MD; Michael Ridner, MD; Chris Rowan, MD; Erick Avelar, MD; Philippe Généreux, MD; Paul Knaapen, MD, PhD; Guus A. de Waard, MD; Gianluca Pontone, MD, PhD; Daniele Andreini, MD, PhD; Mouaz H. Al-Mallah, MD; Yao Lu, MSc; Daniel S. Berman, MD; Jagat Narula, MD, PhD; James K. Min, MD; Jeroen J. Bax, MD, PhD; Leslee J. Shaw, PhD; for the CREDENCE Investigators

IMPORTANCE Stress imaging has been the standard for diagnosing functionally significant coronary artery disease. It is unknown whether novel, atherosclerotic plaque measures improve accuracy beyond coronary stenosis for diagnosing invasive fractional flow reserve (FFR) measurement.

OBJECTIVE To compare the diagnostic accuracy of comprehensive anatomic (obstructive and nonobstructive atherosclerotic plaque) vs functional imaging measures for estimating vessel-specific FFR.

DESIGN, SETTING, AND PARTICIPANTS Controlled clinical trial of diagnostic accuracy with a multicenter derivation-validation cohort of patients referred for nonemergent invasive coronary angiography. A total of 612 patients (64 [10] years; 30% women) with signs and symptoms suggestive of myocardial ischemia from 23 sites were included. Patients were recruited from 2014 to 2017. Data analysis began in August 2018.

INTERVENTIONS Patients underwent invasive coronary angiography with measurement of invasive FFR, coronary computed tomographic angiography (CCTA) quantification of atherosclerotic plaque and FFR by CT (FFR-CT), and semiquantitative scoring of rest/stress myocardial perfusion imaging (by magnetic resonance, positron emission tomography, or single photon emission CT). Multivariable generalized linear mixed models were derived and validated calculating the area under the receiver operating characteristics curve.

MAIN OUTCOMES AND MEASURES The primary end point was invasive FFR of 0.80 or less.

RESULTS Of the 612 patients, the mean (SD) age was 64 (10) years, and 426 (69.9%) were men. An invasive FFR of 0.80 or less was measured in 26.5% of 1727 vessels. In the derivation cohort, CCTA vessel-specific factors associated with FFR 0.80 or less were stenosis severity, percentage of noncalcified atheroma volume, lumen volume, the number of lesions with high-risk plaque (≥2 of low attenuation plaque, positive remodeling, napkin ring sign, or spotty calcification), and the number of lesions with stenosis greater than 30%. Fractional flow reserve–CT was not additive to this model including stenosis and atherosclerotic plaque. Significant myocardial perfusion imaging predictors were the summed rest and difference scores. In the validation cohort, the areas under the receiver operating characteristic curve were 0.81 for CCTA vs 0.67 for myocardial perfusion imaging ($P < .001$).

CONCLUSIONS AND RELEVANCE A comprehensive anatomic interpretation with CCTA, including quantification of obstructive and nonobstructive atherosclerotic plaque, was superior to functional imaging in the diagnosis of invasive FFR. Comprehensive CCTA measures improve prediction of vessel-specific coronary physiology more so than stress-induced alterations in myocardial perfusion.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02173275.

JAMA Cardiol. doi:10.1001/jamacardio.2020.3409
Published online August 19, 2020.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The CREDENCE Investigators members appear at the end of the article.

Corresponding Author: Leslee J. Shaw, PhD, Dalio Institute of Cardiovascular Imaging, 413 E 69th St, Ste 108, New York, NY 10021 (les2035@med.cornell.edu).

For decades, the diagnostic evaluation of patients with stable chest pain has largely relied on stress myocardial perfusion imaging (MPI) and other functional tests for assessment of inducible ischemia. The presence and severity of inducible abnormalities are the basis for decisions on ischemia-guided management including invasive coronary angiography (ICA) and coronary revascularization.[1-3] Among noninvasive imaging tests, MPI, including single-photon emission computed tomography (SPECT), positron emission tomography (PET), and cardiac magnetic resonance imaging (CMR), are commonly used to determine functionally significant coronary artery disease (CAD) based on the extent and severity of inducible myocardial ischemia.[4,5] Evidence has emerged to support the role of coronary computed tomography angiography (CCTA) as an alternative noninvasive, anatomic diagnostic imaging modality.[6-8]

Discerning the physiologic significance of a stenosis is a major goal of stress testing and is fundamental to guide management of ischemic heart disease. Anatomic approaches focusing on the detection of a stenosis are often considered incomplete without incorporation of physiologic parameters. To date, comparative diagnostic accuracy evidence does not uniformly reveal superiority of functional vs anatomic testing when estimating invasive fractional flow reserve (FFR) measurement.[5,9] Moreover, comparative findings from prior diagnostic accuracy trials generally focus on the accuracy of stenosis severity and did not include the entirety of anatomic data available, namely, volumetric and compositional atherosclerotic plaque.[5-7,10,11] To our knowledge, a comparison of comprehensive noninvasive anatomic, including quantification of nonobstructive and obstructive atherosclerotic plaque, vs functional imaging has not been performed as it relates to predicting invasive FFR. The aim of the Computed Tomographic Evaluation of Atherosclerotic Determinants of Myocardial Ischemia (CREDENCE) trial was to derive, validate, and compare an optimized CCTA with MPI assessment for the prediction of functionally significant CAD, determined by vessel-specific invasive FFR.

Key Points

Question Are atherosclerotic plaque measurements associated with physiologic measures of invasive fractional flow reserve?

Findings In this analysis of the CREDENCE clinical trial that included 612 patients, nonobstructive and obstructive measures of atherosclerotic plaque were significantly associated with invasive fractional flow reserve. A comprehensive set of atherosclerotic plaque features improved the accuracy of classifying vessel-specific reduced fractional flow reserve vs rest/stress myocardial perfusion imaging measurements.

Meaning Using coronary computed tomographic angiography for detection of atherosclerotic plaque features associated with coronary physiology may improve diagnostic certainty and guide clinical management of symptomatic patients.

Methods

Study Design

The CREDENCE trial is a prospective, multicenter diagnostic derivation-validation, controlled clinical trial recruiting patients from 2014 to 2017. A detailed design article is available.[12] Enrolled patients underwent CCTA and MPI followed by ICA with FFR measurements (≤60 days). Eligibility criteria (eAppendix 1 in the Supplement) included referral to nonemergent ICA. All index tests were interpreted blindly by core laboratories. Local sites were not blinded to test data. The institutional review board of each site approved the study protocol, and patients provided written informed consent.

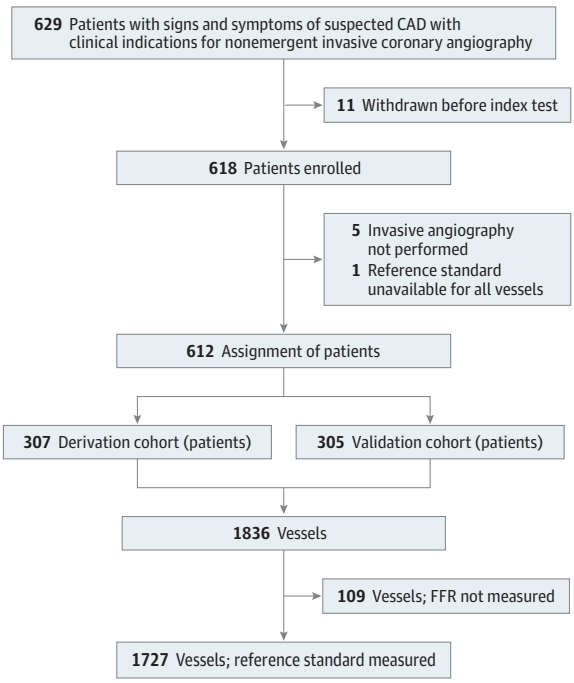
Derivation and Validation Cohorts

The study population comprised 612 patients with stable symptoms and without a prior diagnosis of CAD referred for nonemergent ICA (**Figure 1**; eAppendix 2 in the Supplement). Patients were recruited across 23 centers (eAppendix 3 and 4 in the Supplement). Trial participants were assigned to 2 subsets with the first half of enrollees at each site assigned to the derivation (n = 307) and the second half to the validation (n = 305) data set.

End Point of Invasive Vessel-Specific FFR

The primary aim was to compare the area under the receiver operating characteristics curve (AUC) of an integrated CCTA vs MPI assessment for the discrimination of vessel-specific FFR of 0.80 or less by ICA.

Figure 1. Standards for Reporting of Diagnostic Accuracy Studies Diagram for the Computed Tomographic Evaluation of Atherosclerotic Determinants of Myocardial Ischemia (CREDENCE) Trial



CAD indicates coronary artery disease; FFR, fractional flow reserve.

Imaging Protocols

Coronary computed tomographic angiography was performed using a single- or dual-source CT scanner with at least 64 detector rows and a detector row width of 75 mm or less. Sites were instructed to perform CCTA in accordance with guidelines from the Society of Cardiovascular Computed Tomography.[13] Image quality for CCTA was acceptable in 99% of patients.

Rest/stress MPI was performed using SPECT, PET, or CMR in accordance with guidelines of the American Society of Nuclear Cardiology or Society of CMR.[14,15] Six MPI patients had missing or corrupted scan data. Image quality for MPI was acceptable in 95% of patients. Imaging protocols and Core Laboratories methods are in eAppendices 4-6 in the Supplement.

Invasive Coronary Angiography and Measurement of FFR

Invasive coronary angiography was performed in agreement with clinical indications and imaging standards. 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.

Noninvasive Imaging Interpretation and Candidate Variables

All noninvasive imaging was interpreted at a core laboratory by physicians blinded to clinical and test results. Coronary CTA images were interpreted on per-lesion and per-segment basis for lumen and vessel volume, diameter stenosis, plaque composition and volume, number of lesions, and the presence of high-risk plaque features using semiautomated plaque analysis software (QAngioCT Research Edition, version 3.1.4.1; Medis Medical Imaging). The percentage of atheroma volume was calculated by dividing plaque volume/vessel volume × 100%; with compositional subgroups. The lumen volume was divided by vessel length. High-risk plaque was defined by at least 2 of the following: positive remodeling (≥1.1), spotty calcification (<3.0 mm), napkin ring sign, or low attenuation plaque (Hounsfield unit density <30).[16] Segmental results were summed to per-vessel and per-patient values.[13] Six patients had missing plaque measurements. Fractional flow reserve by CT (FFR-CT) was measured by Heartflow. In the setting of at least 25% focal stenosis, FFR-CT was coregistered to the segment of maximal diameter stenosis by readers blinded to the other test findings.[17] An FFR-CT of 0.80 or less was considered abnormal. Fractional flow reserve CT was nonevaluable in 135 patients; commonly owing to significant calcification, arterial motion, missing segment, image misalignment, or noise.

Rest/stress MPI scans were scored by segments and expressed as summed rest score (SRS) and summed difference scores (SDS) using the percentage of myocardium.[14,18,19] Segmental scores were aggregated per patient and vascular territory. Measurements of left ventricular ejection fraction (LVEF) and electrocardiographic ST segment changes with stress were available. Rest and stress LVEF was missing in 28 and 57 patients, respectively.

Reference Standard Measurement

All lesions with a diameter stenosis of at least 30% on visual estimation were measured with quantitative coronary angiography by a core laboratory, blinded to clinical and test results. Vessels with quantitative coronary angiography less than 40% or at least 90% diameter stenosis without FFR interrogation were deemed normal or ischemic. An FFR of 0.80 or less was graded as abnormal.

Statistical Methods

Analysis was performed on an intention-to-diagnose basis. In the derivation set, the best overall prediction model for vessel-specific abnormal FFR was fit using a generalized linear mixed model with logistic link function to estimate the probability of an abnormal, invasive FFR. For CCTA, model building was performed first, including diameter stenosis severity; second, adding atherosclerotic plaque characteristics (volumetric measurements both total and compositional lumen volume and high-risk plaque features); and third, adding FFR-CT. Data unavailable owing to clinical reasons or artifact were coded as missing not at random. Fractional flow reserve CT data were coded using a separate category for missing measurements. Similar approaches were used for the LVEF data. For MPI, model building initially included rest/stress MPI; second, adding rest/stress LVEF; and third, adding exercise ECG findings. The selection procedure (with Akaike information criterion as a stopping rule) and clinical domain expertise was used for variable selection and model development. Interactions were assessed by clinical plausibility and statistical significance using a likelihood ratio test. Marginal risk[20] was calculated from the optimal models and receiver operating characteristics (ROC) curves derived from marginal risk were used to compare diagnostic accuracy. The area under the ROC curve (AUC) and 95% confidence intervals were summarized. The primary analysis included estimation of invasive FFR using CCTA vessel and MPI vascular territory data. Based on variables included in the multivariable model for CCTA and MPI, predicted probabilities of invasive FFR were calculated. A per-patient analysis was also performed.

A necessary sample size of 868 vessels (or 305 patients) was calculated with 90% power (α = .05) to detect 5% superiority in the AUC of CCTA vs MPI. A 2-sided *P* value less than .05 was considered statistically significant. Analyses were performed using R, version 3.5.2 (The R Foundation) and SAS, version 9.4 (SAS Institute Inc). Data analysis began in August 2018.

Results

Descriptive Characteristics of the Trial Patients

Of the eligible patients, 11 patients withdrew before any index test was performed and ICA data were unavailable in 6 patients (Figure 1). The final enrollment included 612 patients (307 in the derivation and 305 in the validation set).

Patients were a mean (SD) age of 64 (10) years and mostly men (426 [69.6%]). A comparison of the clinical characteristics of age, sex, race/ethnicity, and risk factor prevalence were largely similar between the derivation and validation subgroups (**Table 1**; eTable 1 in the Supplement) except dyslipidemia and atypical chest pain, which were more prevalent in the validation cohort.

Table 1. CCTA Findings in the Derivation and Validation Subgroups From the CREDENCE Trial

Variable	%		*P* value
	Derivation	Validation	
Per-patient analysis			
No.	307	305	NA
Age, mean (SD), y	64 (10)	64 (10)	.69
Female	29	31	.56
Stenosis severity, %			
0	4	2	.07
1-24	7	8	
25-49	33	25	
50-69	34	38	
70-99[a]	14	21	
100	7	6	
≥50% Stenosis in proximal left anterior descending artery	23	28	.15
≥50% Stenosis in left main artery	7	9	.64
No. of vessels with ≥50% stenosis			
1 Vessel CAD	32	32	.12
2-3 Vessel CAD	23	30	
FFR-CT ≤0.80, No. (%)[b]	239 (60)	247 (66)	.19
Per-vessel analysis			
No.	859	868	NA
Stenosis severity, %[a]			
0	13	15	.001
1-24	22	19	
25-49	35	29	
50-69	20	25	
70-99	6	10	
100	3	2	
No. of lesions with >30% stenosis, mean (SD)	0.6 (0.7)	.6 (0.80)	.14
Lumen volume, mean (SD), per mm	5.2 (1.9)	5.2 (1.8)	.82
Atheroma volume, mean (SD), %	14.0 (13)	13.1 (12)	.12
Noncalcified atheroma volume, mean (SD), %	7.5 (8.1)	7.2 (8.2)	.03
High-risk plaque			
Low attenuation plaque <30 HU	15	13	.22
Positive remodeling ≥1.1	71	70	.68
Spotty calcification <3.0 mm	14	16	.59
No. of features			
0	27	28	.51
1	50	48	
2	19	20	
3	4	4	
FFR-CT ≤0.80[b]	16	22	.009

Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomographic angiography; CREDENCE, Computed Tomographic Evaluation of Atherosclerotic Determinants of Myocardial Ischemia; FFR-CT, fractional flow reserve by computed tomography, NA, not applicable.

[a] Stenosis severity is based on the qualitative interpretation.

[b] Fractional flow reserve CT was nonevaluable in 135 patients owing to significant coronary calcification, arterial motion, a missing segment, or image misalignment or noise.

Invasive Coronary Angiography Measures of Coronary Stenosis and FFR

Among 1727 epicardial coronary arteries, 26.5% exhibited ischemia by FFR of 0.80 or less. On ICA, approximately half of the patients had an obstructive stenosis of at least 50%. eTable 2 in the Supplement reports the angiographic findings across the major epicardial vessels. On a per-vessel basis, the mean (SD) diameter stenosis was 28.8% (29.6%). The prevalence of an abnormal FFR was highest in the left anterior descending coronary artery.

Coronary CTA Findings of Obstructive CAD, Atherosclerotic Plaque, and FFR-CT

On CCTA, the prevalence of CAD stenosis of at least 50% on a per-patient basis was 58%; with nearly half of these stenoses having an abnormal FFR-CT. Table 1 summarizes per-patient and per-vessel CCTA findings in the derivation and validation cohort. On a per-vessel basis, the prevalence of CCTA-observed stenosis was higher in the validation cohort at the 50% and 70% threshold (P = .001). High-risk plaque features, especially positive remodeling, were commonly ob-

Table 2. Rest and Stress MPI Findings in the Derivation and Validation Subgroups From the CREDENCE Trial

Variable	%		*P* value
	Derivation	Validation	
Per-patient analysis			
No.	307	305	NA
Type of MPI performed			
CMR	16	17	.58
PET	8	6	
SPECT	76	77	
Type of stress performed for nuclear			
Exercise stress	16	19	.63
Pharmacologic stress	84	81	
Exercise duration, mean (SD), min	9.6 (11.0)	7.6 (6.9)	.57
Exercise-induced ST segment depression ≥1.0 mm	33	23	.30
Heart rate, mean (SD), bpm			
Rest	69 (38)	68 (12)	.40
Peak stress			
Peak exercise	137 (17)	137 (19)	.53
Pharmacologic stress	82 (17)	81 (14)	.75
Blood pressure, mean systolic/diastolic, mm Hg			
Rest	132/79	137/79	.002/.49
Peak stress			
Peak exercise	179/90	180/91	>.99/.95
Pharmacologic stress	132/76	132/74	.82/.03
Limiting or nonlimiting chest pain	10	10	>.99
≥5% Ischemic myocardium			
Anterior vascular territory	13	16	.29
Inferior vascular territory	12	13	.67
Lateral vascular territory	8	9	.85
≥10% Ischemic myocardium	18	19	.94
LVEF<50%[a]			
Rest	2	5	.13
Poststress	11	9	.43
Per-vessel analysis			
No.	859	868	NA
MPI, % myocardium			
SRS, mean (SD)	0.8 (2.6)	0.7 (2.0)	.38
≥5% Of the myocardium abnormal	5	6	
SSS, mean (SD)	2.3 (5.0)	2.4 (4.4)	.008
≥5% Of the myocardium abnormal	16	18	
SDS, mean (SD)	1.5 (3.9)	1.7 (3.6)	.001
≥5% Of the myocardium ischemic	11	12	

Abbreviations: CMR, cardiovascular magnetic resonance; bpm, beats per minute; CREDENCE, Computed Tomographic Evaluation of Atherosclerotic Determinants of Myocardial Ischemia; LVEF, left ventricular ejection fraction; MPI, myocardial perfusion imaging; PET, positron emission tomography; SDS, summed difference scores; SPECT, single-photon emission computed tomography; SRS, summed rest score; SSS, summed stress score.

[a] LVEF was missing in 57 patients (n = 28 for rest and n = 57 for stress).

served. Positive remodeling of at least 1.1 was identified in 70.2% of patients (n = 430). Low attenuation plaque was identified in 14.1% of patients (n = 86). Spotty calcification was identified in 15.4% of patients (n = 94). The concordance between invasive FFR and FFR-CT was moderate (κ = 0.45); 91% of normal FFR-CT also had a normal invasive FFR while only 51% of abnormal FFR-CT had an abnormal invasive FFR.

Rest and Stress MPI Findings

On MPI, nearly one-third of patients had at least mild ischemia encumbering at least 5% of the myocardium; with most having a preserved LVEF. **Table 2** summarizes per-patient and per-vessel MPI findings according to the derivation and validation cohort. Pharmacologic stress MPI SPECT imaging was commonly performed. Exertional ST-segment depression of at least 1.0 mm occurred in 27% of patients. Overall, nearly 1 in 5 patients had moderate to severe ischemia encumbering at least 10% of the myocardium. On a per-vessel basis, the mean (SD) SRS and SDS within derivation and validation was 0.8% (2.6%) and 0.7% (2.0%) (*P* = .38) and 1.5% (3.9%) and 1.7% (3.6%) (*P* = .001) of the myocardium, respectively. The negative predictive value of an SDS less than 5% of the myocardium to exclude obstructive CAD stenosis (≥50%) was high (93%). Conversely, the positive predictive value to detect an

obstructive stenosis of at least 50% using a threshold of at least 5% ischemic myocardium was low (22%). Similar values were reported for the anterior, inferior, and lateral vascular territories, respectively (negative predictive value ranges: 92%-94% and positive predictive value ranges: 18%-25%). The positive and negative predictive value was also similar by type of MPI imaging modality.

Model Building For Vessel-Specific Measurements Within the Derivation Cohort

The ROC curve analysis for prediction of invasive FFR for derivation models MPI and CCTA are plotted in **Figure 2**. The AUC for CCTA stenosis severity was 0.82. Significant atherosclerotic plaque predictors included percentage of noncalcified atheroma volume, lumen volume, the number of lesions with high-risk plaque, and the number of lesions with greater than 30% diameter stenosis (**Table 3**). Adding atherosclerotic plaque significantly improved the AUC to 0.88 ($P < .001$). Subsequent addition of FFR-CT to atherosclerotic plaque and stenosis severity did not improve discrimination within ROC curve analysis (AUC = 0.88). In the subgroup with at least 50% stenosis (n = 182 vessels), 85% (n = 74 vessels) of the abnormal FFR-CT were concordant with invasive FFR. The AUC curve for stress MPI, including the SRS and SDS within specific vascular territories, was 0.69 (Figure 2). The AUC did not change by stepwise addition of LVEF (AUC, 0.69) or with exercise electrocardiogram (ECG) findings (AUC, 0.70). In the final model, factors significantly associated with invasive FFR of 80 or less for MPI included the vascular territory summed rest score and summed difference score (eTable 3 in the Supplement). Based on these findings, for every 5% of the myocardium that was ischemic in a specific vascular territory, there was a 30% increased odds of ischemia by invasive FFR ($P < .001$).

Model Comparison in the Validation Cohort

With regard to the primary objective comparing the AUC by modality, the results revealed that an optimized CCTA model was superior to the overall MPI model for the diagnosis of abnormal FFR (AUC, 0.81; 95% CI, 0.78-0.84 vs 0.67; 95% CI, 0.63-0.71; $P < .001$; Figure 2). The AUC results were comparable when analyzed on a per-patient basis (eFigure 1 in the Supplement). Subgroup analyses revealed similarly higher AUC for CCTA when compared with MPI in subgroups of women, men, and for those younger than 65 years and 65 years and older (all $P < .001$, eTable 4 in the Supplement). Similar results were also observed when the MPI analysis was limited to patients undergoing SPECT imaging (0.84 vs 0.69; $P < .001$, eTable 4 in the Supplement). Plots of the predicted probability of invasive FFR 0.80 or less for each of the variables in the CCTA (Table 3) and MPI (eTable 3 in the Supplement) multivariable models are reported in eFigures 2 and 3 in the Supplement. Predicted probabilities for CCTA variables had a generally wider range of measurements than MPI variables. A comparison of the predicted probabilities for CCTA and MPI for each of the presented models is plotted in eFigure 4 in the Supplement, revealing that many patients categorized with a lower predicted probability by MPI are in higher probability tertiles by CCTA.

Discussion

In this derivation-validation trial, an anatomic approach using CCTA, including multiple atherosclerotic plaque measures, demonstrated improved diagnostic accuracy as compared with functional assessment using rest/stress MPI for the prediction of invasive FFR. We extend prior results revealing that various qualitative and quantitative CCTA-derived atherosclerotic plaque characteristics were highly predictive of invasive FFR.[21,22] From the CREDENCE trial, we report a strong association between volumetric measures of atherosclerotic plaque, especially that which is noncalcified, and lumen size as significantly associated with invasive FFR. These findings capture the instability thought to be associated with more lipid-rich, atherosclerotic plaque[23] and reveal the importance of vessel size as an important marker of FFR abnormality. Our findings of the association between atherosclerotic plaque and invasive FFR were similar in the derivation and validation cohorts.

Importance of Atherosclerotic Plaque to Guide Clinical Decision-Making

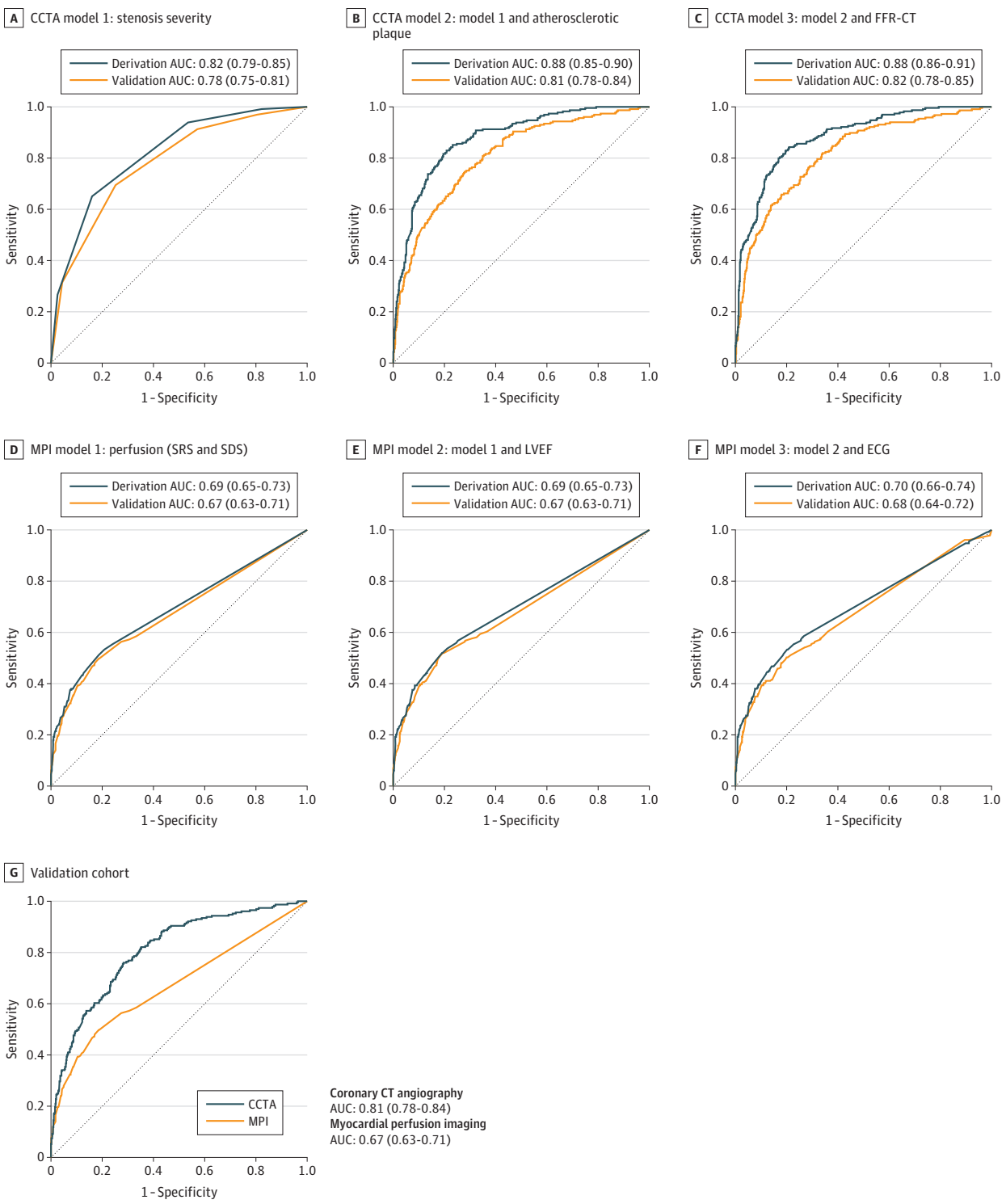
Clinical guidelines support ischemia-guided management of a focal coronary stenosis, based on evidence from several trials supporting FFR-guided revascularization.[1,2] The evidence that functional testing is the basis for evaluation and management of patients with stable chest pain is longstanding.[24,25] However, prior evidence did not examine detailed quantification of atherosclerotic plaque in the estimation of vessel-specific FFR on ICA. Given this, identification of CCTA atherosclerotic plaque with coronary stenosis findings may provide sufficient evidence to guide preventive treatment and reduce the need for confirmatory functional testing or even use of invasive FFR.

We validated the well-known association between significant luminal stenosis and reduced FFR. However, our findings also provide unique insight and potentially a working model as to nonobstructive atherosclerotic disease factors influencing epicardial coronary artery ischemia. A smaller lumen volume may reflect diffuse atherosclerosis and/or impaired hyperemia. This is similarly noted in the number of greater than 30% stenoses, which was significantly associated with invasive FFR. Both factors combined, with the percentage of atheroma volume and noncalcified plaque volume, provide further evidence as to the importance of quantifying atherosclerotic plaque for detection of at-risk patients. This supports the intriguing findings of atherosclerotic plaque precursors of symptoms or ischemia in the setting of nonobstructive CAD.[21,22] In combination with the characteristic features of high-risk plaque, previously shown to predict acute coronary syndromes and major CAD events,[16,26] we have identified factors that define vessel instability and potentially identify patients who may benefit from intensive preventive care resulting in improved outcome as compared with standard care approaches.[27-29]

Association of MPI Abnormalities With Invasive FFR

Functional imaging has been the cornerstone of ischemia-guided management for decades. Our findings revealed that the extent and severity of MPI ischemia exhibited a moderate association

Figure 2. Receiver Operating Characteristic Curve Analysis for Prediction of Invasive Fractional Flow Reserve (FFR)



This analysis details the results on a per-vessel basis. Separate lines are included for the derivation and validation series for each of the sequential models. The top row includes sequential models for coronary computed tomographic angiography (CCTA) including stenosis severity, atherosclerotic plaque, and FFR-CT. The bottom row includes sequential models for myocardial perfusion imaging (MPI) including the summed rest score (SRS) and summed difference score (SDS), left ventricular ejection fraction (LVEF), and electrocardiogram (ECG) abnormalities. On the right are the data from the validation cohort, showing the overall primary aim including the final model for CCTA (area under the curve [AUC], 0.81) compared with the final model for MPI (area under the curve, 0.67). In the derivation cohort, using a more distal FFR-CT measurement, the $P = .30$ for model 3. OCTA indicates optical coherence tomography angiography.

Table 3. Multivariable Generalized Linear Mixed Model Based on CCTA Vessel Measurements of Stenosis Severity and Atherosclerotic Plaque Estimating Invasive FFR from the CREDENCE Trial[a,b]

Model parameters for per vessel	Odds ratio (95% CI)	χ^2	*P* value
Stenosis severity, %[c]			
0	1 [Reference]		
1-24	1.93 (0.37-10.06)		
25-49	3.32 (0.65-16.86)	53.9	<.001
50-69	10.01 (1.82-58.10)		
≥70	88.05 (14.14-548.39)		
Atheroma volume, %	1.02 (0.99-1.05)		
Quartile measurement[a]			
0.00-3.60	1 [Reference]		
3.61-10.93	0.71 (0.21-2.41)	2.8	.15
10.94-21.16	0.77 (0.31-2.85)		
≥21.17	1.79 (0.43-7.48)		
Noncalcified atheroma volume, %	1.05 (1.01-1.09)		
Quartile measurement[a]			
≤1.67	1 [Reference]		
1.68-5.51	1.56 (0.60-4.90)	4.1	.04
5.52-10.96	1.56 (0.46-5.27)		
≥10.97	2.50 (0.67-9.26)		
Lumen volume, per mm	0.72 (0.61-0.86)		
Quartile measurement, per mm[a]			
≥5.97	1 [Reference]		
4.74-5.96	1.82 (0.82-4.01)	14.3	<.001
3.93-4.73	2.47 (1.15-5.33)		
<3.92	4.89 (2.20-10.86)		
No. of lesions			
With high-risk plaque	1.99 (1.26-3.14)	8.9	.003
With >30% stenosis	1.81 (1.25-2.62)	9.8	.002
At a bifurcation	1.34 (0.99-1.81)	3.7	.06

Abbreviations: CCTA, coronary computed tomographic angiography; CREDENCE, Computed Tomographic Evaluation of Atherosclerotic Determinants of Myocardial Ischemia; FFR-CT, fractional flow reserve by computed tomography.

[a] This final model was based on variables included in the final CCTA model from Figure 2. For ease of presentation, we also present a second model that includes stenosis severity subgroups and quartile measures for percent atheroma volume, noncalcified plaque volume, and lumen volume. FFR-CT was not statistically significant and not entered into the final multivariable model.

[b] Quartile measurements are presented for descriptive purposes.

[c] Stenosis severity was based on a qualitative interpretation.

with invasive vessel-specific ischemia, reflecting the variable findings noted in the literature.[5,10,11,30,31] Although the AUC values were not as high as with CCTA, significant MPI predictors included the extent and severity of myocardial perfusion defects measured at rest and stress. Resting perfusion deficits represent the extent of scarred myocardium and an association with more severe coronary stenosis is expected. Moreover, invasive FFR would also associate with the subtended myocardial vascular beds and thereby relate to the extent and severity of MPI ischemia. However, when MPI was compared with CCTA findings, the CREDENCE trial data support that the underlying burden of anatomically defined CAD, including atherosclerotic plaque and stenosis, had a stronger link to invasive FFR than the physiologic consequences of myocardial perfusion.

We propose several reasons for the reduced concordance between invasive FFR and MPI ischemia. First, variability likely is greatest when comparing ischemic myocardium vs vessel-specific FFR measurements, whereby invasive FFR is a solely epicardial measurement while perfusion reflects myocardial uptake from both epicardial arteries, microvasculature, and collateral vessels. Second, the proportion of patients with more extensive and severe myocardial ischemia was likely insufficient to improve the strength of this association. As well, there are notable challenges with attenuation and other artifacts, especially with SPECT, that contributed to the reduced accuracy of MPI. The diminished concordance between myocardial ischemia and invasive FFR is multifactorial but a reduced sensitivity (eg, 57%) of SPECT was reported in trials conducted in 2015 and 2017.[10,11]

Atherosclerotic Plaque and Invasive FFR

Although prior studies have not provided a comprehensive comparative analysis between CCTA and stress MPI, the association between plaque characteristics, such as plaque burden and morphology, with reduced FFR has been explored. Gaur et al[23] investigated 254 patients using CCTA and reported that noncalcified plaque volume predicted an FFR of 0.80 or less, independent of other plaque and stenosis characteristics. Park et al[32] demonstrated that high-risk plaque features (ie, positive remodeling and low attenuation plaque) and aggregated plaque volume were independently associated with invasive FFR. These results were confirmed by a recent post hoc analysis from the Prospective Comparison of Cardiac PET/CT, SPECT/CT Perfusion Imaging and CT Coronary Angiography With Invasive Coronary Angiography (PACIFIC) trial whereby positive remodeling and noncalcified atherosclerotic plaque volume reduced both absolute myocardial blood flow with ^{15}O-labeled water PET and invasive FFR, independent of luminal stenosis.[33] These prior findings align with the CREDENCE analyses that observed noncalcified plaque volume, presence of high-risk plaque, and vessel size as independently associated with invasive FFR, independent of stenosis severity. The use of an integrated plaque assessment of CCTA,

and not just luminal stenosis, contributes to an important difference between our results and other research findings.

Fractional reserve flow CT did not significantly improve discrimination of normal vs abnormal invasive FFR; supporting the concept that a reduced pressure difference is a response to specific underlying atherosclerotic plaque characteristics. In the subgroup with at least 50% stenosis, only 51% of the abnormal FFR-CT were concordant with invasive FFR. These findings emphasize the complex, multifaceted nature of coronary ischemia, which is influenced by more than coronary artery lumen features that are analyzed during the derivation of FFR-CT.

Limitations

All clinical investigations enrolling large samples of patients from diverse institutions and health care settings have limitations. Although all patients underwent multiple procedures, the test strategy was not randomized and selection bias cannot be excluded. Also, follow-up therapeutic care and ensuing prognostic data were not collected. Lastly, quantitative CCTA measurements are, at present, time-consuming.

Conclusions

In this multicenter, controlled clinical trial, comprehensive CCTA interpretation was superior to MPI for the diagnosis of vessel-specific FFR. Combined with measures of stenosis severity, quantification and characterization of atherosclerotic plaque prove optimal for detection of invasive vessel-specific FFR. The incorporation of whole-vessel quantification of epicardial coronary atherosclerosis provides a more comprehensive view of the underlying disease burden and vessel FFR compared with examination of a given focal stenosis alone. Future explorations including assimilation of the CREDENCE findings into clinical practice should support a broader inclusion of atherosclerotic plaque findings as meaningful to assess coronary physiology.

ARTICLE INFORMATION

Accepted for Publication: June 4, 2020.

Published Online: August 19, 2020. doi:10.1001/jamacardio.2020.3409

Author Affiliations: Dalio Institute of Cardiovascular Imaging, Department of Radiology, New York-Presbyterian Hospital and the Weill Cornell Medical College, New York (Stuijfzand, van Rosendael, Lin, van den Hoogen, Gianni, Y. Lu, Min, Shaw); Amsterdam University Medical Center, VU University Medical Center, Amsterdam, the Netherlands (Stuijfzand, Driessen, Bom, Knaapen, de Waard); Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands (van Rosendael, van den Hoogen, Bax); Division of Cardiology, Severance Cardiovascular Hospital and Severance Biomedical Science Institute, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea (Chang); Department of Molecular Medicine, Section of Cardiology, University of Pavia, Pavia, Italy (Gianni); Pusan National University Hospital, Busan, South Korea (Choi); Division of Cardiology, Inje University Ilsan Paik Hospital, Goyang, South Korea (Doh); Kang Won National University Hospital, Chuncheon, South Korea (Her); Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea (Koo); Cardiovascular Center, Keimyung University Dongsan Hospital, Daegu, South Korea (Nam); Division of Cardiology, Department of Internal Medicine, International St Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, South Korea (Park); Division of Cardiology, Department of Internal Medicine, Ewha Women's University Seoul Hospital, Seoul, South Korea (Shin); Mobile Cardiology Associates, Mobile, Alabama (Cole); Department of Imaging, Fondazione Toscana Gabriele Monasterio, Pisa, Italy (Gimelli); Cardiac Center of Texas, McKinney (Khan); State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, Beijing, China (B. Lu, Gao); Houston Methodist Hospital, Houston, Texas (Nabi); Cardiovascular Center, St. Luke's International Hospital, Tokyo, Japan (Nakazato); Medical University of South Carolina, Charleston (Schoepf); St Luke's Mid America Heart Institute, Kansas City, Missouri (Thompson); Kaiser Permanente Hospital, Oakland, California (Jang); Heart Center Research, LLC, Huntsville, Alabama (Ridner); Renown Heart and Vascular Institute, Reno, Nevada (Rowan); Oconee Heart and Vascular Center, St Mary's Hospital, Athens, Georgia (Avelar); Gagnon Cardiovascular Institute at Morristown Medical Center, Morristown, New Jersey (Généreux); Centro Cardiologico Monzino, IRCCS Milan, Italy (Pontone, Andreini); Houston Methodist DeBakey Heart and Vascular Center, Houston Methodist Hospital, Houston, Texas (Al-Mallah); Department of Imaging and Medicine, Cedars Sinai Medical Center, Los Angeles, California (Berman); Mount Sinai Heart, Zena and Michael A. Wiener Cardiovascular Institute, Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Icahn School of Medicine at Mount Sinai, New York, New York (Narula).

Author Contributions: Dr Shaw had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: van Rosendael, Chang, Her, Park, Cole, Nakazato, Driessen, Ridner, Pontone, Al-Mallah, Berman, Narula, Bax, Shaw.
Acquisition, analysis, or interpretation of data: Stuijfzand, van Rosendael, Lin, Chang, van den Hoogen, Gianni, Choi, Doh, Koo, Nam, Shin, Gimelli, Khan, B. Lu, Gao, Nabi, Nakazato, Schoepf, Driessen, Bom, Thompson, Jang, Ridner, Rowan, Avelar, Genereux, Knaapen, de Waard, Andreini, Y. Lu, Min, Shaw.
Drafting of the manuscript: Stuijfzand, Lin, Choi, Nam, Nakazato, Pontone, Andreini, Y. Lu, Min, Shaw.
Critical revision of the manuscript for important intellectual content: van Rosendael, Lin, Chang, van den Hoogen, Gianni, Doh, Her, Koo, Park, Shin, Cole, Gimelli, Khan, B. Lu, Gao, Nabi, Nakazato, Schoepf, Driessen, Bom, Thompson, Jang, Ridner, Rowan, Avelar, Genereux, Knaapen, de Waard, Pontone, Andreini, Al-Mallah, Y. Lu, Berman, Narula, Bax, Shaw.
Statistical analysis: Stuijfzand, Lin, Jang, Y. Lu, Shaw.
Obtained funding: Shaw.
Administrative, technical, or material support: Stuijfzand, van Rosendael, Lin, Chang, van den Hoogen, Gianni, Choi, Her, Park, Khan, B. Lu, Gao, Nabi, Nakazato, Schoepf, Driessen, Bom, Rowan, Avelar, Andreini, Min.
Supervision: Stuijfzand, Lin, Doh, Cole, Nabi, Schoepf, Thompson, Ridner, Knaapen, Andreini, Narula, Bax, Shaw.

Conflict of Interest Disclosures: Dr Andreini receives institutional research grant support from GE Healthcare and Bracco Diagnostics. Dr Pontone receives institutional research grant support and is a speaker for Heartflow, Medtronic, GE Healthcare, Bracco Diagnostics, and Bayer Life Sciences. Dr Berman receives software royalties from Cedars-Sinai Medical Center. Dr. Min previously worked at Weill Cornell Medical College but is now an employee and has equity interest in Cleerly Health. Dr Shaw is a scientific advisor for Covanos, Inc. Dr Stuijfzand receives funding from the Dalio Foundation, National Institutes of Health, and GE Healthcare. Dr Min serves on the scientific advisory board of Arineta and GE Healthcare and has an equity interest in Cleerly. Dr Jones has equity interest in Cleerly. Dr Shaw receives funding from the National Institutes of Health. Dr van Rosendael reported grants from Weill Cornell Medicine during the conduct of the study. Dr Schoepf has received institutional research support and/or honoraria for speaking and consulting from Astellas, Bayer, Bracco, Elucid BioImaging, General Electric, Guerbet, HeartFlow Inc, and Siemens Healthineers. Dr Pontone reported grants and personal fees from GE Healthcare and Bracco and grants from Heartflow outside the submitted work. Dr Bax reported grants from Biotronik, Edwards Lifesciences, Abbott, Boston Scientific, Bioventrix, Medtronic, and GE Healthcare and personal fees from Abbott Vascular outside the submitted work. No other disclosures were reported.

Funding/Support: This trial was supported by a grant from the National Institutes of Health National Heart, Lung, and Blood Institute (R01HL118019).

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

CREDENCE Trial investigators: Dante Chiappino, MD, Department of Imaging, Fondazione Toscana

Gabriele Monasterio, Pisa, Italy; Venkata Chilakapati, MD, Ahmed Ladak, MD, Irfan Ullah, MD, Cardiac Center of Texas, McKinney, Texas; Chaowei Mu, MD, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, Beijing, China; Hiroyuki Niinuma, MD, PhD, Cardiovascular Center, St. Luke's International Hospital, Tokyo, Japan; Daniel H. Steinberg, MD, Medical University of South Carolina Charleston, SC; Roel Driessen, MD, University Medical Center, Amsterdam, Netherlands; Jessica M. Peña, MD, Erica C. Jones, MD, Subhi J. Al'Aref MD, Daria Frestad MD, Amit Kumar MSc, Department of Radiology, New York-Presbyterian Hospital, Weill Cornell Medicine, New York, New York.

REFERENCES

1. Montalescot G, Sechtem U, Achenbach S, et al; Task Force Members; ESC Committee for Practice Guidelines; Document Reviewers. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34(38):2949-3003. doi:10.1093/eurheartj/eht296

2. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60(24):2564-2603. doi:10.1016/j.jacc.2012.07.012

3. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;64(18):1929-1949. doi:10.1016/j.jacc.2014.07.017

4. Shaw LJ, Marwick TH, Zoghbi WA, et al. Why all the focus on cardiac imaging? *JACC Cardiovasc Imaging*. 2010;3(7):789-794. doi:10.1016/j.jcmg.2010.05.004

5. Greenwood JP, Ripley DP, Berry C, et al; CE-MARC 2 Investigators. Effect of care guided by cardiovascular magnetic resonance, myocardial perfusion scintigraphy, or NICE guidelines on subsequent unnecessary angiography rates: the CE-MARC 2 randomized clinical trial. *JAMA*. 2016;316(10):1051-1060. doi:10.1001/jama.2016.12680

6. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med*. 2008;359(22):2324-2336. doi:10.1056/NEJMoa0806576

7. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol*. 2008;52(21):1724-1732. doi:10.1016/j.jacc.2008.07.031

8. Meijboom WB, Meijs MF, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. *J Am Coll Cardiol*. 2008;52(25):2135-2144. doi:10.1016/j.jacc.2008.08.058

9. Nagel E, Greenwood JP, McCann GP, et al; MR-INFORM Investigators. Magnetic resonance perfusion or fractional flow reserve in coronary disease. *N Engl J Med*. 2019;380(25):2418-2428. doi:10.1056/NEJMoa1716734

10. Neglia D, Rovai D, Caselli C, et al; EVINCI Study Investigators. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. *Circ Cardiovasc Imaging*. 2015;8(3):e002179. doi:10.1161/CIRCIMAGING.114.002179

11. Danad I, Raijmakers PG, Driessen RS, et al. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. *JAMA Cardiol*. 2017;2(10):1100-1107. doi:10.1001/jamacardio.2017.2471

12. Rizvi A, Hartaigh BO, Knaapen P, et al. Rationale and design of the CREDENCE Trial: computed TomogRaphic evaluation of atherosclerotic DEtermiNants of myocardial IsChEmia. *BMC Cardiovasc Disord*. 2016;16(1):190. doi:10.1186/s12872-016-0360-x

13. Leipsic J, Abbara S, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr*. 2014;8(5):342-358. doi:10.1016/j.jcct.2014.07.003

14. Hesse B, Tägil K, Cuocolo A, et al; EANM/ESC Group. EANM/ESC procedural guidelines for myocardial perfusion imaging in nuclear cardiology. *Eur J Nucl Med Mol Imaging*. 2005;32(7):855-897. doi:10.1007/s00259-005-1779-y

15. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E; Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized Protocols. Standardized cardiovascular magnetic resonance imaging (CMR) protocols, society for cardiovascular magnetic resonance: board of trustees task force on standardized protocols. *J Cardiovasc Magn Reson*. 2008;10:35. doi:10.1186/1532-429X-10-35

16. Chang HJ, Lin FY, Lee SE, et al. Coronary atherosclerotic precursors of acute coronary syndromes. *J Am Coll Cardiol*. 2018;71(22):2511-2522. doi:10.1016/j.jacc.2018.02.079

17. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA*. 2012;308(12):1237-1245. doi:10.1001/2012.jama.11274

18. Tilkemeier PL, Cooke CD, Ficaro EP, Glover DK, Hansen CL, McCallister BD Jr; American Society of Nuclear Cardiology. American Society of Nuclear Cardiology information statement: standardized reporting matrix for radionuclide myocardial perfusion imaging. *J Nucl Cardiol*. 2006;13(6):e157-e171. doi:10.1016/j.nuclcard.2006.08.014

19. Hundley WG, Bluemke D, Bogaert JG, et al. Society for Cardiovascular Magnetic Resonance guidelines for reporting cardiovascular magnetic resonance examinations. *J Cardiovasc Magn Reson*. 2009;11:5. doi:10.1186/1532-429X-11-5

20. Pavlou M, Ambler G, Seaman S, Omar RZ. A note on obtaining correct marginal predictions from a random intercepts model for binary outcomes. *BMC Med Res Methodol*. 2015;15:59. doi:10.1186/s12874-015-0046-6

21. Ahmadi A, Stone GW, Leipsic J, et al. Association of coronary stenosis and plaque morphology with fractional flow reserve and outcomes. *JAMA Cardiol*. 2016;1(3):350-357. doi:10.1001/jamacardio.2016.0263

22. Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms: results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. *J Am Coll Cardiol*. 2011;58(19):1989-1997. doi:10.1016/j.jacc.2011.06.066

23. Gaur S, Øvrehus KA, Dey D, et al. Coronary plaque quantification and fractional flow reserve by coronary computed tomography angiography identify ischaemia-causing lesions. *Eur Heart J*. 2016;37(15):1220-1227. doi:10.1093/eurheartj/ehv690

24. Shaw LJ, Berman DS, Maron DJ, et al; COURAGE Investigators. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation*. 2008;117(10):1283-1291. doi:10.1161/CIRCULATIONAHA.107.743963

25. De Bruyne B, Fearon WF, Pijls NH, et al; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med*. 2014;371(13):1208-1217. doi:10.1056/NEJMoa1408758

26. Ferencik M, Mayrhofer T, Bittner DO, et al. Use of high-risk coronary atherosclerotic plaque detection for risk stratification of patients with stable chest pain: a secondary analysis of the PROMISE randomized clinical trial. *JAMA Cardiol*. 2018;3(2):144-152. doi:10.1001/jamacardio.2017.4973

27. Newby DE, Adamson PD, Berry C, et al; SCOT-HEART Investigators. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med*. 2018;379(10):924-933. doi:10.1056/NEJMoa1805971

28. Williams MC, Hunter A, Shah ASV, et al; SCOT-HEART Investigators. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. *J Am Coll Cardiol*. 2016;67(15):1759-1768. doi:10.1016/j.jacc.2016.02.026

29. Blankstein R, Bittencourt MS, Bhatt DL. Coronary CTA in the evaluation of stable chest pain: clear benefits, but not for all. *J Am Coll Cardiol*. 2017;69(14):1771-1773. doi:10.1016/j.jacc.2017.02.011

30. Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol*. 2010;55(25):2816-2821. doi:10.1016/j.jacc.2009.11.096

31. Melikian N, De Bondt P, Tonino P, et al. Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. *JACC Cardiovasc Interv*. 2010;3(3):307-314. doi:10.1016/j.jcin.2009.12.010

32. Park HB, Heo R, Ó Hartaigh B, et al. Atherosclerotic plaque characteristics by CT angiography identify coronary lesions that cause ischemia: a direct comparison to fractional flow reserve. *JACC Cardiovasc Imaging*. 2015;8(1):1-10. doi:10.1016/j.jcmg.2014.11.002

33. Driessen RS, Stuijfzand WJ, Raijmakers PG, et al. Effect of plaque burden and morphology on myocardial blood flow and fractional flow reserve. *J Am Coll Cardiol*. 2018;71(5):499-509. doi:10.1016/j.jacc.2017.11.054