JACC: CARDIOVASCULAR IMAGING VOL. 16, NO. 2, 2023

ORIGINAL RESEARCH

AI Evaluation of Stenosis on Coronary CTA, Comparison With Quantitative Coronary Angiography and Fractional Flow Reserve

A CREDENCE Trial Substudy

William F. Griffin, MD,[a] Andrew D. Choi, MD,[a] Joanna S. Riess, MD,[a] Hugo Marques, MD,[b] Hyuk-Jae Chang, MD, PhD,[c] Jung Hyun Choi, MD, PhD,[d] Joon-Hyung Doh, MD,[e] Ae-Young Her, MD,[f] Bon-Kwon Koo, MD, PhD,[g] Chang-Wook Nam, MD, PhD,[h] Hyung-Bok Park, MD,[i] Sang-Hoon Shin, MD,[j] Jason Cole, MD,[k] Alessia Gimelli, MD,[l] Muhammad Akram Khan, MD,[m] Bin Lu, MD,[n] Yang Gao, MD,[o] Faisal Nabi, MD,[p] Ryo Nakazato, MD,[o] U. Joseph Schoepf, MD,[q] Roel S. Driessen, MD,[r] Michiel J. Bom, MD,[r] Randall Thompson, MD,[s] James J. Jang, MD,[t] Michael Ridner, MD,[u] Chris Rowan, MD,[v] Erick Avelar, MD,[w] Philippe Généreux, MD,[x] Paul Knaapen, MD, PhD,[r] Guus A. de Waard, MD,[r] Gianluca Pontone, MD, PhD,[y] Daniele Andreini, MD, PhD,[y] James P. Earls, MD[a]

ABSTRACT

BACKGROUND Clinical reads of coronary computed tomography angiography (CTA), especially by less experienced readers, may result in overestimation of coronary artery disease stenosis severity compared with expert interpretation. Artificial intelligence (AI)-based solutions applied to coronary CTA may overcome these limitations.

OBJECTIVES This study compared the performance for detection and grading of coronary stenoses using artificial intelligence–enabled quantitative coronary computed tomography (AI-QCT) angiography analyses to core lab–interpreted coronary CTA, core lab quantitative coronary angiography (QCA), and invasive fractional flow reserve (FFR).

METHODS Coronary CTA, FFR, and QCA data from 303 stable patients (64 ± 10 years of age, 71% male) from the CREDENCE (Computed TomogRaphic Evaluation of Atherosclerotic DEtermiNants of Myocardial IsChEmia) trial were retrospectively analyzed using an Food and Drug Administration–cleared cloud-based software that performs AI-enabled coronary segmentation, lumen and vessel wall determination, plaque quantification and characterization, and stenosis determination.

RESULTS Disease prevalence was high, with 32.0%, 35.0%, 21.0%, and 13.0% demonstrating ≥50% stenosis in 0, 1, 2, and 3 coronary vessel territories, respectively. Average AI-QCT analysis time was 10.3 ± 2.7 minutes. AI-QCT evaluation demonstrated per-patient sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 94%, 68%, 81%, 90%, and 84%, respectively, for ≥50% stenosis, and of 94%, 82%, 69%, 97%, and 86%, respectively, for detection of ≥70% stenosis. There was high correlation between stenosis detected on AI-QCT evaluation vs QCA on a per-vessel and per-patient basis (intraclass correlation coefficient = 0.73 and 0.73, respectively; $P < 0.001$ for both). False positive AI-QCT findings were noted in in 62 of 848 (7.3%) vessels (stenosis of ≥70% by AI-QCT and QCA of <70%); however, 41 (66.1%) of these had an FFR of <0.8.

CONCLUSIONS A novel AI-based evaluation of coronary CTA enables rapid and accurate identification and exclusion of high-grade stenosis and with close agreement to blinded, core lab–interpreted quantitative coronary angiography. (Computed TomogRaphic Evaluation of Atherosclerotic DEtermiNants of Myocardial IsChEmia [CREDENCE]; NCT02173275) (J Am Coll Cardiol Img 2023;16:193–205) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

ISSN 1936-878X https://doi.org/10.1016/j.jcmg.2021.10.020

JACC: CARDIOVASCULAR IMAGING, VOL. 16, NO. 2, 2023
FEBRUARY 2023:193–205

ABBREVIATIONS AND ACRONYMS

AI = artificial intelligence

AI-QCT = artificial intelligence–enabled quantitative coronary computed tomography

AUC = area under the receiver-operating characteristic curve

CAD = coronary artery disease

CP = calcified plaque

CTA = computed tomography angiography

FDA = Food and Drug Administration

FFR = fractional flow reserve

GEE = generalized estimating equation

IVUS = intravascular ultrasound

QCA = quantitative coronary angiography

RCA = right coronary artery

Coronary computed tomography angiography (CTA) has emerged as a robust noninvasive tool for identification and exclusion of coronary artery disease (CAD). Prior multicenter trials demonstrated high diagnostic performance of coronary CTA against invasive quantitative coronary angiography (QCA) reference standards.[1-3] The clinical use of coronary CTA has been evaluated in an array of multicenter clinical trials that have observed the ability of coronary CTA to guide clinical decision making in a manner that improves event-free survival,[4] reduces unnecessary invasive angiography,[5] and expedites safe discharge of symptomatic patients presenting to emergency departments.[6] Coronary CTA is now recognized as a first-line test for evaluation of CAD in professional societal guidelines and appropriate use criteria.[4,7-9]

Despite high diagnostic performance in large-scale trials, the real-world performance of coronary CTA when interpreted by nonexpert readers is less sanguine. In a substudy of the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial, among 4347 patients undergoing coronary CTA, there was 16% discordance between site and expert core lab readers. Further, this discordance was most prominent in severe stenosis, with site readers overestimating severe stenosis ≥50% in 41% of cases.[10] As use of coronary CTA continues to rise over time, these findings raise concerns that inaccurate evaluation of coronary CTA may precipitate unnecessary downstream resource utilization.

Machine learning has been proposed as a useful tool to augment coronary CTA evaluation in clinical settings.[11-17,19] Machine learning has demonstrated promising results in the automated identification and exclusion of coronary artery stenoses on coronary CTA.[16,19] However, to date, there has been minimal published evaluation of an artificial intelligence (AI)-based solution in a multicenter clinical trial against invasive fractional flow reserve (FFR) or quantitative coronary angiography (QCA) using expert core lab readers blinded to coronary CTA findings. We thus performed a study leveraging a novel U.S. Food and Drug Administration (FDA)-cleared semi-automated cloud-based software service to perform quantitative analysis of coronary CTA to determine its performance against a reference standard of invasive QCA and FFR.

METHODS

SUBJECTS. We retrospectively evaluated data from 303 patients including coronary CTA, FFR, and QCA from the derivation arm of the CREDENCE (Computed TomogRaphic Evaluation of Atherosclerotic DEtermiNants of Myocardial IsChEmia; NCT02173275) trial.[18,19] The CREDENCE trial was a prospective, multicenter diagnostic derivation-validation, controlled clinical trial recruiting patients from 2014 to 2017.[18,19] Sites and Investigators are listed in

From the [a]Department of Radiology and Division of Cardiology, George Washington University School of Medicine, Washington, DC, USA; [b]Department of Cardiology, Faculdade de Ciências Médicas, Nova Medical School, Lisbon, Portugal; [c]Division of Cardiology, Severance Cardiovascular Hospital and Severance Biomedical Science Institute, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea; [d]Department of Cardiology, Pusan National University Hospital, Busan, South Korea; [e]Division of Cardiology, Inje University Ilsan Paik Hospital, South Korea; [f]Department of Cardiology, Kang Won National University Hospital, Chuncheon, South Korea; [g]Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; [h]Cardiovascular Center, Keimyung University Dongsan Hospital, Daegu, South Korea; [i]Division of Cardiology, Department of Internal Medicine, International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, South Korea; [j]Division of Cardiology, Department of Internal Medicine, Ewha Women's University Seoul Hospital, Seoul, South Korea; [k]Department of Cardiology, Mobile Cardiology Associates, Mobile, Alabama, USA; [l]Department of Imaging, Fondazione Toscana Gabriele Monasterio, Pisa, Italy; [m]Department of Cardiology, Cardiac Center of Texas, McKinney, Texas, USA; [n]State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, Beijing, China; [o]Cardiovascular Center, St. Luke's International Hospital, Tokyo, Japan; [p]Department of Cardiology, Houston Methodist Hospital, Houston, Texas, USA; [q]Department of Radiology, Medical University of South Carolina, Charleston, South Carolina, USA; [r]Department of Cardiology, Amsterdam University Medical Center, VU University Medical Center, Amsterdam, the Netherlands; [s]Department of Cardiology, St. Luke's Mid America Heart Institute, Kansas City, Missouri, USA; [t]Department of Cardiology, Kaiser Permanente Hospital, Oakland, California, USA; [u]Heart Center Research, LLC, Huntsville, Alabama, USA; [v]Department of Cardiology, Renown Heart and Vascular Institute, Reno, Nevada, USA; [w]Oconee Heart and Vascular Center, St Mary's Hospital, Athens, Georgia, USA; [x]Gagnon Cardiovascular Institute, Morristown Medical Center, Morristown, New Jersey, USA; and the [y]Department of Cardiology, Centro Cardiologico Monzino IRCCS, Milan, Italy.

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

Manuscript received January 26, 2021; revised manuscript received October 18, 2021, accepted October 22, 2021.

Supplemental Table 1. All enrolled CREDENCE subjects underwent coronary CTA, FFR, and QCA. The Institutional Review Board of each site approved the study protocol, and patients provided written informed consent. Inclusion and exclusion criteria and clinical sites are listed in Supplemental Table 2. This study is an investigator-initiated study, and Cleerly, Inc had no role in study design or performance. Cleerly, Inc performed the coronary CTA analyses for the study in a blinded manner and provided statistical services as determined and requested by the study investigators.

CT IMAGING PROTOCOLS. Coronary CTA was performed using a CT scanner with ≥64-detector rows. Sites were instructed to perform coronary CTA in accordance with guidelines from the Society of Cardiovascular Computed Tomography (Supplemental Methods).[18-20]

QUANTITATIVE CORONARY ANGIOGRAPHY. Invasive coronary angiography was performed in agreement with clinical indications and imaging standards. A dedicated core lab performed blinded QCA in 2 orthogonal views on a per-lesion basis of every lesion visually for ≥30% diameter stenosis in vessels with a reference vessel diameter ≥2.0 mm. Lesions estimated to be <30% were recorded as no stenosis (Supplemental Table 3).

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/kg^{-1}/min^{-1}) adenosine infusion to achieve maximal hyperemia.[18,19]

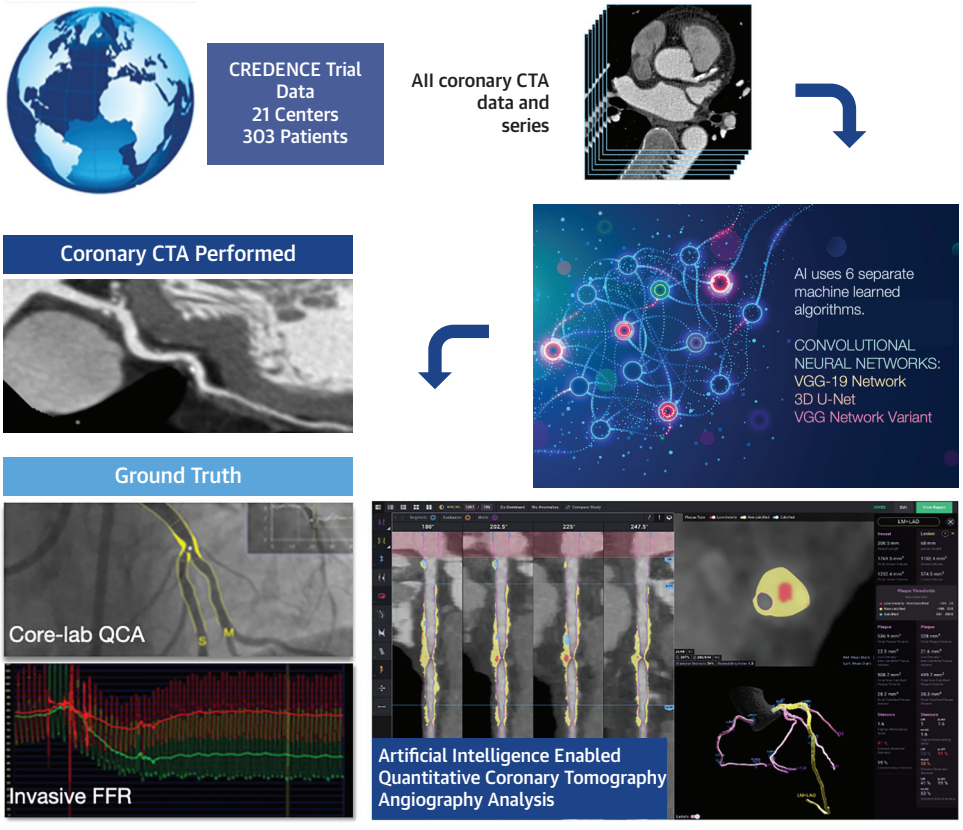
AI-BASED SEGMENTATION AND STENOSIS QUANTIFICATION. The AI-based approach to coronary CTA interpretation in this study was performed using an FDA-cleared software service (Cleerly Lab; Cleerly, Inc) that performs automated analysis of coronary CTA using a series of validated convolutional neural network models (including VGG [Visual Geometry Group]-19 network, 3D U-Net, and VGG Network Variant) for image quality assessment, coronary segmentation and labeling, lumen wall evaluation and vessel contour determination, and plaque characterization.[21] Training and testing were performed on a proprietary database. The centerline algorithm was developed from 1,007,945 images, which comprised 23,068 vessels from 3,671 patients. The lumen and vessel wall algorithms were developed from 1,414,877 images, which comprised 8,555 vessels from 3,676 patients. First, the AI-aided approach produces a centerline along each coronary artery, and then for lumen and outer vessel wall contouring. This is applied to each phase of the examination and the 2 optimal series are identified for further analysis. These top 2 phases are evaluated interactively on a per-vessel basis (eg, the right coronary artery [RCA] will be reconstructed from the phase that yields the highest RCA image quality, while the posterior descending artery may come from the second phase if the posterior descending artery has a higher image quality on that phase). Once coronary artery segmentation is performed, an automated labeling is done to classify arteries by their location as well the proximal, mid, and distal portions within a single vessel. Utilizing a normal proximal reference vessel cross-sectional slide, the start and the end of the lesion, and the cross-sectional slice that demonstrates the greatest absolute narrowing, % diameter stenosis severity is automatically calculated. After the AI algorithm has finished all operations, a cardiac

TABLE 1 Patient and Scan Characteristics

Patient parameters	
Age, y	64 ± 10
Male	71.0 (218)
BMI, kg/m^2	26 ± 4
Race	
Black	2.0 (7)
Asian	71.0 (217)
White	27.0 (82)
Hypertension	64.0 (197)
Hyperlipidemia	44.0 (136)
Diabetes	31.0 (95)
Current smoker	17.0 (53)
Prior smoker	34.0 (103)
Diseased vessel territories (≥50% coronary CTA stenosis)	
0	32.0 (96)
1	35.0 (105)
2	21.0 (64)
3	13.0 (38)
Scan parameters	
Scanner vendor	
GE	18.0 (54)
Philips	2.0 (5)
Siemens	43.0 (132)
Toshiba	38.0 (116)
Tube voltage	
70 kV	0.3 (1)
80 kV	6.0 (17)
100 kV	38.0 (116)
120 kV	52.0 (160)
Other	4.0 (11)
Gating technique	
Prospective/sequential	31.0 (95)
Retrospective helical	61.0 (188)
Single beat acquisition	8.0 (23)

Values are mean ± SD or n (%), unless otherwise indicated.
BMI = body mass index; CTA = computed tomography angiography.

CENTRAL ILLUSTRATION **AI-Based Evaluation of Coronary Artery Stenosis on Coronary CTA Demonstrated High Accuracy to Core Lab–Interpreted QCA and Invasive FFR**

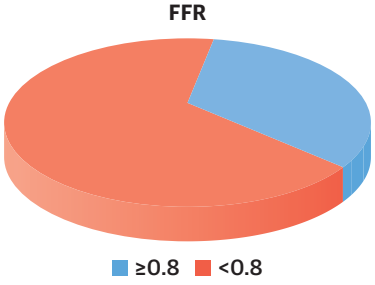


AI-QCT Analysis Enables Rapid and Accurate Identification and Exclusion of High-Grade Stenosis With Close Agreement to Blinded, Core-Lab Interpreted QCA

AI-QCT vs QCA for Detection of Stenosis, Per Patient

AI-QCT vs QCA	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy	AUC
≥50% Stenosis	94%	68%	81%	90%	84%	0.88
≥70% Stenosis	94%	82%	69%	97%	86%	0.92

Discordant Cases:
When AI-QCT ≥70% and QCA <70%
FFR is <0.8 in 67%



Griffin WF, et al. J Am Coll Cardiol Img. 2023;16(2):193–205.

Continued on the next page

CT-trained technician reviews the results of the AI analysis in all cases with manual adjustment if necessary.

For stenosis evaluation, the software selects the mean coronary diameter at the closest normal proximal reference cross section as the reference diameter (D_{ref}), and the mean diameter on the cross section demonstrating the greatest absolute stenosis (D_s). The % diameter stenosis is then automatically calculated using the following formula: % diameter stenosis = $[1 - (D_s/D_{ref})] \times 100$.

STENOSIS COMPARISON QCA VS AI-ENABLED QUANTITATIVE CORONARY CTA. QCA stenosis was measured by core lab readers in each vessel territory, and AI-based stenosis evaluation was measured for each coronary segment, if present, using a Society of Cardiovascular Computed Tomography 18-segment coronary tree model. The maximum QCA and AI-based diameter stenosis were calculated across segments for each vessel. Performance of artificial intelligence-enabled quantitative coronary computed tomography (AI-QCT) was also evaluated in vessels in which the calcified plaque (CP) volume was ≥50% of the total plaque volume and compared with performance in vessels in which the non-CP was ≥50% of the total plaque volume.

DETERMINATION OF STENOSIS SIGNIFICANCE WITH FFR. We also evaluated the ability of QCA and the AI-QCT stenosis evaluation to predict a vessel specific FFR of 0.8 or less. This was performed on a per-patient and a per-vessel basis. Performance was evaluated using both 50% and 70% diameter thresholds.

STATISTICAL ANALYSIS. Analysis was performed using SAS software version 9.4 (SAS Institute). The diagnostic performance of AI-based diameter stenosis as well as the core lab diameter stenosis was evaluated by calculating the sensitivity, specificity, and diagnostic accuracy relative to the determination of ≥50% and ≥70% stenosis, using QCA as the reference standard, on the per-segment, per-vessel, per-territory, and per-patient bases. Areas under the receiver-operating characteristic curve (AUCs) were used to evaluate the diagnostic performance for ≥50% and ≥70% stenosis per QCA as well as to evaluate the prediction of FFR for both QCA and AI-QCT. The comparability of the continuous measures of diameter stenosis for AI and QCA were assessed via correlation using Pearson's correlation coefficients and calculation of the mean difference (bias). Sensitivity, specificity, and diagnostic performance for ≥50% diameter stenosis per territory were compared across patient subgroups using logistic generalized estimating equation (GEE) regression models, to account for the potential correlation of multiple vessel territories per patient. Diagnostic performance parameters of AI-QCT-measured stenosis were calculated on a per-patient and per-territory basis, for predicting ≥50% stenosis and ≥70% stenosis using QCA as the reference standard. The results are stratified by those with ≥50% of CP and those with ≤50% CP. The 95% CIs were generated using the Agresti-Coull method for per-patient measures and using logistic GEE regression for per-territory and per-vessel measures. Diagnostic performance was compared across strata using chi-square or Fisher's exact tests for per-patient measures and logistic GEE for per-territory and per-vessel measures.

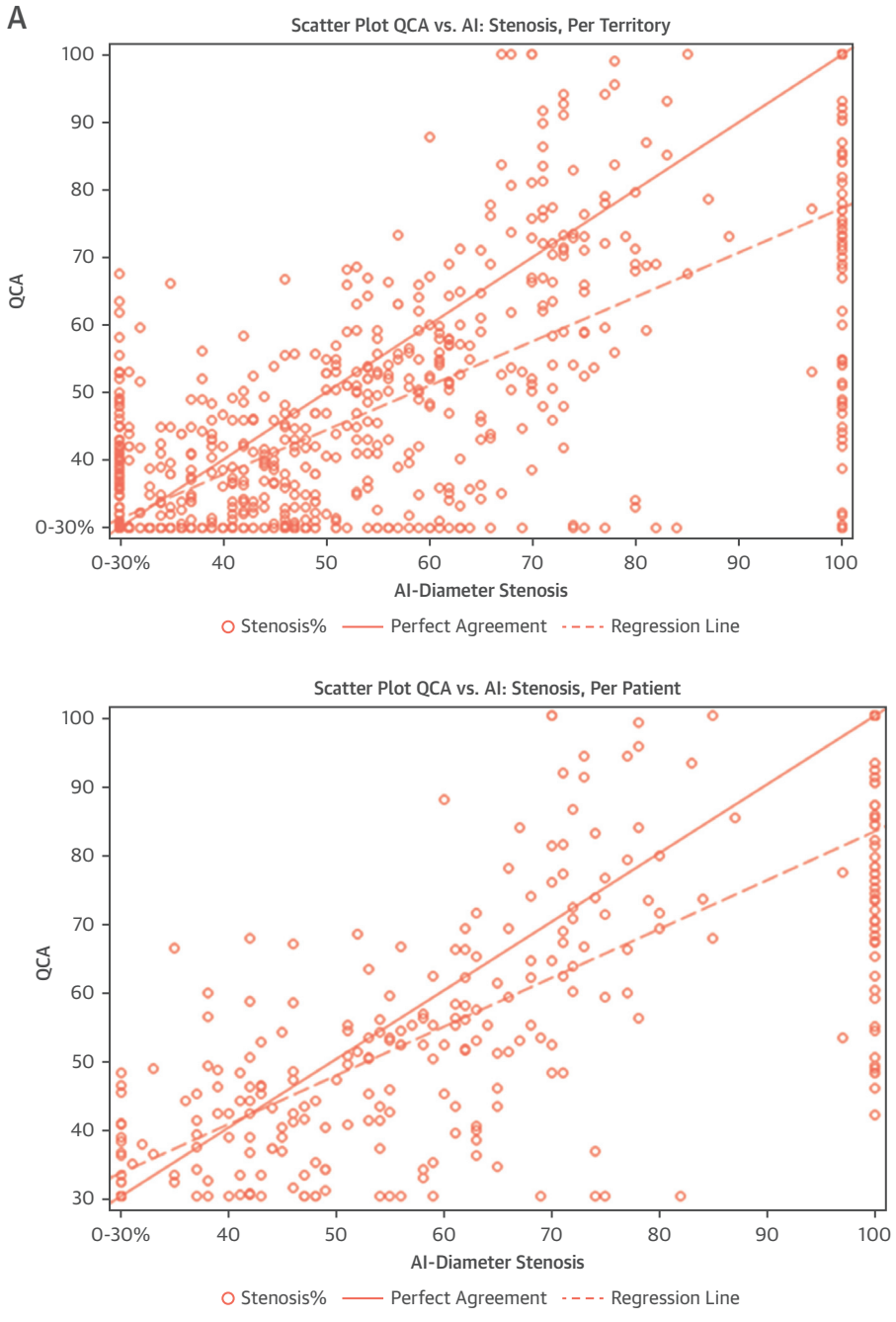
RESULTS

Baseline characteristics of the study population can be seen in Table 1. A total of 303 (98.0%) of the 307 subjects from 23 centers of the CREDENCE cohort[18,19] were included; 4 patients were excluded caused by corruption of CT imaging data. CT scan parameters are listed in Table 1. AI computational analysis time was 10.3 ± 2.7 minutes. No cases were excluded because of impaired image quality. If impaired image quality was present caused by motion, poor opacification, beam hardening, or other artifact, just the portion of the coronary artery with poor quality was marked as excluded from analysis. Any quantitative data from the excluded segment were not included in the final report. Among the 171,195 mm of vessel

CENTRAL ILLUSTRATION Continued

Coronary computed tomography angiography (CTA), fractional flow reserve (FFR), and quantitative coronary angiography (QCA) data from 303 stable patients (64 ± 10 years of age, 71.0% male) from the CREDENCE (Computed TomogRaphic Evaluation of Atherosclerotic DEtermiNants of Myocardial IsChEmia) trial were retrospectively analyzed using an Food and Drug Administration-cleared cloud-based software that performs artificial intelligence (AI)-enabled coronary segmentation, lumen and vessel wall determination, plaque quantification and characterization, and stenosis determination. Diagnostic performance against QCA on both a per-vessel and per-patient basis was excellent. The area under the receiver-operating characteristic curve (AUC) for detection of a ≥50% stenosis was 0.88 and for 70% stenosis was 0.92 on a per-territory basis. There were 62 vessels with AI-QCT findings of ≥70% stenosis that were considered discordant or false positive because they had a QCA of <70%; however, 41 (66.1%) of these had an FFR of <0.8, and some of the QCA findings may have been false negative. 3D = 3-dimensional; AI-QCT = artificial intelligence-enabled coronary computed tomography angiography; VGG = Visual Geometry Group.

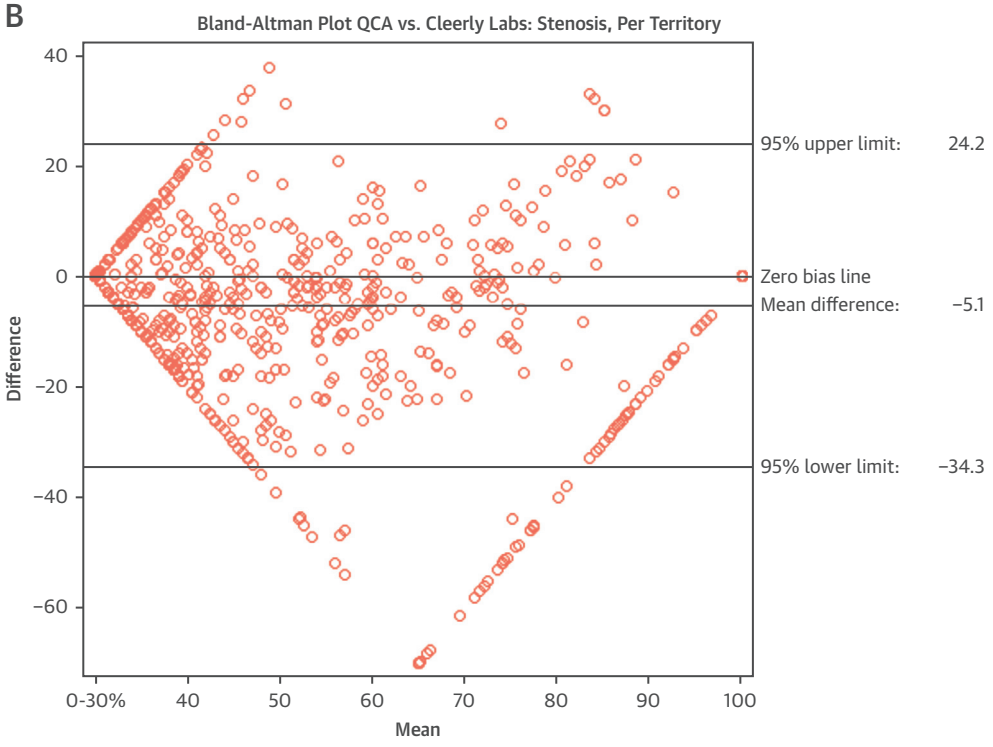
FIGURE 1 Scatterplot Analysis



(A) Correlation of artificial intelligence (AI)-based evaluation vs quantitative coronary angiography (QCA) for % stenosis on a per-territory and per-patient basis was 0.728 and 0.717, respectively ($P < 0.0001$ for both). **(B)** A Bland-Altman plot of QCA vs AI-QCT for 50% stenosis per vessel depicted a mean bias of −5.1% (95% CI: −6.1% to −4.0%) per territory and a mean bias of −6.8% (95% CI: −8.6% to −5.0%) per patient. AI-QCT = artificial intelligence-enabled quantitative coronary computed tomography.

Continued on the next page

FIGURE 1 **Continued**



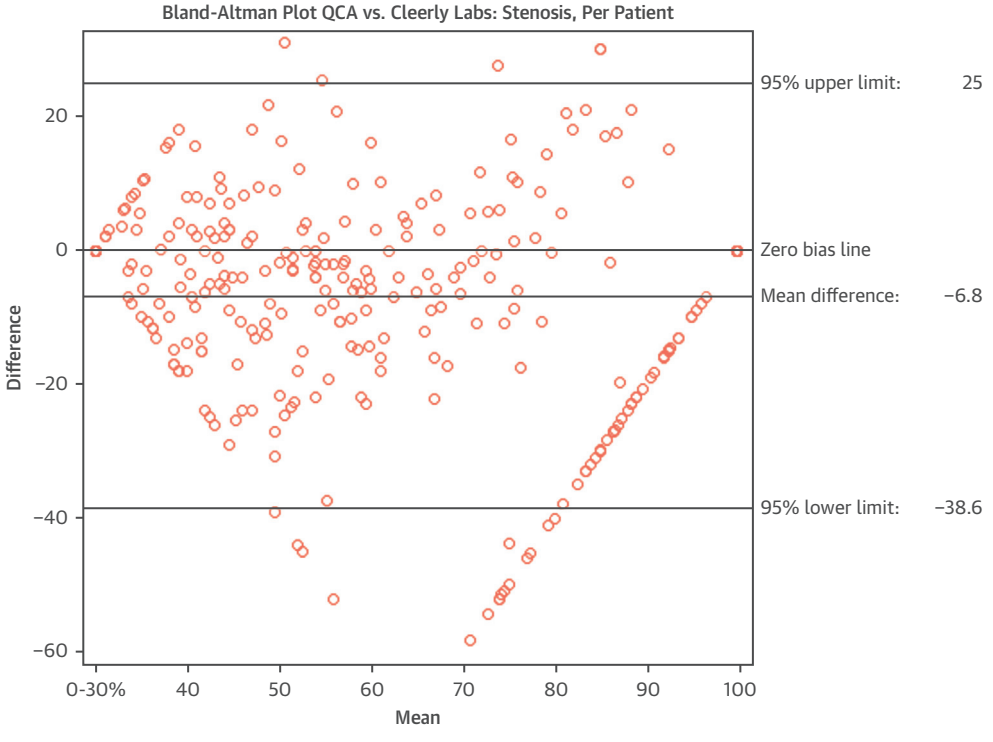
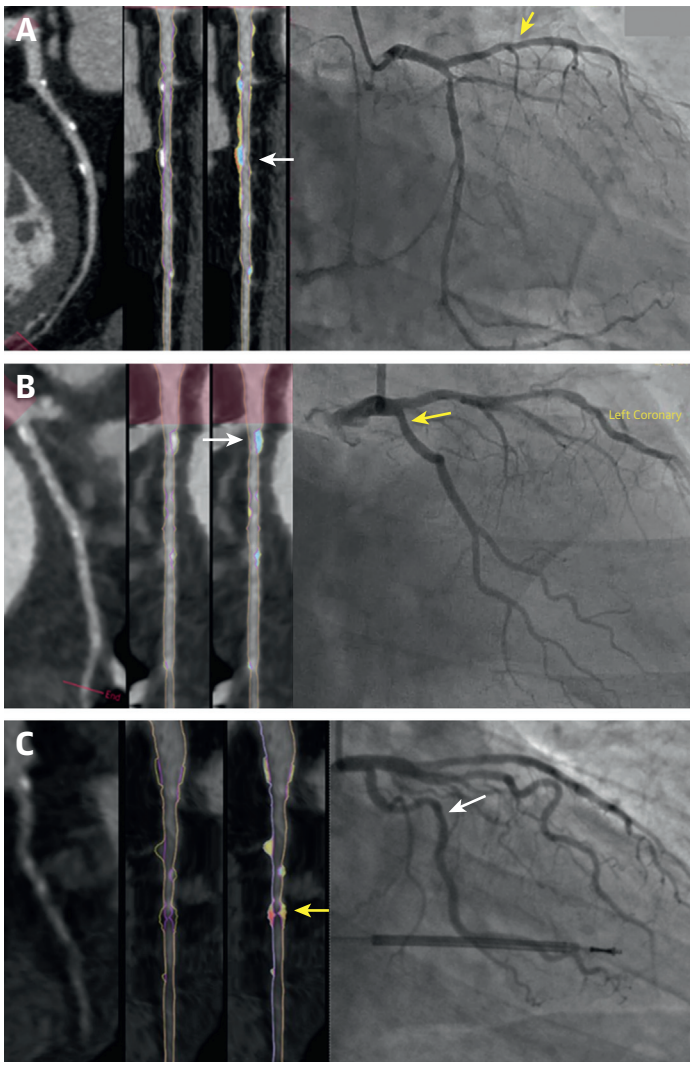


FIGURE 2 Discordant Cases



Three discordant cases in which significant stenosis was depicted on AI-QCT but <30% stenosis was reported on QCA. **(A)** Patient 1, left anterior descending artery. Curved multiplanar reformatted image (MPR) **(left)**, and straightened MPR **(second from left)** with the lumen boundary **(purple line)** and outer vessel wall boundary **(yellow line)** overlay, and with color plaque overlay **(second from right)** (**red** is low-density non-calcified plaque [<30 HUs], **yellow** is noncalcified plaque [31-350 HU], and **blue** is calcified plaque [>350 HU]). AI depicted a 60% stenosis **(white arrow)** in the proximal vessel segment. **(Right)** The left coronary invasive angiogram, in which QCA analysis depicted no stenosis **(yellow arrow)**. **(B)** Patient 2, left circumflex artery. Curved MPR **(left)** and straightened MPR **(second from left)** with the lumen boundary **(purple line)** and outer vessel wall boundary **(yellow line)** overlay, and with color plaque overlay **(second from right)**. AI depicted a 60% stenosis in the proximal vessel **(white arrow)**. **(Right)** The left coronary invasive angiogram, in which QCA analysis depicted no stenosis **(yellow arrow)**. **(C)** Patient 3, ramus intermedius artery. Curved MPR **(left)** and straightened MPR **(second from left)** with the lumen boundary **(purple line)** and outer vessel wall boundary **(yellow line)** overlay, and with color plaque overlay **(second from right)**. AI depicted a 75% stenosis in the mid vessel **(yellow arrow)**, but the vessel is poorly opacified and likely false positive. **(Right)** QCA analysis depicted no stenosis in that region **(white arrow)**. Abbreviations as in Figure 1.

length evaluated in the entire cohort, a total of 1,861 mm (1.1%) of the vessel length was excluded. The length of an exclusion averaged 14.1 ± 13.9 mm and was longer in the RCA (15.2 ± 6.7 mm) than in the left anterior descending artery (7.62 ± 4.12 mm) or the left circumflex artery (7.58 ± 8.13 mm). This included 132 focal exclusions in 81 (26.7%) of patients. A majority (85.0%) of the exclusions were in the RCA, and the remaining were evenly distributed in the left anterior descending artery (7.6%) and left circumflex artery (7.4%). In 127 (96.2%) of the exclusions, less than a full coronary segment was involved, and in the remaining 5 (3.8%), more than an entire segment was excluded.

DISEASE PREVALENCE. Prevalence of stenosis ≥50% was observed in 67.0% (n = 202 of 303) of patients and 36.0% (n = 308 of 848) of vessels, while presence of stenosis ≥70% was observed in 39.0% (n = 119 of 303) of patients and 19.0% (n = 157 of 848) of vessels. A ≥50% stenosis was observed in 1, 2, and 3 coronary vessel territories in 32.0% (n = 96 of 303), 21.0% (n = 105 of 303), and 13.0% (n = 38 of 303) of subjects, respectively.

DIAGNOSTIC PERFORMANCE. The per-patient sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for ≥50% stenosis were 94%, 68%, 81%, 90%, and 84%, respectively, and for detection of ≥70% stenosis were 94%, 82%, 69%, 97%, and 86%, respectively (**Central Illustration**). The AUCs on a per-territory and per-patient basis were 0.90 and 0.88, respectively, for ≥50% stenosis and 0.95 and 0.92, respectively, for ≥70% stenosis (**Table 2**).

Correlations of AI-QCT vs QCA for % stenosis on a per-territory and per-patient basis were 0.728 and 0.717, respectively ($P < 0.0001$ for both) (**Figure 1A**). The intraclass correlation coefficient was 0.73 per territory ($P < 0.0001$) and 0.73 per patient ($P < 0.0001$). The mean paired differences (AI - QCA) were 5.1% (95% CI: −6.1% to −4.0%) per territory and 6.8% (95% CI: −8.6% to −5.0%) per patient, indicating a small positive bias. Analysis of numeric agreement using categorical variables of 0% to 49%, 50% to 69%, and 70% to 100% on both a per-territory and per-patient basis yielded a Cohen's kappa of 0.674 per territory and 0.670 per patient. A Bland-Altman analysis is included (**Figure 1B**).

We evaluated the performance of AI-QCT in predominantly calcified (≥50% CP) as compared with predominantly noncalcified (<50% CP) vessels (Supplemental Table 4). At the 50% stenosis threshold, predominantly calcified specificity was significantly lower ($P < 0.05$) per vessel (86.0% calcified vs 95.3%

TABLE 2 Diagnostic Performance AI-QCT Versus QCA on a Per-Patient and Per-Territory Basis

Stenosis	Basis	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
≥50%	Per territory (n = 909)	91 (87.1-94.2)	84 (79.6-86.1)	69 (64.1-74.4)	96 (93.8-97.3)	86 (83.2-88.1)	0.90 (0.88-0.93)
	Per patient (n = 303)	94 (89.8-97.0)	68 (59.7-75.8)	81 (74.7-85.5)	90 (87.2-94.4)	84 (78.8-87.3)	0.88 (0.84-0.92)
≥70%	Per territory (n = 909)	90 (83.3-94.4)	91 (88.0-92.8)	58 (51.0-66.3)	99 (97.3-99.2)	91 (88.5-92.8)	0.95 (0.94-0.97)
	Per patient (n = 303)	94 (87.3-97.9)	82 (76.4-86.8)	69 (60.5-76.6)	97 (93.5-99.0)	86 (81.4-89.3)	0.92 (0.89-0.95)

Values are % (95% CI). Subgroups based on detection of ≥50% stenosis.

AI-QCT = artificial intelligence–enabled quantitative coronary computed tomography; AUC = area under the receiver-operating characteristic curve; NPV = negative predictive value; PPV = positive predictive value; QCA = quantitative coronary angiography.

noncalcified; $P < 0.0001$), per territory (69.7% calcified vs 87.3% noncalcified; $P < 0.0001$), and per patient (47.8% calcified vs 72.8% noncalcified; $P = 0.0199$), and accuracy was lower per vessel (85.4% calcified vs 92.9% noncalcified; $P < 0.0001$) and per territory (78.3% calcified vs 88.3% noncalcified; $P = 0.002$) but not per patient. No differences were found for sensitivity, positive predictive value, or negative predictive value. For the 70% threshold, specificity was significantly lower per vessel (92.7% calcified vs 92.9% noncalcified; $P < 0.0001$) and per territory (84.6% calcified vs 93.0% noncalcified; $P = 0.0013$), the positive predictive value was lower per vessel (42.9% calcified vs 66.3% noncalcified; $P < 0.0001$), and accuracy was lower per vessel (90.8% calcified vs 96.8% noncalcified; $P < 0.0001$) and per territory (85.0% calcified vs 92.8% noncalcified; $P = 0.0022$).

There was discordance of >30% between the AI-QCT-determined stenosis and that of QCA in 74 (8.1%) of 909 vessels in which 1 or both stenoses was ≥50%. Of the 157 vessels that were ≥70% by AI-QCT, 95 (60.5%) had a concordant QCA of ≥70% and 62 were discordant. Examples of discordance are shown in Figure 2.

FFR COMPARISON. FFR data were available in 848 vessels and 303 patients. Common reasons for not obtaining FFR included distal stenosis, diffuse atherosclerosis, tortuous vessel, artifact, or concern over contrast exposure. Performance of QCA and AI-based coronary CTA evaluation to predict FFR is depicted in Tables 3 and 4. QCA and AI-QCT had similar accuracy (85.0% and 86.2%; $P = 0.217$), respectively for predicting an FFR of <0.8. The AUCs on a per-patient basis were 0.90 (95% CI: 0.88-0.94) for QCA and 0.91 (95% CI: 0.87-0.94) for AI-QCT, respectively ($P = 0.558$); and on a per-vessel basis were 0.953 (95% CI: 0.938-0.967) for QCA and 0.916 (95% CI: 0.894-0.938) for AI-QCT, respectively ($P = 0.0006$). There were 157 vessels that were ≥70% by AI-QCT, of these 62 (39.4%) were considered false positive or discordant because they had a QCA of <70%; however, 41 (66.1%) of these had an FFR of <0.8 (Tables 3 and 4).

SUBGROUP ANALYSIS. Diagnostic performance was evaluated for several subgroups to examine performance by patient demographics, medical history, disease severity and distribution, and plaque types and burden (Supplemental Table 5). While there was no significant difference in sensitivity, AI-based evaluation had improved specificity (91% vs 80%; $P = 0.004$) and accuracy (91% vs 84%; $P = 0.006$) in women. Similarly, age <65 years showed improved specificity (89% vs 79%; $P = 0.003$) and accuracy (89% vs 83%; $P = 0.023$). No differences were seen for body mass index or presence of absence of risk factors, including diabetes, hypertension, dyslipidemia, or tobacco use. For an increasing number of diseased vessel territories, there was a significant increase in sensitivity ($P < 0.001$) but decreases in specificity and accuracy ($P < 0.001$). Similarly, increases in total atherosclerotic plaque burden and CP burden on showed significant increases in sensitivity and decreases in both specificity and accuracy ($P < 0.0077$).

DISCUSSION

We observed high diagnostic performance of the AI-based evaluation for severe stenoses at both the ≥50% and ≥70% levels, along with high correlation to QCA. Importantly, the diagnostic performance of the AI-based evaluation was similar to that observed in prior multicenter clinical trials that have employed expert coronary CTA core lab imagers.[1-3] To our knowledge, this study represents the first validation of any FDA-cleared AI-based evaluation for determining coronary CTA stenosis severity compared with QCA in a multicenter clinical trial of subjects being referred for American College of Cardiology/American Heart Association guideline-indicated invasive coronary angiography.

AI-BASED EVALUATION OF CORONARY CTA. Use of AI applications in diagnostic imaging that

TABLE 3 Diagnostic Performance of QCA and AI-QCT Stenosis to Predict FFR on a Per-Vessel Basis (n = 848)

Diagnostic Performance, 70% Stenosis to Predict FFR, per Vessel	QCA	AI-QCT	*P* Value
Sensitivity	45.6 (103/226) (38.4-52.1)	58.9 (133/226) (51.7-64.9)	<0.0001
Specificity	99.4 (618/622) (97.7-99.8)	96.1 (598/622) (93.1-97.6)	<0.0001
PPV	96.3 (103/107) (89.6-97.8)	84.7 (133/157) (78.6-89.5)	0.0010
NPV	83.4 (618/741) (78.5-84.9)	86.5 (598/691) (81.0-87.0)	0.0005
Accuracy	85.0 (721/848) (81.8-87.1)	86.2 (731/848) (83.2-88.2)	0.2173
AUC	0.953	0.916	0.001

Values are % (n/N) (95% CI), unless otherwise indicated.
FFR = fractional flow reserve; other abbreviations as in Table 2.

leverage deep machine learning approaches has been cited as having high potential to improve accuracy of traditional computer-assisted applications that employ conventional image processing approaches in a manner that may also have benefits on image analysis time. Average analysis time for the AI-based solution was 10.3 ± 2.7 minutes; the quality assurance evaluation time was not recorded in this study, but the AI time plus quality assurance review for this software service was previously reported as 23.7 ± 6.4 minutes.[16,17,19]

Germane to the present study that evaluated ability of AI-based evaluation to identify coronary stenoses, Kang et al[11] employed a structured learning technique and support vector machine algorithms in a small group (n = 42) in comparison with expert consensus readers; they reported high sensitivity (93%), specificity (95%), and accuracy (94%), with an AUC of 0.94 for detection of plaques ≥25%. Similarly, Freiman et al[22] used a deep sparse autoencoder-mixed structure regularization approach in 90 subjects and observed an AUC that ranged from 0.78 to 0.94 for discrimination of mild stenosis <30% to severe stenosis ≥70%. This present study adds to the previously reported findings by evaluating an approach that employs deep convolutional neural networks, is FDA cleared, and is clinically available. Further, our present evaluation was in a large multinational cohort of subjects who were being referred to clinically indicated invasive angiography and established widespread generalizability of the reported approach.

COMPARISON WITH PRIOR RESULTS. Results of the present study are in direct accord with a reported study that assessed the performance of the AI-based evaluation[16,17,19] as compared with the consensus of level 3 expert readers. In the multicenter CLARIFY (CT EvaLuation by ARtificial Intelligence For Atherosclerosis, Stenosis and Vascular MorphologY) trial, diagnostic performance in 232 consecutively acquired coronary CTA data sets revealed excellent performance at both the ≥70% and ≥50% stenosis threshold. The per-patient diagnostic sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the AI-based evaluation for ≥70% were 90.9%, 99.8%, 93.3%, 99.9%, and 99.7%, respectively; and for ≥50% stenosis were 94.8%, 80.0%, 97.0%, 80.0%, and 97.0% for ≥50% stenosis, respectively. The AI-based evaluation and consensus L3 reads agreed within 1 Coronary Artery Disease Reporting and Data System category in 98.3% of patients and 99.9% of vessels, with high correlation and agreement.

Findings from this study amplify those from the CLARIFY trial by extending the performance evaluation to QCA, which is historically considered a "gold standard" for stenosis as well as to FFR, the clinical gold standard for determination of the physiologic significance of a coronary stenosis. We observed lower specificity, positive predictive value, and accuracy when the AI-based evaluation was compared with QCA vs the previously employed reference standard of consensus of L3 expert readers, primarily because of an increase in false positive diagnoses by the AI-based evaluation. As described in the Supplemental Table 5, specificity and accuracy decreased in patients with increasing numbers of diseased vessel territories, higher plaque volume, and higher CP volume. Our study findings are consistent with prior studies that have employed expert core lab readers.[1-3,23-27]

Notably, the discriminatory power of the AI-based evaluation appears to be high, with a per-patient AUC of 0.88 for ≥50% stenosis and of 0.92 for ≥70% stenosis threshold, and a per-vessel AUC of 0.90 for ≥50% stenosis and of 0.95 for ≥70% stenosis. These findings are numerically higher than those observed by expert core lab readers (AUC: 0.69) and site readers (AUC: 0.57) in the multicenter randomized PROMISE trial, albeit in a different study population of lower disease prevalence.[10] Yet together, these data suggest a clinical use of an AI-based evaluation to serve as an important and useful adjunct to clinical coronary CTA interpretation.

The AI-based evaluation also performed well using invasive FFR as a gold standard. Using a 70% diameter stenosis to predict an invasive FFR of <0.8, AI-QCT had moderate sensitivity of 58.9%, but this was

TABLE 4 Comparison of Discordant QCA and AI-QCT Cases at a ≥70% Stenosis Threshold with FFR on a Per-Vessel Basis

Cases With FFR Available (N = 848)	Discordant AI-QCT vs QCA	FFR <0.8	FFR >0.8
AI-QCT ≥70% (n = 157)	62 (39.5)	41	21
AI-QCT <70% (n = 691)	9 (1.2)	8	1

Values are n or n (%).
Abbreviations as in Tables 2 and 3.

significantly greater than that of QCA (45.6%; $P < 0.001$); both AI-QCT and QCA had excellent specificity (96.1% and 99.4%, respectively; $P < 0.001$) and similar accuracy (86.2% and 85.0%, respectively; $P = 0.217$). While the presence of an FFR of <0.8 is likely multifactorial and not simply related to a single stenosis of ≥70%, the presence of an AI-QCT–depicted stenosis reliably predicted the low FFR demonstrating an AUC of 0.916.

DISCORDANT CASES. We analyzed discordant cases wherein the AI-based evaluation and the QCA disagreed on the severity of stenosis. We observed 2 major findings in this analysis: first, there were several cases in which the AI-based evaluation overestimated the severity of stenosis, and this was most common in cases of high calcification that may have contributed to coronary CTA partial volume artifacts. Other causes included poor or heterogeneous lumen opacification. Second, we observed several cases of potential false negative QCA in which coronary CTA demonstrated evident stenoses but in which QCA did not (Figure 2). When the discordant cases were compared with FFR, it appears that many of the false positive AI-QCT findings were found to have an FFR of <0.8. There were 157 vessels that were ≥70% by AI-QCT and had FFR available, and of these 62 (39.4%) were considered false positive or discordant because they had a QCA of <70%; however, 41 (66.1%) of these had an FFR of <0.8.

These apparent discordances can be explained by a multitude of reasons. Coronary CTA is a 3-dimensional volumetric technique, and QCA is a 2-dimensional technique that relies on orthogonal assessment of stenosis. In cases of eccentric stenoses and image foreshortening, it may be that QCA sometimes underestimates the severity of the narrowing. This has been observed in previous studies in which QCA, compared with intravascular ultrasound (IVUS), frequently underestimates disease. Fernandes et al[28] reported that 68% of lesions (in 71% of the patients) diagnosed as moderate stenosis by invasive coronary angiography had severe stenosis using IVUS. Further, while widely accepted as a gold standard, the interobserver variability even with QCA is non-negligible, with previous reports observing agreement only 65% of the time for ≥50% stenosis in the proximal or mid left anterior descending coronary artery.[29,30] As the field moves forward, it may well be that a hybrid endpoint that combines 2- and 3-dimensional imaging with both QCA and coronary CTA serving as the most accurate reference standard. In this regard, Kerl et al[31] acknowledged the presence of false negative invasive coronary angiography studies and found that the use of a composite reference standard combining findings from both coronary CTA and invasive coronary angiography tests can control for the effect of false negative CCA results.

SUBGROUP ANALYSIS. We performed subgroup analysis in order to assess the AI-QCT evaluation for factors that related to age, sex, risk factors, and CAD extent and severity. The excellent diagnostic performance of AI-QCT was generally consistent across all subgroups, although there trended toward higher sensitivity and lower specificity and accuracy as the disease extent increased. AI-based evaluation had improved specificity and accuracy in women and patients <65 years of age. No differences were seen for body mass index or presence of absence of risk factors, including diabetes, hypertension, dyslipidemia, or tobacco use. For increasing CAD extent and severity—including number of vessel territories ≥50% stenosis and increasing total or CP burden—there was a significant increase in sensitivity and concomitant decrease in specificity and accuracy. In addition, the study population was not optimally heterogeneous, and comprised 71.0% Asian, 27.0% Caucasian, and 2.0% African American individuals; further studies in a more heterogeneous population should be performed to exclude any bias introduced.

STUDY LIMITATIONS. This present study was a post hoc analysis of the CREDENCE trial, and while it is unexpected that significant bias would be introduced in a retrospective evaluation leveraging blinded core lab readers, it nevertheless emphasizes the absence of a prospective clinical trial that should be performed in the future. Further, this study evaluated the AI-based evaluation for measures of stenosis severity, rather than for plaque volume, composition, vascular remodeling, and other important CAD metrics. This is currently being evaluated in the multicenter INVICTUS (A Retrospective and Prospective, Multicentre Registry of Coronary Computed Tomography Angiography, Intravenous Ultrasound and Optical Coherence Tomography to Compare Invasive and Non-invasive Imaging Modalities for the Determination of Severity, Volume and Type of Coronary

Atherosclerosis) trial (NCT04066062), which is enrolling patients undergoing coronary CTA and IVUS, optical coherence tomography, or near-field infrared spectroscopy, and we plan to report these findings upon study completion. Also, the ground truth in this present study was core lab-interpreted QCA for any stenosis >30%, in keeping with prior multicenter studies employing QCA. Because of this, we are not able report the diagnostic performance of the AI-based evaluation for the presence of stenosis in this range. Stenoses in this range have been historically considered inconsequential by QCA, although newer data suggest a prognostic significance to these "mild" lesions that may nevertheless possess high-risk atherosclerotic characteristics. The INVICTUS trial will help to address this limitation of the present study.

CONCLUSIONS

In this analysis of the multinational CREDENCE trial, an AI-based evaluation demonstrated high diagnostic performance for the identification, exclusion, discrimination, and correlation to a QCA reference standard. Given the rapid turnaround time of this AI-QCT and its superior performance to previous coronary CTA core lab and site readers, this approach may augment clinical coronary CTA interpretation.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Drs Choi and Marques have equity interest in Cleerly Inc. Dr Earls has equity interest in and as of April 1, 2021, is an employee of Cleerly Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr James P. Earls, The George Washington University School of Medicine, 2150 Pennsylvania Avenue NW, Washington, DC 20037, USA. E-mail: jearls@mfa.gwu.edu. Twitter: @JPEarls, @AChoiHeart.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: An AI-based evaluation of coronary CTA enables rapid and accurate identification and exclusion of high-grade coronary artery stenosis with close agreement to blinded, core lab-interpreted QCA.

TRANSLATIONAL OUTLOOK: Because clinical reads of coronary CTA, especially by less experienced readers, may result in overestimation of CAD stenosis severity compared with expert interpretation, this AI-based solution applied to coronary CTA may overcome these limitations.

REFERENCES

1. 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.

2. Meijboom WB, van Mieghem CA, Mollet NR, et al. 64-Slice computed tomography coronary angiography in patients with high, intermediate, or low pretest probability of significant coronary artery disease. *J Am Coll Cardiol*. 2007;50(15):1469–1475.

3. 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.

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

5. Chang HJ, Lin FY, Gebow D, et al. Selective referral using CCTA versus direct referral for individuals referred to invasive coronary angiography for suspected cad: a randomized, controlled, open-label trial. *J Am Coll Cardiol Img*. 2019;12(7 Pt 2):1303–1312.

6. Litt HI, Gatsonis C, Snyder B, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. *N Engl J Med*. 2012;366(15):1393–1403.

7. Choi AD, Geske JB, Lopez-Mattei JC, et al. Cardiovascular imaging through the prism of modern metrics. *J Am Coll Cardiol Img*. 2020;13(5):1256–1269.

8. Knuuti J, Wijns W, Saraste A, et al, ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407–477.

9. Kelion AD, Nicol ED. The rationale for the primacy of coronary CT angiography in the National Institute for Health and Care Excellence (NICE) guideline (CG95) for the investigation of chest pain of recent onset. *J Cardiovasc Comput Tomogr*. 2018;12(6):516–522.

10. Lu MT, Meyersohn NM, Mayrhofer T, et al. Central core laboratory versus site interpretation of coronary CT angiography: agreement and association with cardiovascular events in the PROMISE trial. *Radiology*. 2018;287(1):87–95.

11. Kang D, Dey D, Slomka P, et al. Structured learning algorithm for detection of nonobstructive and obstructive coronary plaque lesions from computed tomography angiography. *J Med Imaging*. 2015;2(1):014003.

12. Singh G, Al'Aref SJ, Van Assen M, et al. Machine learning in cardiac CT: basic concepts and contemporary data. *J Cardiovasc Comput Tomogr*. 2018;12(3):192–201.

13. Al'Aref S, Anchouche K, Singh G, et al. Clinical applications of machine learning in cardiovascular disease and its relevance to cardiac imaging. *Eur Heart J*. 2019;40(24):1975–1986.

14. Zreik M, Lessmann N, van Hamersvelt RW, et al. Deep learning analysis of the myocardium in coronary CT angiography for identification of patients with functionally significant coronary artery stenosis. *Med Image Anal*. 2018;44:72–85.

15. Muscogiuri G, Chiesa M, Trotta M, et al. Performance of a deep learning algorithm for the evaluation of CAD-RADS classification with CCTA. *Atherosclerosis*. 2020;294:25–32.

16. Choi AD, Marques H, Kumar V, et al. CT EvaLuation by ARtificial Intelligence For Atherosclerosis, Stenosis and Vascular MorphologY (CLARIFY): a multi-center, international study. *J Cardiovasc Comput Tomogr*. 2021;15(6):470–476. https://doi.org/10.1016/j.jcct.2021.05.004

17. Choi A, Marques H, Kumar V, et al. CT Evaluation by Artificial Intelligence for Atherosclerosis,

Stenosis and Vascular Morphology (CLARIFY): plaque volume, plaque characterization and high risk plaque compared with consensus of level III expert readers. Paper presented at: Society of Cardiovascular Computed Tomography Annual Scientific Meeting; July 17, 2020; Virtual.

18. Rizvi A, Hartaigh BÓ, 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.

19. Stuijfzand WJ, van Rosendael AR, Lin FY, et al, CREDENCE Investigators. 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. *JAMA Cardiol*. 2020;5(12):1338–1348. https://doi.org/10.1001/jamacardio.2020.3409

20. 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.

21. U.S. Food and Drug Administration. Cleerly Labs 510 (k) premarket notification. Accessed April 12, 2021. https://www.accessdata.fda.gov/cdrh_docs/pdf19/K190868.pdf

22. Freiman M, Manjeshwar R, Goshen L. Unsupervised abnormality detection through mixed structure regularization (MSR) in deep sparse autoencoders. *Med Phys*. 2019;46(5):2223–2231.

23. Burgstahler C, Reimann A, Drosch T, et al. Cardiac dual-source computed tomography in patients with severe coronary calcifications and a high prevalence of coronary artery disease. *J Cardiovasc Comput Tomogr*. 2007;1(3):143–151. https://doi.org/10.1016/j.jcct.2007.09.003

24. Mollet NR, Cademartiri F, van Mieghem CA, et al. High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography. *Circulation*. 2005;112(15):2318–2323.

25. Pundziute G, Schuijf JD, Jukema JW, et al. Impact of coronary calcium score on diagnostic accuracy of multislice computed tomography coronary angiography for detection of coronary artery disease. *J Nucl Cardiol*. 2007;14(1):36–43.

26. Ong TK, Chin SP, Liew CK, et al. Accuracy of 64-row multidetector computed tomography in detecting coronary artery disease in 134 symptomatic patients: influence of calcification. *Am Heart J*. 2006;151(6):1323.e1–1323.e6.

27. Qi L, Tang LJ, Xu Y, et al. The diagnostic performance of coronary CT angiography for the assessment of coronary stenosis in calcified plaque. *PLoS One*. 2016;11(5):e0154852.

28. Fernandes MR, Silva GV, Caixeta A, et al. Assessing intermediate coronary lesions: angiographic prediction of lesion severity on intravascular ultrasound. *J Invasive Cardiol*. 2007;19(10):412–416.

29. Borren N, Maas A, Ottervanger J. Stop invasive coronary angiography as the gold standard for the diagnosis of stable angina. *Interv Cardiol*. 2015;7(5):1–4.

30. Zir LM, Miller SW, Dinsmore RE, Gilbert JP, Harthorne JW. Interobserver variability in coronary angiography. *Circulation*. 1976;53(4):627–632.

31. Kerl JM, Schoepf UJ, Zwerner PL, et al. Accuracy of coronary artery stenosis detection with CT versus conventional coronary angiography compared with composite findings from both tests as an enhanced reference standard. *Eur Radiol*. 2011;21(9):1895–1903.

KEY WORDS artificial intelligence, atherosclerosis, coronary artery disease, coronary CTA, coronary computed tomography, fractional flow reserve, quantitative coronary angiography

APPENDIX For an expanded Methods section and supplemental tables, please see the online version of this paper.