JACC: CARDIOVASCULAR IMAGING VOL. 6, NO. 9, 2013

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcmg.2013.02.011

Predictors of Inaccurate Coronary Arterial Stenosis Assessment by CT Angiography

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OBJECTIVES This study sought to investigate the clinical and imaging characteristics associated with diagnostic inaccuracy of computed tomography angiography (CTA) for detecting obstructive coronary artery disease (CAD) defined by quantitative coronary angiography (QCA).

BACKGROUND Although diagnostic performance metrics of CTA have been reported, there are sparse data on predictors of diagnostic inaccuracy by CTA.

METHODS The clinical characteristics of 291 patients (mean age: 59 ± 10 years; female: 25.8%) enrolled in the multicenter CorE-64 (Coronary Artery Evaluation Using 64-Row Multi-detector Computed Tomography Angiography) study were examined. Pre-defined CTA segment-level characteristics of all true-positive (N = 237), false-positive (N = 115), false-negative (FN) (N = 159), and a random subset of true-negative segments (N = 511) for ≥50% stenosis with QCA as the reference standard were blindly abstracted in a central core laboratory. Factors independently associated with corresponding levels of CTA diagnostic inaccuracies on a patient level and coronary artery segment level were determined using multivariable logistic regression models and generalized estimating equations, respectively.

RESULTS An Agatston calcium score of ≥1 per patient (odds ratio [OR]: 5.2; 95% confidence interval [CI]: 1.1 to 24.6) and the presence of within-segment calcification (OR: 10.2; 95% CI: 5.2 to 19.8) predicted false-positive diagnoses. Conversely, absence of within-segment calcification was an independent predictor of an FN diagnosis (OR: 2.0; 95% CI: 1.2 to 3.5). Prior percutaneous revascularization was independently associated with patient-level misdiagnosis of obstructive CAD (OR: 4.2; 95% CI: 1.6 to 11.2). Specific segment characteristics on CTA, notably segment tortuosity (OR: 3.5; 95% CI: 2.4 to 5.1), smaller luminal caliber (OR: 0.48; 95% CI: 0.36 to 0.63 per 1-mm increment), and juxta-arterial vein conspicuity (OR: 2.1; 95% CI: 1.4 to 3.2), were independently associated with segment-level misdiagnoses. Attaining greater intraluminal contrast enhancement independently lowered the risk of an FN diagnosis (OR: 0.96; 95% CI: 0.94 to 0.99 per 10-Hounsfield unit increment).

CONCLUSIONS We identified clinical and readily discernible imaging characteristics on CTA predicting inaccurate CTA diagnosis of obstructive CAD defined by QCA. Knowledge and appropriate considerations of these features may improve the diagnostic accuracy in clinical CTA interpretation. (Diagnostic Accuracy of Multi-Detector Spiral Computed Tomography Angiography Using 64 Detectors [CORE-64]; NCT00738218) (J Am Coll Cardiol Img 2013;6:963–72) © 2013 by the American College of Cardiology Foundation

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Delineating the presence and anatomic extent of obstructive coronary artery disease (CAD) provides vital prognostic information and guides the management of patients with ischemic heart disease (1–4). Accumulating evidence from single-center and multicenter studies has demonstrated high accuracy of contemporary computed tomography angiography (CTA) for the diagnosis of obstructive CAD (5–8). Accordingly, CTA has been included in recent American and European recommendations as a valuable noninvasive alternative in the diagnostic evaluation of patients at low-to-intermediate probability for CAD (9,10).

Although numerous factors affect the comparison between CTA and invasive quantitative coronary angiography (QCA) (11), there is a paucity of data on how clinical and CTA imaging characteristics influence the diagnostic accuracy of CTA. Accordingly, the objective of this study is to examine patient clinical and coronary arterial segment characteristics on CTA associated with inaccurate diagnosis of obstructive CAD as defined by QCA.

ABBREVIATIONS AND ACRONYMS

BMI = body mass index
CAD = coronary artery disease
CI = confidence interval
CTA = computed tomography angiography
FN = false-negative
FP = false-positive
OR = odds ratio
QCA = quantitative coronary angiography
TN = true-negative
TP = true-positive

METHODS

Study design and population. The CorE-64 (Coronary Artery Evaluation Using 64-Row Multi-detector Computed Tomography Angiography) study is a prospective, multicenter investigation to examine the diagnostic accuracy of CTA to detect CAD in comparison with QCA (12). Its study design and primary results have been reported (7,12). Briefly, patients aged ≥40 years who were referred for clinically indicated invasive coronary angiography were recruited from 9 international centers. Exclusion criteria included prior cardiac surgery, percutaneous coronary intervention within the past 6 months, history of iodinated contrast allergy, history of or high-risk features for contrast-induced nephropathy, tachyarrhythmia or second/third-degree atrioventricular block, advanced heart failure or aortic stenosis, body mass index >40 kg/m^2, and contraindications to beta-blocker. Patients with an Agatston score >600 were pre-specified to be excluded from the primary analysis. The study was approved by the local institutional review board of all participating centers. All patients provided written informed consent.

Invasive coronary angiography acquisition and analysis. Clinically indicated invasive angiography was performed within 30 days after CTA using standardized angiographic techniques. Images were forwarded to the QCA core laboratory for centralized blinded analysis. The coronary tree was segmented and analyzed according to a modified 19-segment model (7,12,13). All nonstented coronary segments ≥1.5 mm in diameter were visually assessed for ≥30% stenoses that were quantified by QCA (CASS-II, QCA, version 2.0.1, PIE Medical Imaging, Maastricht, the Netherlands). The most severe stenosis was determined within each segment and for each patient. Significant obstructive CAD was defined on QCA as luminal diameter narrowing of ≥50%.

CTA acquisition and post-processing. All images were acquired using a commercially available computed tomography scanner (Aquilion 64, Toshiba Medical Systems, Tochigi, Japan). Noncontrast imaging was performed using prospective electrocardiogram gating for Agatston calcium scoring. CTA was completed with retrospective electrocardiogram gating. Beta-blockers were administered in compliance with local institutional standards at each center when the resting heart rate was >70 beats/min to achieve a target heart rate of <70 beats/min. Sublingual nitroglycerine was routinely

Doris Duke Charitable Foundation, and Toshiba Medical Systems. Dr. Yan was supported by Fellowship Awards from the Canadian Institutes of Health Research and the Detweiler Travelling Fellowship Award from the Royal College of Physicians and Surgeons of Canada. Dr. Dewey has received research grants from GE Healthcare, Bracco Diagnostics, Inc., Guerbet, and Toshiba Medical Systems; is on the Speakers' Bureau of Toshiba Medical Systems, Guerbet, Cardiac MR Academy Berlin, and Bayer-Schering; is a consultant to Guerbet; has institutional master research agreements with Siemens Medical Solutions, Philips Medical Systems, and Toshiba Medical Systems (the terms of these arrangements are managed by the legal department of Charité, University Medicine Berlin); received research grants from the Heisenberg Program of the German Research Foundation (DFG) for a Professorship (DE 1361/14-1), European Regional Development Fund (20072013 2/05, 20072013 2/48), German Heart Foundation/German Foundation of Heart Research (F/23/08, F/27/10), and joint program of the DFG and the German Federal Ministry of Education and Research (BMBF) for cardiovascular imaging meta-analyses (01KG1013, 01KG1110); is the author of *Coronary CT Angiography* (Springer, 2009) and *Cardiac CTA* (Springer, 2011); and teaches cardiac CT courses in Berlin (www.ct-kurs.de). Dr. Lima has received research support and grant support from Toshiba America Medical Systems, Inc., and Bracco Diagnostics, Inc. Dr. Arbab-Zadeh serves on the steering committee of the CORE320 multicenter study, which is sponsored by Toshiba Medical Systems. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received September 25, 2012; revised manuscript received January 16, 2013, accepted February 21, 2013.

prescribed along with weight-based intravenous administration of iopamidol (Isovue 370, Bracco Diagnostics, Inc., Monroe Township, New Jersey) at 3.5 to 5.0 ml/s before image acquisition as triggered by bolus tracking during a single 12- to 14-s breath-hold.

Raw data were transferred to the CTA core laboratory for post-processing and blinded interpretation per standardized protocols (7,12). Images were reconstructed at 0.5-mm slice thickness with 0.3-mm overlap. Multiple systolic and diastolic phases with the least cardiac motion were routinely reconstructed with standard (FC43) and as appropriate additional sharper (FC05) kernels. Optimal reconstruction was identified for each vessel from which it was segmented and labeled in accordance with the modified 19-segment model for cross-comparison with QCA (12,13).

CTA stenosis interpretation. Two independent CTA readers visually graded each nonstented segment for stenosis according to an ordinal scale (12). All segments with visible luminal narrowing of ≥30% were quantified for maximum percentage luminal diameter stenosis by a semiautomatic contour detection algorithm using commercially available software (Vitrea Version 3.9.0.1, Vital Images, Minnetonka, Minnesota). Segments deemed nonevaluable or with inter-reader visual and/or quantitative stenosis discrepancies crossing the 50% threshold underwent consensus grading incorporating a third experienced observer. After finalization of all qualitative and quantitative segmental stenosis measurements independently by both QCA and CTA core laboratories for the entire trial cohort, an adjudication process was performed to ensure correct cross-modality correspondence of segments as interpreted.

Definitions of CTA diagnostic inaccuracy and abstractions for inaccuracy-associated features. Diagnostic inaccuracy of CTA was examined on both (a) per-patient and (b) per-segment levels, and was defined as diagnostic discordance between quantitative CTA and reference standard QCA for the presence of ≥50% luminal stenosis. Consistent with CorE-64 primary outcome analysis (7), stented and nonevaluable segments were excluded in this substudy. On patient- and segment-based levels, overall diagnostic inaccuracy (i.e., misdiagnoses, all QCA-CTA discordant diagnoses) was further stratified by the (a) presence and (b) absence of obstructive CAD per reference standard QCA, representing correspondingly false-negative (FN) and false-positive (FP) diagnoses. True-positive (TP) and true-negative (TN) findings were conventionally defined as the correct identification and exclusion of obstructive CAD, respectively.

Patient-level factors examined included patient baseline clinical characteristics (demographics, traditional risk factors, prior CAD diagnosis/interventions), physical and laboratory parameters (body mass index, serum creatinine, cholesterol), and selected core laboratory-determined CTA acquisition parameters (mean and variability of acquisition heart rate) and patient-level findings (breathing artifacts and Agatston calcium score) known to affect CTA interpretation.

For this post hoc analysis, all evaluable coronary segments with TP, FN, and FP diagnoses of obstructive CAD together with a randomly selected subset of TN segments were re-evaluated without knowledge of diagnosis or stenosis measurements by either modality for additional prospectively defined segment-level features. Random selection of a TN segment as a referent control was pre-specified in this substudy because characterization of all TN segments (>3,000) was deemed to be impractical. From the entire clinical trial patient cohort, TN segments in number matched to the total of all TP, FN, and FP segments were pre-specified to be randomly selected. To minimize potential effects of clustering, we stipulated a priori that no more than 5 random TN segment samples were to be selected from any one individual patient. Segment-level features examined included: 1) segment image quality (good = absence of motion or other artifacts, adequate = assessable with minor motion artifacts, poor = assessable with substantial motion/other artifacts, and nonevaluable); 2) segmental-arterial calcification (none/presence); 3) tortuosity (segment assuming ≥1 within-segment arc(s) of visually estimated ≥60° on multiplanar and/or maximum-intensity projections); 4) vein crossing (cardiac venous structure(s) visualized as crossing or contacting with arterial segment on maximum-intensity projections of ≤2.5-mm slab thickness); 5) segment reference diameter (most proximal disease-free portion of segment determined by semiautomatic contour detection algorithm with manual contour editing); and 6) segment-specific luminal contrast attenuation (mean Hounsfield units of cross-sectional region of interest excluding wall/plaque/calcification at proximal disease-free portion of segment). All post hoc segmental characteristics were abstracted from restored multiplanar reformations, maximum-intensity projections, and cross-sectional images as used for original stenosis assessment. Reference to adjudicated segmentation

labeling ensured exact correspondence of coronary segments between successive reads and across modalities.

Statistical analysis. Continuous variables unless otherwise stated are reported as medians with interquartile ranges and compared using the Kruskal-Wallis test. Categoric data are presented as counts and percentages with comparisons conducted by the Pearson chi-square or Fisher exact test. Patient-level features and segment-level CTA characteristics were separately examined for respective relationships with patient-level and segment-level diagnostic inaccuracy of CTA. The respective study samples of the entire cohort (N = 291) and their studied segments (N = 1,022) were stratified for unadjusted pairwise comparisons of features by diagnostic discordance versus concordance of CTA versus QCA (a) overall (misdiagnosis vs. accurate diagnosis), among subgroups (b) with (FN vs. TP diagnosis) and (c) without (FP vs. TN diagnosis) obstructive CAD per reference standard QCA. Features significant ($p < 0.05$) on univariable pairwise comparisons were entered into corresponding multivariable logistic regression models to determine their independent association with inaccurate CTA interpretation expressed as odds for QCA-discordant diagnoses. To account for the clustered nature of segment characteristics within patients, complex sample analyses and generalized estimating equations were used for unadjusted and multivariable analyses of segment-level data to compensate for clustering-related underestimation of SEs. Statistical analyses were performed using SPSS v16.0 (SPSS Inc., Chicago, Illinois). Statistical significance was defined as a 2-sided p value <0.05.

RESULTS

Patient-level factors in relation to patient-level CTA diagnostic inaccuracy. Overall, patients with an inaccurate diagnosis of obstructive CAD by CTA were more likely to have known CAD with prior myocardial infarction (32.4% vs. 17.7%, $p = 0.035$) and/or percutaneous coronary intervention(s) (27.0% vs. 7.1%, $p = 0.001$). Specifically, patients with an FN diagnosis more frequently had previous myocardial infarction (45.8% vs. 25.2%, $p = 0.038$) and percutaneous intervention(s) (33.3% vs. 10.1%, $p = 0.006$). Although patients with an accurate diagnosis versus a misdiagnosis had similar Agatston scores (85 vs. 56, $p = 0.89$), there was a heterogeneous relationship between coronary calcification burden and patient-level inaccuracy. Individuals with a TN diagnosis versus an FP diagnosis had lower coronary calcification burden (Agatston score: 1 vs. 49, $p = 0.047$). Conversely, patients with a TP diagnosis versus an FN diagnosis had greater calcium scores: 172 vs. 57 ($p = 0.035$). No other patient-level characteristic was significantly associated with CTA diagnostic inaccuracy. The clinical characteristics, acquisition parameters, and patient-level findings of CTA examination related to the different patient-level inaccuracies are presented in Online Appendix 1.

Independent association between patient-level factors and CTA diagnostic inaccuracy. In multivariable analyses, previous percutaneous coronary intervention was the only patient-level characteristic independently associated with patient-level misdiagnosis, even while considering only nonstented coronary arterial segments (odds ratio [OR]: 4.18; 95% confidence interval [CI]: 1.56 to 11.22). A history of percutaneous coronary intervention(s) was independently associated with patient-level FN diagnosis (OR: 4.29; 95% CI: 1.33 to 13.79), whereas the presence and greater extent of coronary artery calcification independently conferred a lower likelihood of an FN diagnosis (OR: 0.96; 95% CI: 0.93 to 0.99 per 10-U Agatston score increment). The presence of coronary calcification (positive Agatston score) was the only patient-level feature independently associated with an FP diagnosis (OR: 5.22; 95% CI: 1.11 to 24.61; referent: zero Agatston score). These findings were consistent in a series of sensitivity analyses incorporating additional adjustment for previously observed correlates with image quality (14), including body mass index (BMI), heart rate (mean and variability) during image acquisition, and presence of breathing artifact (data not shown).

Segment characteristics on CTA in relation to segment-level CTA diagnostic inaccuracy. The proportional distribution across major coronary vessels of the random TN segment samples examined and the remaining nonselected TN samples in the entire trial cohort was not different ($p > 0.05$ for differences) (Online Appendix 2). The characteristics on CTA examination of all segments with TP, FP, and FN diagnoses, and the random subset of TN segment samples examined are summarized in Table 1. Compared with correctly diagnosed segments, misdiagnosed segments were less likely to reside in the left main artery and more likely to reside in the diagonal branches (Table 1a). Of all segments harboring obstructive CAD, those with an FN diagnosis were disproportionally more frequent

in the diagonal and obtuse marginal/left posterolateral branch or ramus intermedius, but less often in the left anterior descending artery (Table 1b). Among segments without significant disease, FP segments were more likely in the left anterior descending artery and less likely in the posterior descending/posterolateral branches of the right coronary artery (Table 1c).

The angiographic appearances of segments on CTA stratified by diagnostic accuracy (a) overall among all segments and within subgroups exclusively (b) with and (c) without significant stenosis are summarized in Table 1. Segments with misdiagnosis were more likely to be torturous, of smaller caliber, of suboptimal image quality impaired by motion and other artifacts, containing calcification, and visualized with cardiac vein over-crossing (Table 1a). Segments with an FN diagnosis compared with TP segments exhibited similar variations in CTA appearances as with overall misdiagnosis, with the exception of paradoxically less calcification and lower segment-specific luminal contrast opacification (Table 1b). FP segments compared with TN segments revealed similar differences as observed with overall misdiagnosis (Table 1c).

CTA segment-level characteristics independently predictive of CTA segment-level diagnostic inaccuracy. The independent association between segment characteristics on CTA and segment-level diagnostic inaccuracy is presented in Table 2. Segment tortuosity, cardiac vein over-crossing, and smaller luminal diameter each independently conferred increased odds for CTA misdiagnosis (Table 2a), and specifically FN diagnosis (Table 2b) and FP diagnosis (Table 2c). Furthermore, greater

Table 1. Segment Characteristics on CTA According to Segment-Level Diagnostic Concordance Between CTA and QCA for All Studied Segments, Segments With Obstructive CAD on QCA, and Segments Without Obstructive CAD on QCA

	(a) All Segments			(b) Segments With Obstructive CAD on QCA			(c) Segments Without Obstructive CAD on QCA		
	Diagnostic Concordance (CTA Accuracy) (TP and TN) (N = 748)	Diagnostic Discordance (CTA Inaccuracy/ Misdiagnosis) (FP and FN) (N = 274)	p Value*	Diagnostic Concordance (CTA Accuracy) (TP) (N = 237)	Diagnostic Discordance (CTA Inaccuracy) (FN) (N = 159)	p Value*	Diagnostic Concordance (CTA Accuracy) (TN) (N = 511)	Diagnostic Discordance (CTA Inaccuracy) (FP) (N = 115)	p Value*
Segment location									
Left main artery	31 (4.1)	3 (1.1)	0.017	2 (0.8)	1 (0.6)	0.81	29 (5.7)	2 (1.7)	0.081
LAD	187 (25.0)	71 (25.9)	0.77	85 (35.9)	30 (18.9)	<0.001	102 (20.0)	41 (35.7)	0.001
Diagonal branches	70 (9.4)	46 (16.8)	0.001	19 (8.0)	32 (20.1)	0.001	51 (10.0)	14 (12.2)	0.48
RCA	145 (19.4)	52 (19.0)	0.89	55 (23.2)	31 (19.5)	0.43	90 (17.6)	21 (18.3)	0.88
PDA/PLV	82 (11.0)	19 (6.9)	0.081	9 (3.8)	14 (8.8)	0.76	73 (14.3)	5 (4.3)	0.004
LCx	109 (14.6)	29 (10.6)	0.11	25 (10.5)	9 (5.7)	0.10	84 (16.4)	20 (17.4)	0.80
OM/ramus intermedius/ left PLV	124 (16.6)	54 (19.7)	0.22	42 (17.7)	42 (26.4)	0.038	82 (16.0)	12 (10.4)	0.102
Tomographic segment characteristics									
Segment tortuosity	111 (14.9)	102 (37.5)	<0.001	53 (22.6)	66 (41.8)	<0.001	58 (11.4)	36 (31.6)	<0.001
Vein crossing	127 (17.0)	79 (29.0)	<0.001	41 (17.4)	48 (30.4)	0.003	86 (16.9)	31 (27.2)	0.005
Motion artifact–related suboptimal segment image quality	445 (59.5)	207 (75.5)	<0.001	157 (66.2)	129 (81.1)	0.001	288 (56.4)	78 (67.8)	0.027
Presence of segmental coronary calcification	294 (39.8)	164 (61.2)	<0.001	168 (72.4)	79 (51.0)	<0.001	126 (24.9)	85 (75.2)	<0.001
Segment diameter, mm	2.71 ± 0.04	2.33 ± 0.04	<0.001	2.66 ± 0.05	2.21 ± 0.05	<0.001	2.72 ± 0.04	2.50 ± 0.06	0.002
Mean segment luminal opacification, HU	441 ± 8	424 ± 10	0.093	459 ± 10	400 ± 12	<0.001	433 ± 9	457 ± 12	0.078

Values are counts (%) or mean ± SE. *Unadjusted complex sample analysis accounted for within-patient clustering.
CAD = coronary artery disease; CTA = computed tomography angiography; FN = false-negative; FP = false-positive; HU = Hounsfield units; LAD = left anterior descending artery; LCx = left circumflex coronary artery; OM = obtuse marginal branches; PDA = posterior descending artery; PLV = posterolateral ventricular branch; QCA = quantitative coronary angiography; RCA = right coronary artery; TN = true-negative; TP = true-positive.

luminal contrast enhancement was independently associated with a lower likelihood for under-recognizing within-segment stenosis (FN diagnosis) (Table 2b). Although the presence of calcification independently increased the odds for overall misdiagnosis (OR: 2.49; 95% CI: 1.73 to 3.58) and specifically more significantly FP diagnosis (OR: 10.16; 95% CI: 5.23 to 19.77) (Fig. 1), it conferred reduced odds for FN diagnosis (OR: 0.50; 95% CI: 0.29 to 0.86). Conversely, obstructive disease in a segment without calcification, as in noncalcified atherosclerotic plaque, is more likely to be missed, compared with obstructive disease with calcification in segment, independently of other segment characteristics (OR: 2.01; 95% CI: 1.17 to 3.46).

After accounting for segment intrinsic characteristics on CTA, segment location per major vessel categories within the coronary tree was no longer found to be associated with segment-level diagnostic inaccuracy (Table 2). Furthermore, patient-level parameters correlating with patient-level diagnostic performance as observed in this study (e.g., history of CAD) or conceivably image quality (BMI, heart rate, breathing, or ectopy during acquisition) when added to the models were not found to affect the segment-level results or to be associated with segment-level diagnostic inaccuracy (data not shown).

DISCUSSION

Although the diagnostic accuracy of CTA for detecting CAD has been extensively delineated, few data are available addressing factors predicting its diagnostic inaccuracy (15–18). Existing data in this regard were derived from single-center experiences on modest patient and segment samples of which characteristics were qualitatively determined without case-control comparisons (15–18). To the best of our knowledge, this is the first study to report patient clinical and coronary arterial segment characteristics on CTA that are *independently* associated with the different specific CTA inaccuracies on both per-patient and per-segment levels.

Lower patient-level diagnostic accuracy for CTA has been reported in obese patients and patients with poor heart-rate control resulting from images with low signal-to-noise ratio and motion artifacts (8,14,18–22). However, consistent with our prior investigation on this topic (14), we found that neither BMI nor heart rate is an independent predictor of patient-level diagnostic inaccuracy. A potential explanation for this counterintuitive

Table 2. Independent Association Between Segment Characteristics on CTA and Segment-Level CTA Overall Misdiagnosis, False-Negative Diagnosis, and False-Positive Diagnosis, With QCA as Reference Standard

	(a) Overall Misdiagnosis		(b) FN Diagnosis		(c) FP Diagnosis	
	OR* (95% CI)	p Value	OR* (95% CI)	p Value	OR* (95% CI)	p Value
Segment location†						
LAD artery	1.02 (0.27–3.83)	0.97	0.14 (0.008–2.390)	0.17	2.59 (0.45–14.71)	0.28
Diagonal branches	1.06 (0.26–4.40)	0.94	0.22 (0.01–4.37)	0.32	1.52 (0.20–11.67)	0.69
RCA	1.17 (0.31–4.35)	0.82	0.25 (0.01–4.54)	0.35	1.96 (0.33–11.47)	0.46
Right posterior descending artery/right posterolateral branch	0.46 (0.13–1.67)	0.24	0.17 (0.01–3.78)	0.26	0.65 (0.09–4.79)	0.68
Circumflex artery	0.56 (0.15–2.05)	0.38	0.06 (0.01–1.12)	0.06	1.24 (0.22–6.93)	0.81
Obtuse marginal/left posterolateral branches/ramus intermedius	0.79 (0.20–3.22)	0.75	0.16 (0.01–2.91)	0.21	0.65 (0.09–4.79)	0.68
CTA segment characteristics						
Segment tortuosity	3.54 (2.44–5.14)	<0.001	3.12 (1.89–5.17)	<0.001	5.22 (3.00–9.11)	<0.001
Vein crossing	2.13 (1.42–3.19)	<0.001	2.04 (1.14–3.62)	0.016	2.58 (1.28–5.17)	0.008
Motion artifact–related suboptimal segment image quality	1.39 (0.98–1.98)	0.068	1.45 (0.81–2.62)	0.21	1.30 (0.77–2.19)	0.34
Presence of segmental coronary calcification	2.49 (1.73–3.58)	<0.001	0.50 (0.29–0.86)	0.012	10.16 (5.23–19.77)	<0.001
Segment diameter (per 1-mm increment)	0.48 (0.36–0.63)	<0.001	0.40 (0.25–0.65)	0.008	0.49 (0.33–0.73)	<0.001
Mean segment luminal opacification (per 10-HU increment)	1.00 (0.98–1.01)	0.75	0.96 (0.94–0.99)	0.008	1.03 (1.00–1.05)	0.056

*Generalized estimating equations models accounted for within-patient clustering of segment characteristics. †Left main artery as referent.
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

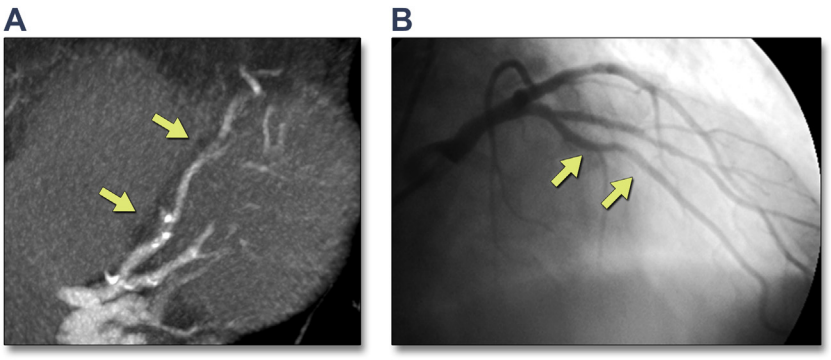

Figure 1. False-Positive Diagnosis of Obstructive Coronary Artery Disease by Computed Tomography Angiography

(A) Example of false-positive (FP) diagnoses by computed tomography angiography (CTA) in the left anterior descending artery **(arrows)**. The interpretation of the mid portion of the vessel is affected by focal tortuosity, motion, and coronary calcification, whereas the distal site reveals poor contrast opacification in addition to motion artifacts. **(B)** The corresponding conventional angiography without significant stenoses at the specified sites **(arrows)**.

finding may be our adaptive adjustment of tube current to BMI and protocol-stipulated prescription of beta-blockers. A history of percutaneous coronary intervention surrogated higher disease prevalence among nonstented coronary segments in our studied population and independently conferred an increased risk for patient-level FN diagnosis, confirming the dependency of CTA accuracy on the pre-test probability of CAD (23).

We and others have shown that high calcium scores are associated with lower patient-level specificity and negative predictive level (5,19,20,23). Consistent with these reports, the current study found that a higher Agatston score independently increases the risk of patient-level FP diagnosis. Of note, we also found that the absence of coronary calcification is an independent predictor of stenosis under-recognition. We have previously reported among our trial cohort that the absence of coronary calcification does not exclude obstructive CAD (24) and that *overall* segment-level diagnostic inaccuracy is lower in noncalcified arterial segments of lower disease prevalence than in calcified coronary artery segments (25). In the present study, we establish the absence of coronary calcification as an underappreciated independent risk marker for FN diagnoses. Our results suggest that the absence of calcification may reduce a reader's vigilance for stenoses and that potential lesions—without obvious (i.e., calcified) evidence of atherosclerosis—may be dismissed as artifacts.

Despite technological advancement of scanners provisioning better spatial resolution, small vessels remain diagnostically challenging. With the use of contemporary 64-detector technology, segment-level sensitivity was lower among smaller segments (6). Our study extended beyond these unadjusted observations and demonstrated that smaller luminal caliber is an independent attributor to segment-level misdiagnoses. For the first time, we established arterial segment tortuosity as an independent predictor of segment-level diagnostic inaccuracy (Fig. 1). Of note, cardiac motion degraded segment-level image quality, which was associated with segment-level misdiagnosis (Fig. 2) but not after adjustment for other segment-level factors (Table 2). This may suggest that cardiac motion may be more tolerable in the absence of other features independently attributable for misinterpretation. Likewise, our findings also underscore that specific segment-level characteristics as reported, rather than segment location per se, are independent parameters affecting diagnostic accuracy.

Aside from intrinsic segment properties, intra-arterial luminal enhancement and conspicuity of juxta-arterial cardiac veins emerge as independent factors affecting segment-level accuracy. Previous studies have shown higher unadjusted segment-level sensitivity and positive predictive value in patients achieving greater vascular contrast enhancement at the aortic root and origins of the left main and right coronary arteries (26). Our adjusted *segment-specific* luminal attenuation analyses affirm the importance of optimizing luminal contrast opacification to avert FN diagnoses (Fig. 3). Conspicuity of juxta-arterial venous structures is first identified associated with segment-level misinterpretations. Consequential to partial volume averaging, focal luminal attenuation at the over-crossed arterial

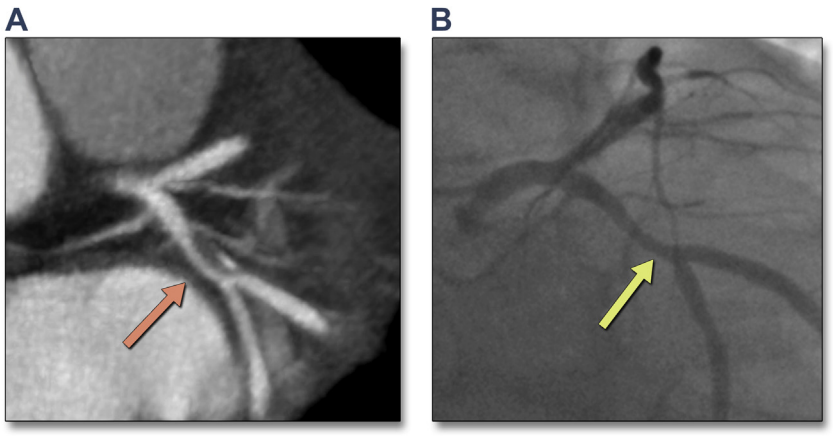

Figure 2. Minor Cardiac Motion Affecting the Quantification of Coronary Artery Stenosis by CTA

(A) Minor cardiac motion can lead to slightly smaller lumen appearance by computed tomography **(arrow)** compared with conventional angiography **(arrow, B)**. Overestimation of lumen narrowing by CTA compared with quantitative conventional angiography resulted in FP diagnosis of obstructive coronary artery disease. Visualization of atherosclerotic plaque at the lesion site by computed tomography also may have contributed to the impression of significant lumen narrowing. Abbreviations as in Figure 1.

segment may appear artifactually lower or higher, potentially mimicking or masking stenosis, respectively (Fig. 4). These pitfalls advocate for optimized contrast bolus timing to achieve high intra-arterial while minimizing venous contrast enhancement.

Study limitations. The principal limitation of this investigation is the use of categoric decision points for determining the absence or presence of obstructive CAD, which, although almost invariably used for clinical investigations, may not reflect clinical practice. The use of specific thresholds to define disease is also associated with observer bias that may affect diagnostic accuracy (23). Our study was performed in a selected cohort with clinical indications for invasive coronary angiography. Our findings may not necessarily generalize to lower-risk populations, for whom CTA is more intended for CAD assessment. Although this is one of the largest multicenter investigations, the number of misdiagnosed patients is still modest; thus, implications of our patient-level associations should be considered as hypothesis generating, advocating for larger

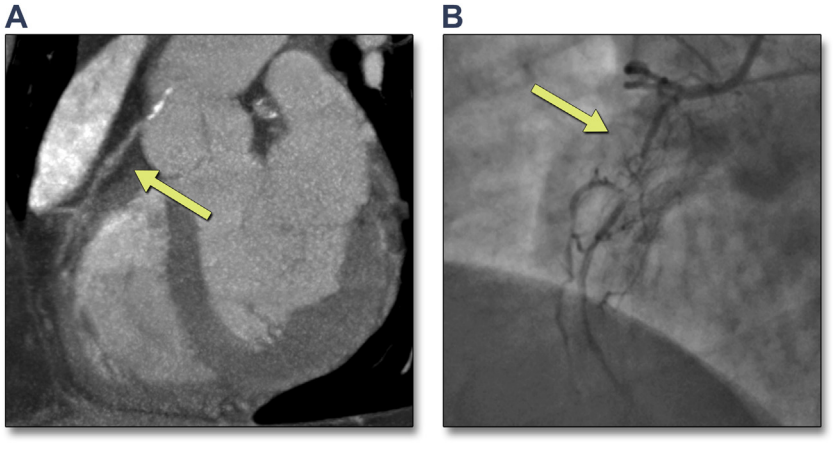

Figure 3. FN Diagnosis of Obstructive Coronary Artery Disease by CTA

(A) Right coronary artery with poor contrast filling, which does not allow visualizing the site of a subtotal occlusion **(arrow)**. **(B)** The corresponding invasive angiogram revealing the subtotal occlusion in the proximal right coronary artery **(arrow)**. Abbreviations as in Figures 1 and 2.

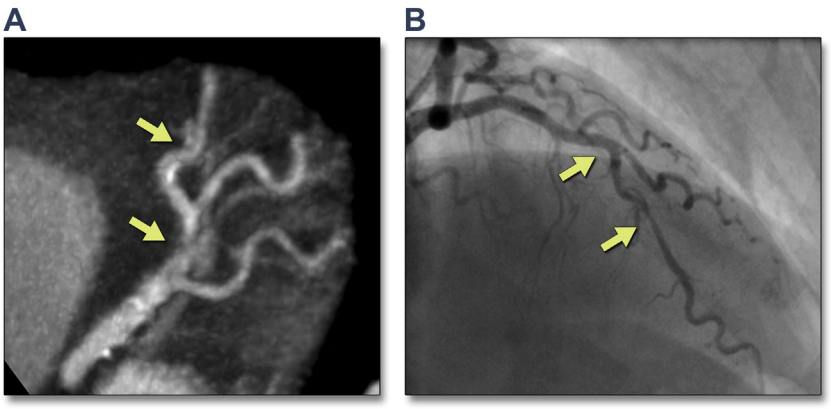

Figure 4. Cardiac Veins Affecting Coronary Arterial Lumen Assessment by CTA

(A) An adjacent cardiac vein (through partial volume effect) can mimic a focal noncalcified stenosis **(proximal arrow)** leading to FP diagnosis. The **distal arrow** marks false-negative (FN) diagnosis (CTA = 15%, quantitative coronary angiography = 74% stenosis) masked by an adjacent cardiac vein. **(B)** The conventional angiogram correlation revealing no stenosis at the proximal site **(proximal arrow)** but a significant lesion at the distal site **(distal arrow)**. Abbreviations as in Figure 1.

confirmative studies. Given the effort entailed in our detailed segment-level analysis and the large number of TN segments within our entire multicenter cohort, we pre-specified and analyzed segment-level features of diagnostic inaccuracy on only a randomly selected TN-segment subset as comparative control. Our TN segment characteristics may thus be subjected to potential selection bias. However, we verified that the proportional constitution of segments of the different major vessels within this randomly selected TN-segment subset and the remainder of all nonselected TN segments in our entire patient cohort was not significantly different (Online Appendix 2).

CONCLUSIONS

In this systematic evaluation of factors associated with diagnostic inaccuracy for coronary artery stenosis assessment by CTA compared with QCA in a multicenter diagnostic study, we observed pitfalls as well as clinical and CTA features predictive of patient- and segment-level CTA misdiagnoses. Our observations particularly reveal the absence of coronary calcification as an independent risk marker for under-recognition of stenoses defined by QCA. Specific segment-level CTA features, notably small segment caliber, segment tortuosity, suboptimal intra-arterial contrast enhancement, and juxta-arterial venous conspicuity, are independent predictors for segment-level misdiagnoses. Knowledge and appropriate considerations of these CTA predictors of misdiagnosis may improve limitations awareness, and accuracy in clinical CTA interpretation.

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Key Words: accuracy ■ computed tomography angiography ■ false-negative ■ false-positive.

▶ APPENDIX

For additional tables, please see the online version of this article.