The Accuracy of Coronary CT Angiography in Patients with Coronary Calcium Score above 1000 Agatston Units: Comparison with Quantitative Coronary Angiography

Short title: Coronary CT Angiography in High Coronary Calcium

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Abbreviations:

BMI: Body mass index

CAC: Coronary artery calcium

CACs: Coronary artery calcium score

CAD: Coronary artery disease

CCTA: Coronary CT angiography

ICA: Invasive coronary angiography

NPV: Negative predictive value

PPV: Positive predictive value

QCA: Quantitative coronary angiography

SCCT: Society of Cardiovascular CT

ABSTRACT

Background: High amounts of coronary artery calcium (CAC) pose challenges in interpretation of coronary CT angiography (CCTA). The accuracy of stenosis assessment by CCTA in patients with very extensive CAC is uncertain.

Methods: Retrospective study was performed including patients who underwent clinically directed CCTA with CAC score >1000 and invasive coronary angiography within 90 days. Segmental stenosis on CCTA was graded by visual inspection with two-observer consensus using categories of 0%, 1-24%, 25-49%, 50-69%, 70-99%, 100% stenosis, or uninterpretable. Blinded quantitative coronary angiography (QCA) was performed on all segments with stenosis ≥25% by CCTA. The primary outcome was vessel-based agreement between CCTA and QCA, using significant stenosis defined by diameter stenosis ≥ 70%. Secondary analyses on a per-patient basis and inclusive of uninterpretable segments were performed.

Results: 726 segments with stenosis ≥25% in 346 vessels within 119 patients were analyzed. Median coronary calcium score was 1616 (1221-2118). CCTA identification of QCA-based stenosis resulted in a per-vessel sensitivity of 79%, specificity of 75%, positive predictive value (PPV) of 45%, negative predictive value (NPV) of 93%, and accuracy 76% (68 false positive and 15 false negative). Per-patient analysis had sensitivity 94%, specificity 55%, PPV 63%, NPV 92%, and accuracy 72% (30 false-positive and 3 false-negative). Inclusion of uninterpretable segments had variable effect on sensitivity and specificity, depending on whether they are considered as significant or non-significant stenosis.

Conclusions: In patients with very extensive CAC (>1000 Agatston units), CCTA retained a negative predictive value > 90% to identify lack of significant stenosis on a per-vessel and per-patient level, but frequently overestimated stenosis.

INTRODUCTION

Coronary Computed Tomography angiography (CCTA) is rapidly assuming a central role for assessing symptomatic patients for coronary artery disease (CAD). A high burden of coronary artery calcium (CAC) is known to affect the diagnostic information from CCTA due to partial volume effects and beam hardening.[1, 2] Recent generation CT systems with faster temporal resolution, increased spatial resolution, improved x-ray filtering, and new reconstruction algorithms have provided opportunity to improve imaging in highly calcified coronary arteries.[3] However, the diagnostic accuracy of CCTA, even with modern equipment and reconstructions in the presence of very extensive calcification, has not been assessed. It is important for clinicians ordering CCTA and cardiac imagers protocoling studies and reading images to understand the limitations of scan interpretation and the reliability of reporting of coronary stenosis in order to effectively use this technology in these patients.

The aim of our study was to assess the performance of clinical CCTA using second and third generation dual-source CT scanner platforms in patients with coronary artery calcium score (CACs) exceeding 1000. We compared stenoses (≥ 25% diameter) identified by CCTA to invasive quantitative coronary angiography (QCA) measurement to determine the accuracy of clinical CCTA interpretation in patients with high CACs. Recognizing the known challenges to CT imaging of highly calcified vessels,[4-7] we hypothesized that CCTA with contemporary approaches would be effective at ruling out significant stenosis, but that overall accuracy would remain limited by low specificity.

METHODS

Study Sample

Subjects were selected post-hoc from a prospective cohort of patients who underwent CCTA for clinical purposes using second and third generation dual source scanners at a single center from 2013-2018 (Figure 1). One-hundred and nineteen consecutive patients who had a clinical CCTA, CACs > 1000 Agatston units, and underwent invasive coronary angiography (ICA) within 90 days after CCTA were included. Patients who had previous stenting (n=43) or coronary artery bypass grafts (n=12) were excluded. The study was approved by the local IRB and all patients gave written informed consent.

Outcome Measures

The primary outcome was per-vessel agreement of CCTA with QCA for presence of ≥ 70% maximum diameter stenosis. All ≥ 2 mm diameter vessels with a qualitative CCTA-graded stenosis ≥ 25% were included in the primary analysis. Secondary analyses included per-patient agreement, as well as per-vessel and per-patient analyses with inclusion of segments deemed by CCTA to be "uninterpretable due to calcification." The uninterpretable segment analyses were twofold, assessing testing characteristics if uninterpretable segments were arbitrarily assigned to either ≥ 70% or < 70% CCTA stenosis category and compared to measured QCA. In order to assess for selection bias due to restriction of the study population to those who received ICA with 90 days, the proportion of patients with uninterpretable calcification in significant locations was compared between the study population and all patients during the same timeframe with CACs > 1000 regardless of subsequent referral to ICA. In order to assess for causes of incorrect interpretation we compared factors between correctly and incorrectly graded vessels and patients. Tested variables included demographics: age and sex; risk factors: BMI, CACs, CACs plus total valvular and aortic calcium, vessel-based calcium, symptoms, hypertension, hyperlipidemia, diabetes, insulin use, family history of coronary artery

disease, dialysis status, peripheral arterial disease, history of smoking and history of stroke; and acquisition factors: contrast volume, max heart rate, acquisition mode, use of beta blockade, nitroglycerin, and kVp.

Imaging Acquisition

CAC scanning and CCTA was performed on two dual-source CT platforms (Siemens Flash and Force scanners, Siemens Healthineers, Erlangen, Germany), using standard clinical coronary imaging protocols as previously described.[8] Prior to the exam, beta blockers were administered in patients with heart rates >65 beats per minute. Sublingual nitroglycerin spray (0.4-0.8mg) was given for coronary vasodilation. A non-contrast ECG-gated coronary calcium scan was acquired prior to CCTA at 60-70% of the R-R interval using 120 kVp and mAs 80) and was reconstructed with 2.5-3.0mm slice thickness. Patients received prospectively gated protocols if feasible, and helical scans if body mass index (BMI) >35 kg/m^2 or atrial fibrillation was present. Kilovoltage peak ranged between 80-120 kV at the discretion of the technologist. Automatic exposure control was used with further adjustment at the discretion of the technologists. The standard contrast agent was Iohexol (Omipaque 350mg/mL, GE Healthcare, Buckinghamshire, UK), administered via large-bore intravenous catheter. Contrast volume varied between 85 to 200 mL with injection rate 5 to 8 mL/s, adapted to BMI and followed by saline flush. Automated bolus tracking or timing bolus was used to trigger acquisition. Imaging reconstruction was performed with a 0.6 mm slice thickness and default medium-sharp cardiac reconstruction kernel (B36) with iterative reconstruction (SAFIRE or ADMIRE, Siemens Healthineers, Erlangen, Germany) with option for additional sharper kernels or non-iterative reconstruction at the request of the reading physician to use in an integrated assessment.

Coronary Calcium Score and CT Angiography Analysis

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The Agatston scoring was performed by an experienced technologist using semiautomated software (NetraMD, ScImage, Los Altos, California) and was reviewed by the interpreting physicians.[9] CCTA interpretation was performed as per standard laboratory protocol on a separate workstation (Syngo.Via, SiemensHealthineers, Erlangen, Germany) by two clinicians, with initial reading by an advanced cardiac imaging fellow and over-read by a senior imaging cardiologist with extensive experience with CCTA. The coronary artery tree was divided into standard segments[10] which were graded into categories of stenosis by viewing of axial imaging, curved multiplanar images, and double-oblique views for all vessels ≥ 2 mm in diameter. Diameter stenosis categories for this study were: no stenosis, 1-24%, 25-49%, 50-69%, 70-99%, 100% stenosis or uninterpretable. Uninterpretable segments were coded as being due to calcification or not well seen. For the primary analyses, segments which were deemed uninterpretable were excluded. Segments that were uninterpretable due to calcification were included in a secondary analysis; segments that were not well seen for other reasons remained excluded. For per-vessel analyses, segments were assigned to four vessel categories: left main, left anterior descending artery plus ramus intermedius and diagonal branches, left circumflex and obtuse marginal branches, and right coronary artery with posterior descending artery and posterolateral branches. The maximum stenosis in each vessel was classified as greater or less than 70% stenosis. For patient-level analyses, the maximum stenosis in any segment was identified as greater or less than 70% stenosis.

Quantitative Coronary Angiography Analysis

All ≥ 2 mm vessel regions with a ≥ 25% stenosis or labeled as "uninterpretable due to calcification" on CCTA were identified. The location of the coronary segment involved, with blinding to the degree of stenosis, was provided to readers to guide invasive quantitative coronary angiography (QCA) analysis. The most recent ICA within 90 days after the CCTA was used for analysis if multiple ICA cases were performed on a patient. Fluoroscopy images were

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analyzed with dedicated software (CAAS Workstation, V8.1, Pie Medical Imaging, Maastricht, Netherlands). View and frame for each segment was selected to minimize foreshortening and overlying vessels and maximize contrast enhancement. If a lesion was clearly eccentric, the view with the greatest stenosis was chosen. Reference diameter was the nearest healthy segment proximal to the lesion. Stenosis percent was 1-(max diameter stenosis within segment / diameter of reference segment) and organized by ordinal categories (stenosis of 1-24%, 25-49%, 50-69%, 70-99%, or 100%). After initial analysis, vessels where QCA and CCTA differed by more than one ordinal category were individually assessed for contributing factors including calcification, motion, or other artifact. Examples of highly calcified lesions resulting in erroneous classification are shown in Figure 2.

Statistical Analysis

Patient and vessel demographic data were reported as mean and standard deviation for normally distributed variables, median and interquartile range for non-normal variables, and as a percent for categorical variables. Agreement for significant vessel-based stenosis was tested using unweighted Cohen's kappa and Kendall's tau. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for prediction of significant stenosis (greater than 70%). Comparison of correctly and incorrectly assessed vessels and patients was performed using two-sample t-test for continuous variables and chi-square test for categorical variables. Analysis was performed with R (v 3.6.1) / R Studio (v 1.2.5019). Statistical significance was pre-specified as $p < 0.05$.

RESULTS

The population consisted of 119 patients with mean age 69 years (Table 1) with 2058 coronary artery segments coded on CCTA. The patients were predominantly male (82%) and frequently overweight or obese. Acquisition energies included 1 (1%) patient with 80 kVp, 4

(3%) patients with 100 kVp, 1 (1%) patient with 110 kVp, and 113 (95%) with 120 kVp. Of the

total coded coronary segments, 1162 (56%) had no disease or stenosis between 1-24%, 39

(2%) were coded as uninterpretable due to inadequate visualization, 129 (6%) were

uninterpretable due to extensive calcification, and 728 had graded stenosis ≥ 25%. Of the 728

segments, QCA analysis could be performed on all but two segments. Our primary analysis

included 346 vessels with 726 (35%) CCTA segments with stenosis ≥ 25%. Secondary analysis

added 125 of the 129 segments coded as uninterpretable due to calcification, as four segments

were inadequately visualized by QCA. The median CACs was 1616 (IQR 1221-2118) and 72%

of the patients had CACs 1000-1999.

By CCTA and QCA, the highest proportion of vessels were in the 25-49% stenosis

group, with descending frequency as stenosis severity increased (Table 2). Comparison of

CCTA categories to QCA showed that the proportion of patients with 70-99% was over 50%

lower by QCA than by CCTA. On a per-vessel basis, by CCTA there were 223 (64%) vessels

with stenosis < 70% and 123 (36%) with stenosis ≥ 70%. By invasive QCA, there were 276

(80%) vessels with <70% and 70 (20%) ≥ 70% stenosis.

For detection of significant stenosis, agreement between CCTA and QCA was present in

263 vessels (76%) and disagreement in 83 vessels (24%) (Table 3A). In vessels with

disagreement, CCTA showed stenosis ≥ 70% when QCA did not in 68 vessels, and QCA

identified stenosis ≥ 70% when CCTA did not in 15 vessels. By category of stenosis, CCTA

overestimated stenosis by >1 category in 29 vessels (8%) and underestimated stenosis by >1

category in 6 vessels (2%) (Table 3B). In these vessels, the discrepancy was in regions with

excessive calcification alone in 11, calcification plus other artifact in 15, due to other artifact

alone in 8, and due to overcall without artifact in 1 (Supplemental Table 1). Measures of

agreement were both significantly correlated with Cohen's Kappa 0.42, p<0.0001, and Kendall's

Tau 0.45, p<0.0001. Per-vessel comparison of ordinal stenosis categories (1-24%, 25-49%, 50-

69%, 70-99%, and 100%) showed exact agreement 43% of the time and agreement within one

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category of the QCA measurement 90% of the time. CCTA overestimated QCA in 145 vessels (42%) and underestimated QCA in 51 vessels (15%). For identification of QCA stenosis ≥ 70%, CCTA had a sensitivity of 79%, specificity of 75%, PPV 45%, NPV 93%, and accuracy 76% (Table 4).

Secondary Analyses

On a per-patient analysis, by CCTA, 39 (32%) of 119 patients had no stenosis ≥ 70% and 80 (68%) had at least one stenosis ≥ 70% (Table 5). QCA identified 66 (55%) patients without stenosis ≥ 70% and 53 (45%) with stenosis ≥ 70%. Agreement between CCTA and QCA was present in 88 patients (74%), and disagreement in 33 patients (26%) (Table 6A). In the patients with disagreement, CCTA showed stenosis ≥ 70% when QCA did not in 30 (25%) cases and showed no stenosis ≥ 70% when QCA identified significant stenosis in 3 (3%) cases. Examination by ordinal categories revealed no cases where CCTA underestimated the maximum stenosis by more than one category and 12 patients where the category was overestimated by more than one category (Table 6B). CCTA had a sensitivity 94%, specificity of 55%, PPV of 63%, NPV of 92%, and accuracy of 72% for predicting QCA ≥ 70% within patients (Table 4).

In the 168 segments in 105 vessels and 61 patients (51%) deemed uninterpretable by CCTA, 129 (76%) segments were due to calcification and 39 (24%) were due to inadequate visualization. Of the segments deemed uninterpretable due to calcification, 4 (2%) could not be assessed by QCA and were excluded from analysis. Inclusion of uninterpretable calcification segments in the analyses in the analysis yielded decreases in accuracy in all groups except for per-patient with uninterpretable as CCTA < 70% (Tables 7a and 7b). On a per vessel basis, when vessels with uninterpretable segments were considered as having obstruction, per-vessel accuracy was significantly reduced (8%) as was the specificity (11%), with minor increase in sensitivity (2%). On a per-patient basis, accuracy was reduced by 10%, specificity by 17%, with

a 1% increase in sensitivity. (Table 7a). In contrast, if these vessels were considered as non-significant, accuracy fell by only 1% per-vessel basis and increased by 2% on a per-patient basis, with the largest worsening being per-vessel sensitivity (6%) and per-patient negative predictive value (5%) and modest (1-2%) improvement in per-vessel PPV, and per-patient specificity and PPV (Table 7b). Overall, the effect of inclusion of the segments uninterpretable due to calcium was minimal when considering the segments as non-significant, which is concordant with the observation that by QCA, including these segments only increased the maximum in 8 (2%) vessels and 6 (5%) patients.

Regarding assessment for selection bias due to ICA, the proportion of patients with uninterpretable segments in significant locations (31 out of 119, 26%) was slightly higher in our population versus the population of patients with CACs > 1000 excluded from the study during the same time period (147 out of 702, 21%). Regarding differences between correctly and incorrectly scored vessels and patients, on a per-patient basis, the only significant variables were circumflex coronary calcium score and history of stroke; however, both of these were in an unexpected direction, that is the group with agreement had both higher circumflex CACs and more frequent stroke history, suggesting that this may not be meaningful. On a per-vessel basis, the vessel analyzed was significant, with left main having a much higher proportion of correctly assessed disease (36 correct, 2 incorrect). Notably, total and vessel-specific calcium measures, BMI, and acquisition factors all were not significantly different between correctly and incorrectly assessed groups (Supplemental table 2).

DISCUSSION

With increasing literature validation and changing guidelines, CCTA is undergoing a rapid increase in utilization.[11] It is likely that there will be a broadening of the pool of patients that are referred, including patients with higher calcification burden as the study becomes more

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widely used in patients with a high likelihood of CAD or known CAD. Further, in the earlier use of CCTA, patients with very high CAC scores (e.g., over 1000) often had CCTA studies canceled, while at the present time, most laboratories are performing CCTA studies in these patients. The main findings of this study of CCTA accuracy in patients with very extensive CAC were three-fold. First, the negative predictive value on the per-vessel and per-patient basis for stenosis on QCA remained high as was the sensitivity in the per-patient analysis; however, positive predictive value and specificity were low. Secondly, CCTA stenosis grading was within 1 category of the QCA in 90% of vessels, but not in a balanced manner: CCTA was significantly more likely to overestimate stenosis on QCA than to underestimate stenosis, and particularly in highly calcified vessels. Third, a large proportion of patients had uninterpretable segments, including in significant locations. Inclusion of these segments as significant resulted in large reductions in accuracy with only minor improvements in sensitivity, but inclusion as non-significant had minimal effect on testing characteristics. Given the higher proportion of patients with uninterpretable segments in significant locations versus the larger population, we may have some degree of selection bias towards more difficult to interpret cases within the CACs > 1000 population.

Previous studies have investigated the ability of CCTA to rule out significant stenosis in patients with varying levels of CAC, have also shown high sensitivity and negative predictive value but limited specificity and accuracy.[4, 12-23] Most of these studies, however, examined a range of calcification, but had small proportions of patients in high calcification groups. Only two studies were confined to high calcification (> 400 Agatston Units).[17, 23] In comparison with prior studies, with the entry criterion of CACs >1000 and an average coronary calcium score of over 1600, the patients in the current study had a much higher degree of calcification and over double the average score of the majority of the prior studies. The overall sensitivities on a per-patient basis of CCTA compared to QCA for ≥ 70% stenosis were high (94% excluding and 95%

including uninterpretable segments), and comparable to studies in which patients with extensive calcification have been excluded; however, specificity was lower.

Causes for CCTA inaccuracy have been previously assessed by Kruk et al., and included anatomical calcium factors including total calcium, length of calcium, thickness, volume, arc, and luminal diameter.[24] We did not have a similar granular anatomical detail in our study, but examined the effects of risk factors, demographics, and acquisition factors, which included the vessel-based calcium burden. The significant factors were limited to left circumflex calcium score and stroke on a per-patient basis; however, the directionality of this association (higher disease burden with better accuracy) leads us to doubt the relevance of this finding. On a per-vessel basis, while it was reassuring that left main assessments had high reliability, we were surprised that vessel-based calcium score did not affect accuracy. This may be related to the quantity of calcium being above a threshold where a difference could be observed – the mean per-vessel calcium score was 569, which given the inclusion of the left main as a vessel, may be underestimated for other territories. The mean total CACs in Kruk et al. was 433. We also observe that there was a strong tendency of our interpreters, despite their experience, toward an overestimation of percent stenosis. This overestimation might be expected to be higher in centers with less experienced interpreters and could result in over-referral to invasive angiography compared to functional studies.[25-27] The effect may be even more than our data suggest, as we have observed that identification of CCTA stenosis ≥ 50% (not only ≥ 70%) often prompts invasive angiography in patients with elevated risk at our center. Of further note, the scanners utilized in this study had higher spatial (0.24-0.33 mm) and temporal resolution (≤75 msec) than in prior studies. Both of these factors reduce calcium blooming by reduction of motion blur and partial volume effects.[1] The findings regarding overestimation of stenosis by CCTA might be greater if scanners with lower spatial and temporal resolution were utilized. On the other hand, impending novel hardware advances in CCTA technology using higher

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resolution CT or photon-counting CT detectors will likely improve visualization in highly calcified coronary arteries in the future.[28-31]

Our study has limitations. The necessary inclusion criteria of patients who had both CCTA and ICA is likely to result in selection bias. In comparing our study population to the overall population of patients with CCTA and CACs > 1000, there were moderate differences in the frequency of uninterpretable segments in significant locations. The effect of this bias may falsely elevate the sensitivity of our results at the cost of specificity. In our analysis of factors related to incorrect assessment, our data did not have enough granularity to examine the effect of very high CAC scores in individual plaques, which may have revealed different results than our per-vessel calcium burden. The distribution of CACs was heavily weighted to the 1000-1999 population, and therefore the study results may be less applicable to patients with higher CACs. The use of CCTA stenoses < 25% as an exclusion has a significant theoretical limitation: if underestimation by CCTA is frequent, these segments would have been excluded from the analyzed dataset. This would be particularly concerning if segments with >70% stenosis were underestimated; however, due to CCTA's high sensitivity, this is unlikely. This study measures anatomic relationships of CCTA and QCA. As known, degree of anatomical stenosis by either method does not necessarily correspond to functional significance measured by fractional flow reserve or perfusion methods. The clinical reading of CCTA employed a semiquantitative visual assessment which was compared to a quantitative invasive angiographic interpretation. Automated software assessment of the degree of stenosis on CCTA might optimize the comparison to QCA. We opted for a vessel-based analysis, instead of direct segmental comparisons to fully blind QCA readers to the CCTA results. Our primary analysis excluded uninterpretable segments. Including these segments in a secondary analysis resulted in significant differences in accuracy; though we recognize that arbitrary assignment to a positive or negative category does not reflect clinical uncertainty that may be conveyed in a report. Since optimal views for all segments were not uniformly performed in the clinical invasive

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angiography procedures, exact correspondence between segments on CCTA and QCA might have been compromised due to foreshortening or overlying vessels.

In conclusion, our study shows that CCTA in patients with CACs > 1000 remains effective to rule out significant stenosis on a per-vessel and per-patient basis but is associated with a systematic overestimation of stenosis, resulting in low positive predictive value. While performing CCTA in patients with very high CAC is reasonable and inevitable given expansion of guidelines regarding use of CCTA patients with a high likelihood of CAD, our results show that the limitations of accuracy and increased uncertainty in this patient population must be appreciated. Given concerns regarding over-referral to invasive angiography by CCTA, these results underscore the need for cardiac imagers to recognize and communicate reduced certainty when present in the categorization of percent stenosis in patients with severely elevated CACs. While there is a tendency of readers to avoid the category of "uninterpretable" regarding coronary segments, the results of this study suggest that this designation is frequently appropriate, and possibly underutilized. Strict interpretation of these segments as necessitating invasive assessment should not be advocated, as QCA measurements affecting maximal stenosis was relatively infrequent from these segments. High coronary calcium remains a significant barrier to accurate CCTA assessment.

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FIGURE LEGENDS

Figure 1. Consort diagram of screening and inclusion. Dashed arrows when changing

screening criteria from patient to segment and segment to vessel.

Figure 2. Examples of calcified lesions resulting in incorrect estimate by coronary CT

angiography (CCTA). Dashed arrow indicates same lesion in CCTA and cardiac catheterization.

(A) Left Panel: Calcified stenosis in the proximal right coronary artery (RCA) graded as 70-99%

stenosis by CCTA. Right Panel: Cardiac catheterization view with 46% stenosis by quantitative

coronary angiography (QCA). (B) Left Panel: Calcified stenosis in the left circumflex artery (LCx)

graded as 70-99% stenosis by CCTA. Right Panel: Cardiac catherization view with 11%

stenosis by QCA. (C) Left Panel: Calcified stenosis in the left anterior descending artery graded

as 70-99% stenosis by CCTA. Right Panel: Cardiac catherization view with 32% stenosis by

QCA. (D) Left Panel: Calcified stenosis in the left main coronary artery graded as 50-69%

stenosis by CCTA. Right Panel: Cardiac catherization view with 6% stenosis by QCA. (E) Left

Panel: Calcified stenosis in the mid RCA, graded as 25-49% stenosis by CCTA. Right Panel:

Cardiac catheterization view with 97% stenosis by QCA. (F) Left Panel: Calcified stenosis in the

LCx graded as 25-49% stenosis by CCTA. Right Panel: Cardiac catherization view with 93%

stenosis by QCA.

TABLES

Table 1. Baseline demographic information for included patients, scan parameters, and coronary segment distribution. CACs: Coronary Artery Calcium Score, BMI: Body Mass Index, LAD: Left anterior descending coronary artery, LCX: Left circumflex coronary artery, RCA: Right coronary artery.

Characteristic	Value
N (Patients)	119
N (Vessels)	346
Age (years)	68.8±9.8
Male	97 (82%)
Median CAC (Agatston)	1616 (1221-2118)
CAC 1000-1999 (N Patients)	86 (72%)
CAC 2000-2999 (N Patients)	21 (18%)
CAC > 3000 (N Patients)	12 (10%)
BMI (kg/m2)	26.6 (24.4-30.1)
Obese, BMI ≥ 30	31 (26%)
Presence of symptoms	86 (72%)
Heart Rate (beats per min)	65.6±14.1
Contrast Volume (ml)	100 (100-100)
Beta Blocker Premedication	29 (24%)
Nitroglycerin Premedication	104 (87%)
N (Segments)	726
Left Main	38 (5%)
LAD	280 (39%)
LCX	171 (24%)
RCA	237 (33%)

Table 2. Distribution of per-vessel stenosis segments by ordinal category and corresponding

QCA measurements.

	CCTA Per-Vessel Maximum Stenosis Frequency (percent)	QCA Per-Vessel Maximum Stenosis Frequency (percent)	%QCA Per-Vessel Maximum Stenosis by CCTA group
1-24%	N/A	12 (3%)	N/A
25-49%	118 (34%)	163 (47%)	42 ± 15%
50-69%	105 (30%)	102 (29%)	48 ± 14%
70-99%	99 (29%)	44 (13%)	63 ± 21%
100%	24 (7%)	25 (7%)	86 ± 21%

CCTA: Coronary CT angiography, QCA: Quantitative coronary angiography.

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Table 3. Comparison of stenosis categories by per-vessel maximum stenosis. Coronary CT angiography versus invasive quantitative coronary angiography. A: Comparison by <70% and ≥ 70% stenosis. B: Comparison by ordinal stenosis categories; black-shaded squares with exact match, grey within one category, and white outside of one category. CCTA: Coronary CT angiography, QCA: Quantitative coronary angiography.

A.

CCTA	QCA	
	< 70%	**≥ 70%**
< 70%	208	15
≥ 70%	68	55

B.

CCTA	QCA				
	1-24%	**25-49%**	**50-69%**	**70-99%**	**100%**
1-24%	N/A	N/A	N/A	N/A	N/A
25-50%	9	78	25	6	0
50-69%	1	61	34	9	0
70-99%	2	21	41	24	11
100%	0	3	2	5	14

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Table 4. Testing characteristics of analyses using per-vessel and per-patient approaches.

Reference standard quantitative coronary angiography stenosis ≥ 70%.

	Per-Vessel	Per-Patient
Sensitivity	79%	94%
Specificity	75%	55%
Positive Predictive Value	45%	63%
Negative Predictive Value	93%	92%
Accuracy	76%	72%

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Table 5. Distribution of per-patient stenosis segments by ordinal category and corresponding QCA measurements.

	CCTA Per-Patient Stenosis Frequency (percent)	QCA Per-Patient Stenosis Frequency (percent)	%QCA Per-Patient Stenosis by CCTA group
1-24%	N/A	0 (0%)	N/A
25-49%	6 (5%)	24 (20%)	45.2 ± 11.3%
50-69%	33 (28%)	42 (35%)	53.9 ± 12.8%
70-99%	59 (50%)	31 (26%)	71.2 ± 18.8%
100%	21 (18%)	22 (18%)	90.2 ± 16.6%

Table 6. Comparison of stenosis categories by per-patient maximum stenosis. Coronary CT angiography versus invasive quantitative coronary angiography. A: Comparison by <70% and ≥ 70% stenosis. B: Comparison by ordinal stenosis categories; black-shaded squares with exact match, grey within one category, and white outside of one category. CCTA: Coronary CT angiography, QCA: Quantitative coronary angiography.

A.

		QCA	
		< 70%	**≥ 70%**
CCTA	**< 70%**	36	3
	≥ 70%	30	50

B.

		QCA			
		25-49%	**50-69%**	**70-99%**	**100%**
CCTA	**25-50%**	3	3	0	0
	50-69%	13	17	3	0
	70-99%	8	18	25	8
	100%	0	4	3	14

Table 7. Testing characteristics of analyses using per-vessel and per-patient approaches with the addition of segments deemed uninterpretable by CCTA due to calcification. A: Analysis with uninterpretable CCTA segments assigned to ≥ 70% stenosis. B. Analysis with uninterpretable CCTA segments assigned to < 70% stenosis. Reference standard quantitative coronary angiography stenosis ≥ 70%.

A.

	Per-Vessel + Uninterpretable	Per-Patient + Uninterpretable
Sensitivity	81%	95%
Specificity	64%	38%
Positive Predictive Value	40%	60%
Negative Predictive Value	92%	88%
Accuracy	68%	66%

B.

	Per-Vessel + Uninterpretable	Per-Patient + Uninterpretable
Sensitivity	73%	92%
Specificity	75%	57%
Positive Predictive Value	46%	68%
Negative Predictive Value	91%	87%
Accuracy	75%	74%

Supplemental Table 1. Individual review of 35 vessels with greater than one category of discrepancy between CCTA and QCA. Artifact definitions were based on previous literature.[1] Highly calcified lesions were defined as occupying > 70% of the lumen in the region of discrepancy with significant blooming. Respiratory motion was defined as complete through-plane misregistration artifact, cardiac motion was defined as a cardiac-only through-plane misregistration or in-plane blurring or streaking. Slab artifact was identified by contrast bands in the ventricles at the same level as the discrepant lesion. Quantum mottle was defined by high noise. Poor contrast enhancement was defined by low difference between luminal contrast intensity and surrounding myocardium. Streak artifact was defined as streaking or shadowing due to metal in the field of view at the same level as the lesion in question. CCTA: Coronary CT angiography, QCA: Quantitative coronary angiography, ICD: Implantable cardioverter-defibrillator, LM: Left main coronary artery, LAD: Left anterior descending coronary artery, LCX: Left circumflex coronary artery, RCA: Right coronary artery.

	Vessel	CCTA Stenosis	QCA Stenosis	Highly Calcified Lesion	Respiratory Motion	Cardiac Motion	Slab Artifact	Quantum Mottle	Poor Contrast Enhancement	Streak Artifact	Adjudication
	LM	50-69%	1-24%	1	0	0	0	0	1	0	High calcification, poor contrast
	LCX	70-99%	1-24%	1	0	0	1	0	0	0	High calcification, plus slab
	LM	70-99%	1-24%	1	0	0	1	0	0	0	High calcification, plus slab
	LAD	70-99%	25-49%	1	0	0	0	0	0	0	High calcification
	LAD	70-99%	25-49%	0	0	0	0	0	0	0	CCTA Overcall
	LAD	70-99%	25-49%	1	0	0	0	0	0	0	CCTA Overcall
	LAD	70-99%	25-49%	1	0	0	0	0	0	0	High calcification
	LAD	70-99%	25-49%	1	0	0	0	0	0	0	High calcification
CCTA > QCA	LAD	70-99%	25-49%	1	0	0	0	1	1	0	High calcification, plus noise and poor contrast
	LCX	70-99%	25-49%	1	0	0	1	0	0	0	Slab artifact
	LCX	70-99%	25-49%	1	0	0	0	0	0	0	High calcification
	LCX	70-99%	25-49%	1	0	0	0	0	0	0	High calcification
	LCX	70-99%	25-49%	0	0	0	0	0	1	0	Poor contrast
	LCX	70-99%	25-49%	1	0	0	1	0	0	0	High calcification, plus slab
	LCX	70-99%	25-49%	1	0	0	1	0	0	0	High calcification, plus slab
	LCX	70-99%	25-49%	1	0	0	1	0	0	0	High calcification, plus slab
	LCX	70-99%	25-49%	1	0	0	0	0	0	0	High calcification
	RCA	70-99%	25-49%	0	0	1	1	1	1	0	High noise, poor contrast

	Vessel	QCA	CCTA								Description
	RCA	70-99%	25-49%	0	0	1	1	0	0	0	Slab artifact
	RCA	70-99%	25-49%	1	0	0	1	0	0	0	High calcification, plus slab
	RCA	70-99%	25-49%	0	0	0	0	0	0	1	ICD lead artifact
	RCA	70-99%	25-49%	0	0	0	1	0	0	0	Slab artifact
	RCA	70-99%	25-49%	1	0	0	0	0	0	1	ICD lead artifact
	RCA	70-99%	25-49%	1	0	0	1	0	1	0	High calcification, poor contrast, plus slab
	LCX	100%	25-49%	0	0	0	1	0	0	0	Slab artifact
	LCX	100%	25-49%	1	0	0	1	0	1	0	High calcification, plus slab
	LCX	100%	25-49%	0	0	0	0	1	1	0	High noise, poor contrast
	LAD	100%	50-69%	1	0	0	0	0	0	0	High calcification
	LAD	100%	50-69%	1	0	0	0	0	0	0	High calcification
QCA > CCTA	LCX	25-49%	70-99%	1	0	0	0	0	0	0	High calcification
	LCX	25-49%	70-99%	1	0	0	0	0	0	0	High calcification
	RCA	25-49%	70-99%	1	0	1	1	0	0	0	Calcification and slab at bifurcation
	RCA	25-49%	70-99%	1	0	1	1	0	0	0	High calcification, plus slab
	RCA	25-49%	70-99%	1	0	1	1	0	0	0	Coronary motion, plus slab
	RCA	25-49%	70-99%	0	0	1	1	0	1	0	Coronary motion, plus slab

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Supplemental Table 2. Comparison of patients and vessels in agreement and disagreement by coronary CT angiography (CCTA) and quantitative coronary angiography (QCA). BMI = Body Mass Index. CACs = Coronary Artery Calcium Score. CAD = Coronary Artery Disease. kVp = Kilovoltage peak.

A. Per-patient continuous variables

Per-Patient	CCTA and QCA Agreement (n= 86)	CCTA and QCA Discrepancy (n = 33)	p value
Age	68.744 (9.411)	68.939 (10.788)	0.923
BMI	28.200 (4.476)	26.734 (4.685)	0.117
Contrast Volume	102.706 (22.248)	102.879 (21.688)	0.97
Max Heart Rate	67.221 (14.931)	65.258 (15.769)	0.544
CACs	1882.035 (923.549)	1674.818 (640.189)	0.239
CACs plus valvular and aortic calcium	4308.809 (4167.710)	3873.633 (2532.257)	0.576
Left Main CACs	76.136 (107.442)	79.085 (145.705)	0.904
Left Anterior Descending CACs	726.993 (429.130)	622.148 (306.282)	0.202
Circumflex CACs	**426.800 (444.069)**	**262.067 (233.453)**	**0.045**
Right Coronary Artery CACs	652.106 (542.320)	711.518 (423.421)	0.572

B. Per-patient categorical variables

Per-Patient		CCTA and QCA Agreement (n= 86)	CCTA and QCA Discrepancy (n = 33)	p value
Sex	Male	72 (83.7%)	25 (75.8%)	0.316
	Female	14 (16.3%)	8 (24.2%)	
Symptoms	Present	61 (70.9%)	25 (75.8%)	0.598
	Absent	25 (29.1%)	8 (24.2%)	
Hypertension	Absent	24 (27.9%)	5 (15.2%)	0.147
	Present	62 (72.1%)	28 (84.8%)	
Hyperlipidemia	Absent	24 (27.9%)	9 (27.3%)	0.945
	Present	62 (72.1%)	24 (72.7%)	
Diabetes	Absent	57 (66.3%)	24 (72.7%)	0.499
	Present	29 (33.7%)	9 (27.3%)	
Insulin Use	Absent	78 (90.7%)	30 (90.9%)	0.972
	Present	8 (9.3%)	3 (9.1%)	
Family History of CAD	Absent	53 (61.6%)	17 (51.5%)	0.316
	Present	33 (38.4%)	16 (48.5%)	
Dialysis	Absent	79 (91.9%)	31 (93.9%)	0.701
	Present	7 (8.1%)	2 (6.1%)	
Peripheral Arterial Disease	Absent	79 (91.9%)	32 (97.0%)	0.319
	Present	7 (8.1%)	1 (3.0%)	
History of Smoking	Absent	79 (91.9%)	29 (87.9%)	0.502
	Present	7 (8.1%)	4 (12.1%)	
History of Stroke	Absent	**75 (87.2%)**	**33 (100.0%)**	**0.031**
	Present	**11 (12.8%)**	**0 (0.0%)**	
Acquisition Mode	Retrospective	60 (69.8%)	22 (66.7%)	0.267
	Prospective	26 (30.2%)	10 (30.3%)	
Beta Blocker Premedication	No	64 (74.4%)	26 (78.8%)	0.619

	Yes	22 (25.6%)	7 (21.2%)	
Nitroglycerin Premedication	No	11 (12.8%)	4 (12.1%)	0.922
	Yes	75 (87.2%)	29 (87.9%)	
kVp	120	82 (95.3%)	31 (93.9%)	0.623
	110	1 (1.2%)	0 (0.0%)	
	100	2 (2.3%)	2 (6.1%)	
	80	1 (1.2%)	0 (0.0%)	

C. Per-vessel continuous variables

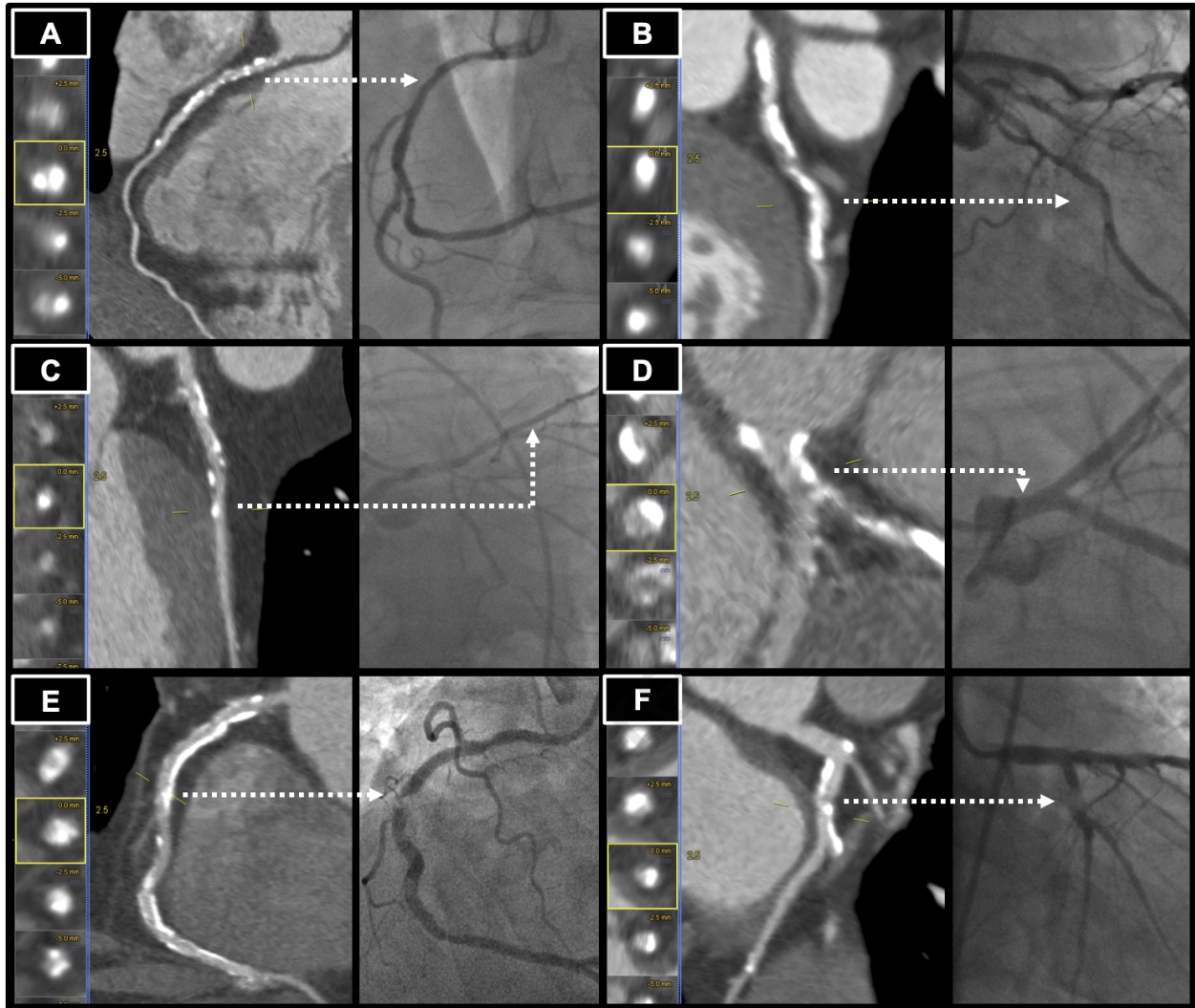| Per-Vessel	CCTA and QCA Agreement (n = 263)	CCTA and QCA Discrepancy (n = 33)	p value
Age	68.867 (9.618)	68.940 (9.128)	0.951
BMI	27.766 (4.464)	27.648 (4.321)	0.832
Contrast Volume	103.192 (22.848)	100.904 (17.911)	0.405
Max Heart Rate	66.213 (14.281)	65.901 (15.776)	0.875
CACs	1831.930 (856.121)	1857.894 (878.979)	0.811
CACs plus valvular and aortic calcium	4204.887 (3987.674)	3943.154 (3058.993)	0.583
Vessel Calcium Score	553.003 (451.995)	619.567 (421.815)	0.236

D. Per-vessel categorical variables

		CCTA and QCA Agreement (n = 263)	CCTA and QCA Discrepancy (n = 33)	p value
Vessel Territory	**LM**	**36 (13.7%)**	**2 (2.4%)**	**0.035**
	LAD	**84 (31.9%)**	**30 (36.1%)**	
	LCX	**63 (24.0%)**	**25 (30.1%)**	
	RCA	**80 (30.4%)**	**26 (31.3%)**	
Sex	Male	218 (82.9%)	68 (81.9%)	0.84
	Female	45 (17.1%)	15 (18.1%)	
Symptoms	Absent	70 (26.6%)	23 (27.7%)	0.844
	Present	193 (73.4%)	60 (72.3%)	
Hypertension	Absent	74 (28.1%)	17 (20.5%)	0.167
	Present	189 (71.9%)	66 (79.5%)	
Hyperlipidemia	Absent	74 (28.1%)	20 (24.1%)	0.471
	Present	189 (71.9%)	63 (75.9%)	
Diabetes	Absent	185 (70.3%)	56 (67.5%)	0.62
	Present	78 (29.7%)	27 (32.5%)	
Insulin Use	Absent	240 (91.3%)	74 (89.2%)	0.565
	Present	23 (8.7%)	9 (10.8%)	
Family history of CAD	Absent	149 (56.7%)	46 (55.4%)	0.844
	Present	114 (43.3%)	37 (44.6%)	
Dialysis	Absent	244 (92.8%)	77 (92.8%)	0.999
	Present	19 (7.2%)	6 (7.2%)	
Peripheral Arterial Disease	Absent	241 (91.6%)	81 (97.6%)	0.063
	Present	22 (8.4%)	2 (2.4%)	
History of Smoking	Absent	241 (91.6%)	73 (88.0%)	0.313
	Present	22 (8.4%)	10 (12.0%)	
History of Stroke	Absent	239 (90.9%)	78 (94.0%)	0.374
	Present	24 (9.1%)	5 (6.0%)	
Acquisition Mode	Retrospective	190 (72.2%)	51 (61.4%)	0.114
	Prospective	71 (27.0%)	30 (36.1%)	

Beta Blocker Premedication	No	199 (75.7%)	63 (75.9%)	0.965
	Yes	64 (24.3%)	20 (24.1%)	
Nitroglycerin Premedication	No	33 (12.5%)	10 (12.0%)	0.904
	Yes	230 (87.5%)	73 (88.0%)	
kVp	120	250 (95.1%)	80 (96.4%)	0.807
	110	3 (1.1%)	0 (0.0%)	
	100	7 (2.7%)	2 (2.4%)	
	80	3 (1.1%)	1 (1.2%)	

Patients with CCTA, CACs > 1000
assessed for eligibility
(n = 821)

Patients Excluded (n = 702)
- No cardiac catheterization within 90 days (n = 645)
- Missing data (n = 2)
- Previous stenting (n = 43)
- Previous CABG (n = 12)

Patients included
(n = 119)

Segments assessed for eligibility
(n = 2058)

Segments Excluded (n = 1332)
- No stenosis ≥ 25% (n = 1162)
- Uninterpretable due to poor visualization (n = 39)
- Uninterpretable due to extensive calcification (n = 129)
- QCA unable to visualize segments (n = 2)

Segments included
(n = 726)

Vessels included
(n = 346)

Conflict of Interest

All authors report no conflicts of interest

Table of Contents Summary:

The accuracy of coronary CTA (CCTA) in patients with coronary calcium score > 1000 and invasive coronary angiography (ICA) was assessed by comparing visual CCTA reading to quantitative coronary analysis (QCA) of ICA for per-vessel and per-patient significant stenosis (≥ 70%) in 119 patients. CCTA identification of QCA-based significant stenosis resulted in a per vessel sensitivity of 79%, specificity of 75%, positive predictive value (PPV) of 45%, negative predictive value (NPV) of 93%, and accuracy 76%. Per-patient analysis had sensitivity 94%, specificity 55%, PPV 63%, NPV 92%, and accuracy 72%. Secondary analyses were performed to identify causes for reduced accuracy.