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Prospective, Head-to-Head Comparison of Quantitative Coronary Angiography, Quantitative Computed Tomography Angiography, and Intravascular Ultrasound for the Prediction of Hemodynamic Significance in Intermediate and Severe Lesions, Using Fractional Flow Reserve as Reference Standard (from the ATLANTA I and II Study)

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Abstract

The objective of this study was to compare the diagnostic accuracy of quantitative coronary angiography (QCA), coronary computed tomography angiography (CTA), and intravascular ultrasound (IVUS) with fractional flow reserve (FFR) measurements. Eighty-five lesions (40% to 99% diameter stenosis) in 85 patients were prospectively interrogated by QCA, CTA, IVUS, and FFR. Minimal lumen diameter (MLD), percent diameter stenosis (%DS), minimal lumen area (MLA), and percent area stenosis (%AS) were measured. Correlation, receiver operating characteristic analysis, kappa statistics, and multivariable logistic regression was used to assess relation between anatomic measurements and FFR. Average age was 61.3 ± 7.8 ; 62% were men. QCA-derived mean %DS was $55.3\% \pm 19.5\%$; mean FFR 0.81 ± 0.17 ; 27% had FFR < 0.75 . QCA had the strongest correlation, followed by CTA and then IVUS for MLD ($r = 0.67, 0.47$, and 0.29 , respectively) and for %DS ($r = -0.63, -0.52$, and -0.22 , respectively); QCA-derived MLD had area under the curve of 0.96, with 95% sensitivity and 82% specificity. Cut-point, area under the curve, sensitivity, and specificity for CTA-MLA and IVUS-MLA were 3.11 mm^2 , 0.86, 81%, and 81% and 2.68 mm^2 , 0.75, 70%, and 80%. In multivariable analysis for each modality, MLD on QCA (odds ratio [OR]: 0.002), %AS on CTA (OR: 1.09) and MLA on IVUS (OR: 0.28) remained

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independent predictors. In conclusion, in intermediate-to-severe lesions, QCA-, CTA-, and IVUS-derived quantitative anatomic measurements correlated with FFR. CTA-derived cut-points were similar to respective measurements on QCA and IVUS and had similar or better diagnostic performance compared with IVUS.

Progressively increasing atherosclerotic plaque burden leads to increasing luminal stenosis and thus to hemodynamic compromise across lesions. Anatomic features of atherosclerotic plaque can be imaged with intravascular ultrasound (IVUS) and coronary computed tomography angiography (CTA), whereas luminal stenosis can be quantified by quantitative coronary angiography (QCA), CTA, and IVUS. Previous studies have shown that anatomic measurements by QCA,¹ CTA,^{2,3} and IVUS⁴ have relatively poor accuracy for the prediction of hemodynamically significant stenosis as measured by fractional flow reserve (FFR). QCA-, CTA- and IVUS-derived luminal measurements have not previously been compared head-to-head for the prediction of FFR.

Methods

The ATLANTA (Assessment of Tissue characteristics, Lesion morphology and hemodynamics by Angiography with fractional flow reserve, intravascular ultrasound and virtual histology and Non-invasive computed Tomography in Atherosclerotic plaques; clinicaltrials.gov identifier NCT #00817102) I-II study was an investigator-initiated, prospective, single-center study, approved by the Institutional Review Board of Piedmont Healthcare. Patients with signs and symptoms of myocardial ischemia were included and prospectively CTA, x-ray angiography (XRA), IVUS/virtual histology (VH), and FFR measurements were performed in a prespecified study lesion with 40% to 99% luminal diameter stenosis. One prespecified, isolated, non-tandem study lesion was prospectively identified in each patient based on either a clinically performed XRA or CTA, and this lesion underwent IVUS and FFR, as well as the other imaging modality. If the clinically indicated invasive angiography was performed first, the patient then underwent research CTA; if the clinically indicated CTA was performed first, the patient was then referred for invasive angiography, IVUS, and FFR. In Phase I, we enrolled patients with intermediate lesions (40% to 70%) and obstructive lesions (>70%) in Phase II. The initial 60 patients were scanned on a 32 × 2 multidetector computed tomography scanner system (Siemens Somatom 64, Forchheim, Germany), and 25 patients were scanned on a 320-detector row system (Toshiba America Medical Systems, Otawara, Japan). Contrast-enhanced CTA on a 32 × 2 scanner system was performed using retrospective electrocardiogram gating as previously described.⁵ Coronary image acquisition on the 320-slice platform was performed using intravenous contrast (Visipaque, GE Amersham Health, Little Chalfont, Buckinghamshire, United Kingdom). We used a prospectively triggered, volumetric image acquisition method. Gantry rotation was 350 milliseconds, tube voltage 120 kV, tube current 122 to 500 mA. Images were reconstructed at 0.5-mm intervals. Deidentified data sets were transferred to a workstation (Vitrea 2.0; Vital Images; Minnetonka, Minnesota) and were analyzed using our 3-dimensional approach by a single interpreter. In each study lesion, we quantitatively measured minimal lumen diameter (MLD), percent diameter stenosis (%DS), minimal lumen area (MLA), and percent area stenosis (%AS) in a 3-dimensional fashion.

Invasive XRA was performed based on standard institutional protocols, with 5 views of the left coronary, 2 views of the right coronary, and 2 orthogonal views of the target lesion. Deidentified angiographic data sets were analyzed by a single interpreter, as previously published (Encompass, version 2.0, B17, HeartLab, Westerly, Rhode Island). MLD was measured in the view with the greatest degree of stenosis. Proximal and distal reference diameters were measured and averaged to calculate %DS.

After intracoronary injection of nitroglycerin (mean total dose per case: 561.5 mcg) and placing a guiding catheter, a 3.2F 20-mHz ultrasound catheter (Eagle Eye; Volcano Inc.; Rancho Cordova, California), was advanced in the target lesion. Automated pullback was performed at a rate of 0.5 mm/s (R-100; Volcano Inc.). De-identified IVUS data sets were analyzed using a dedicated software (pcVH 3.0.394, Volcano Inc.) as previously validated. We measured MLD, %DS, MLA, and %AS; percent stenosis was calculated based on a proximal and distal reference segment defined as <40% plaque burden.

After obtaining aortic pressure measurements as the proximal reference, a pressure wire (Volcano Prime Wire, Volcano Inc.) was advanced 2 cm distal to the lesion. Intracoronary adenosine (mean total dose per case: 441 mcg) was injected and the lowest pressure was recorded. Measurements were repeated 3 times, and the mean FFR was calculated.

Normally distributed continuous variables are expressed as mean $\pm$ SD; non-normally distributed variables as median (interquartile range). The primary end point was the correlation between anatomic measurements (MLD, %DS, MLA, and %AS) and FFR, each expressed as a continuous variable. Accordingly, the primary statistical procedure for the analysis was correlation analysis. The secondary end points were the diagnostic accuracy of anatomic measurements to predict obstructive FFR, defined as FFR $\leq$ 0.75. Accordingly, the secondary statistical procedure was receiver operating characteristics (ROC) analysis to determine optimal cut-point and diagnostic performance for each parameter and to compare the area under the ROC curve (AUC) among QCA-, IVUS-, and CTA-derived parameters. Finally, we performed multivariable, stepwise logistic regression analysis for each modality (QCA: MLD, %DS, lesion length; CTA: MLD, %DS, MLA, %AS, lesion length; and IVUS: MLD, %DS, MLA, %AS, lesion length, and plaque burden) to predict obstructive FFR.

Results

General demographic features of the population are listed in Table 1. In the 85 patients enrolled, the mean age was 61.3 ± 7.8 years; 62% were men. Interpretable QCA, CTA, IVUS, and FFR data were available in 84, 83, 70, and 82 patients. The distribution of the coronary lesions in the 85 patients is listed in Table 2. Average %DS by QCA, CTA, and IVUS was $55.3\% \pm 19.5\%$, $54.4\% \pm 19.3\%$, and $30.3\% \pm 11.0\%$. In the entire cohort, mean FFR was 0.81 ± 0.17 , and 23 patients (27%) had an FFR $\leq$ 0.75. Example of a hemodynamically nonobstructive and obstructive lesion of CTA and IVUS are shown in Figure 1.

Results of correlation analysis among QCA-, CTA-, and IVUS-derived anatomic measurements and FFR are listed in Table 3 and shown Figures 2 and 3. For MLD and

%DS, QCA had the strongest correlation to FFR, followed by CTA- and IVUS-derived MLD and %DS. For MLA and %AS, CTA had stronger correlation to FFR, compared with IVUS.

Results of the ROC analysis of CTA-, QCA-, and IVUS-derived anatomic parameters to predict obstructive FFR are listed in Table 4 and shown Figure 4.

For MLD measurements, QCA had best predictive accuracy, followed by CTA and IVUS by AUC, accuracy, and kappa statistics. Optimal MLD cut-points were similar between QCA and CTA (1.15 mm and 1.11 mm), whereas IVUS-derived MLD cut-point was higher (1.73 mm).

For %DS measurements, QCA had best predictive accuracy, followed by CTA and IVUS, on the basis of AUC and kappa statistics; on the basis of accuracy, IVUS was superior to CTA (83% vs 76%). Optimal %DS cut-points were similar between QCA and CTA (64% and 62%), whereas IVUS-derived %DS cut-point was lower (44%).

For MLA measurements, CTA had slightly better predictive accuracy compared with IVUS by AUC, accuracy, and kappa statistics. Optimal MLA cut-points were similar, although CTA-derived MLA was higher (3.11 mm²) compared with IVUS-derived MLA (2.68 mm²).

For %AS measurements, CTA had slightly better predictive accuracy compared with IVUS by AUC and kappa statistics; however, IVUS was superior on the basis of accuracy. Optimal %AS cut-points was similar between CTA and IVUS (64% and 69%).

When we directly compared AUC's (Figure 4), QCA-derived MLD was superior to CTA MLD ($p = 0.02$) and IVUS MLD ($p = 0.003$), whereas AUC's for CTA MLD and IVUS MLD were similar ($p = 0.85$). AUC for QCA %DS was superior to CTA %DS ($p = 0.028$) and to IVUS %DS ($p = 0.001$), and CTA %DS was superior to IVUS %DS ($p = 0.046$). AUC for CTA MLA and IVUS MLA were not different ($p = 0.34$), whereas AUC for CTA %AS was significantly higher than for IVUS %AS (0.012; Figure 4).

In multivariable analysis, only MLD on QCA (odds ratio: 0.0017), %AS on CTA (odds ratio: 1.09), and MLA on IVUS (odds ratio: 0.28) remained independent predictors of FFR <0.75 (Table 5).

Discussion

This study is the first prospective, head-to-head comparison of 3 anatomic modalities (QCA, CTA, and IVUS) against FFR and included intermediate and severe lesions. The study has 3 main findings. First, QCA had the strongest correlation and the best predictive accuracy for obstructive FFR (< 0.75) followed by CTA and then IVUS. Second, CTA-derived cut-points to predict obstructive FFR by ROC analysis were similar to QCA and IVUS, providing internal validity to the results. Third, CTA-derived cut-points to predict obstructive FFR were similar to historical cut-points for QCA and IVUS, providing external validity to the results.

Overall, our study confirmed that QCA-derived measurements perform relatively well for the prediction of FFR and validates the continued use of invasive angiography for anatomic assessment of stenosis; the optimal ROC-derived cut-point was 1.15 mm and similar to historical cut-points⁵ with a sensitivity and specificity of 95% and 82% and an accuracy of 85%. QCA measurements were slightly better to predict FFR of 0.75, compared with 0.80. One of the main novel findings of our study was that quantitative CTA measurements performed similarly to QCA- and IVUS-derived anatomic measurements of stenosis, suggesting that CTA may be used as an alternative to assess luminal stenosis and to serve as gatekeeper to invasive FFR measurements in patients presenting with chest pain syndromes. CTA-derived optimal MLA cut-point was 3.11 mm², which falls in the historically reported range of MLA values on IVUS (2.7 to 4.0 mm²).²

In our study, the diagnostic performance of CTA was better than previously reported.^{2,3} Sarno et al. evaluated the diagnostic accuracy of CTA based on visual grading of stenosis (50% diameter stenosis) using FFR 0.75 as reference for obstructive coronary artery disease in 116 vessels of 81 patients.³ The sensitivity and specificity of CTA was 79% and 64%. In our study, the ROC-derived % DS cut-points of 62% had a sensitivity and specificity of 81% and 75%, and the ROC-derived MLA cut-point of 3.11 mm² had a sensitivity and specificity of 81% and 81%. In another study, Meijboom et al. evaluated 89 lesions in 79 patients by XRA and QCA and by visual and quantitative CTA, using 50% diameter stenosis as cut-point and using FFR 0.75 as the reference for obstructive coronary artery disease.² Accuracy of CTA was lower in their study compared with ours; kappa statistic was 0.16 for visual CTA analysis and 0.20 for quantitative CTA, which were lower than kappa values for %DS (kappa = 0.48) or MLA (kappa = 0.56). They found that visual CTA analysis had higher sensitivity (94%) and quantitative CTA analysis had higher specificity (75%), which was the same as the specificity of quantitative %DS in our study (75%). Importantly, XRA and QCA had poor diagnostic performance in this study, with respective kappa statistics of 0.15 and 0.25, which are lower than those found in our study. Finally, correlation coefficients between quantitative QCA-derived and CTA-derived %DS were lower compared with those found in our study ($r = -0.30$ vs -0.63 for QCA and $r = -0.32$ vs -0.52 for CTA).

Potential explanations for improved diagnostic accuracy of CTA in our measurements include that we used a per-lesion analysis, in which a prespecified lesion was interrogated with all 4 modalities, and we used a fully quantitative, 3-dimensional analysis of the entire vessel segment, rather than 1 cross-sectional slice, using our validated analysis method.⁵⁻⁷ In addition, more advanced scanner and postprocessing technology were used.

Of the IVUS-derived measurements, MLD had the strongest correlation to FFR, whereas MLA was the best predictor by ROC and multivariable analysis. Importantly, our MLA cut-point (2.68 mm²) by ROC analysis was similar to values that had been previously reported.^{8,9} Interestingly, MLA cut-points to predict FFR had been decreasing since the original publications. In 1999, Takagi et al. reported an MLA cut-point of 3.0 mm² was optimal,⁴ and in 2001, Briguor et al. described a cut-point of 4.0 mm².¹⁰ However, recent studies reported smaller MLA cut-points; these studies include Kang et al.,⁹ 2.4 mm²; Koo

et al.,⁸ 2.75 mm²; and Lee et al.,¹¹ 2.0 mm². Our study shows an MLA cut-point of 2.68 mm².

Furthermore, our IVUS-related AUC, overall accuracy, and kappa statistics were similar to those reported in the past, although the correlation was lower than in previous reports. This may be explained by an important difference between our study and most previous ones: our study included intermediate and severe lesions. Given the size of the IVUS catheter, the most severe lesions cannot be crossed, and IVUS measurements cannot be obtained. This has introduced a bias in which even the most severe lesions could be interrogated by CTA, thus increasing its performance while decreasing the accuracy of IVUS.

Importantly, ROC-derived cut-points were similar between the 3 independent imaging modalities, thus lending internal consistency to the data. QCA- and CTA-derived MLD and % DS were almost identical (1.15 mm and 1.11 mm for MLD and 64% and 62% for %DS). Also, CTA-derived MLA was higher compared with IVUS-derived MLA (3.11 vs 2.68 mm). This may be explained by our previously published data that CTA overestimates MLA compared with IVUS by 27%.⁵

There are important clinical implications of this study. On the basis of recent national guidelines, the assessment of functional significance of lesions should guide management decisions for medical therapy and revascularization.¹² We found that the predictive accuracy of CTA-derived anatomic measurements of stenosis severity had similar diagnostic accuracy compared with QCA and IVUS. This suggests that in the appropriate clinical setting, CTA as a first-line test may be used to triage patients for medical therapy, versus invasive evaluation with FFR, and potential revascularization. In the future, novel, computational fluid dynamics approaches may supplement the anatomic information obtained by CTA by providing accurate estimation of FFR based on the resting CTA data set alone.¹³

Our study has several limitations. First, it was a single-center study. Second, the most severe lesions could not be crossed by the IVUS catheter, and this may have resulted in slightly lower correlation between FFR and IVUS. Also, many of the computed tomography scans were performed on a 32 × 2 multislice scanner; more updated scanner platforms and advanced image acquisition techniques are now available.

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Figure 1.

Nonobstructive and obstructive lesion by CTA and IVUS. A calcified plaque causing moderate luminal stenosis by coronary CTA criteria is shown (*long axis, A; short axis, B*) and the corresponding IVUS/VH in long axis (*C*) and short axis (*D*). FFR reveal no hemodynamic compromise ($\text{FFR} = 0.92$) (*E*). A noncalcified plaque causing severe stenosis is shown in long axis (*F*) and short axis (*G*) and corresponding long axis (*H*) and short axis (*I*) IVUS/VH. FFR reveal an obstructive lesion ($\text{FFR} = 0.63$) (*J*).

Figure 2.

Linear correlations between CTA- and IVUS-derived anatomic measurements and FFR.

Figure 3.

Scatterplots demonstrating the relation between QCA-, CTA-, and IVUS-derived luminal measurements and FFR in individual Patients. Scatterplots demonstrating the distinguishing ability of QCA MLD (A), QCA %DS (B), CTA MLD (C), CTA %DS (D), CTA MLA (E), CTA %AS (F), IVUS MLD (G), IVUS %DS (H), IVUS MLA (I), and IVUS %AS (J) against FFR 0.75.

Figure 4.

ROC analysis of CTA-, QCA- and IVUS-derived anatomic measurements to predict obstructive FFR. QCA-derived MLD (A) was superior to CTA MLD ($p = 0.02$) and IVUS-MLD ($p = 0.003$), whereas AUCs for CTA-MLD and IVUS-MLD were similar ($p = 0.85$). AUC for QCA %DS (B) was superior to CTA %DS ($p = 0.028$) and to IVUS %DS ($p = 0.001$), and CTA %DS was superior to IVUS %DS ($p = 0.046$). AUC for CTA MLA and IVUS MLA did not differ ($p = 0.34$) (C), whereas AUC for CTA %AS was significantly higher than for IVUS %AS ($p = 0.012$) (D).

Table 1
General demographic parameters

Characteristics	Frequency or Value
Subjects (n)	85
Age (yrs), mean $\pm$ SD	61.3 $\pm$ 7.8
Men	53 (62%)
Caucasian	79 (93%)
African-American	6 (7%)
Hypertension	66 (78%)
Dyslipidemia	77 (91%)
Tobacco use (former or current)	17 (20%)
Diabetes mellitus	18 (21%)
Framingham Risk Score (10-yr risk; mean $\pm$ SD)	8.7 $\pm$ 6.3
Angina pectoris	43 (50.6%)
Dyspnea	22 (25.9%)
Medications	
Aspirin	69 (81%)
β blocker	40 (47%)
Angiotensin converting enzyme inhibitor	28 (33%)
Angiotensin receptor blocker	8 (9%)
Nitrate	7 (8%)
Statin	59 (69%)
Ezetimibe	15 (18%)
Niacin	13 (15%)
Fibric acid derivative	9 (1%)
Total cholesterol (mg/dl)	153.4 $\pm$ 40.5
Low-density lipoprotein (mg/dl)	86.9 $\pm$ 34.3
High-density lipoprotein (mg/dl)	38.3 $\pm$ 11.7

Hypertension was defined as systolic blood pressure persistently of ≥ 140 mm Hg or diastolic ≥ 90 . Dyslipidemia was defined as elevated total or low-density lipoprotein cholesterol levels or low levels of high-density lipoprotein cholesterol.

Table 2**Lesion and reference segment characteristics (n = 85)**

	MLD lesion (mm)	Mean Reference Diameter (mm)	%DS	MLA lesion (mm ²)	Mean Reference Area (mm ²)	Area Stenosis (%)
QCA	1.45 ± 0.71	3.23 ± 0.78	55.3 ± 19.5	N/A	N/A	N/A
CTA	1.40 ± 0.68	3.03 ± 0.75	54.4 ± 19.3	4.53 ± 2.8	10.68 ± 4.81	59.01 ± 21.95
IVUS	1.86 ± 0.46	2.55 ± 0.53	30.6 ± 10.9	3.69 ± 1.91	6.41 ± 2.67	47.6 ± 14.9

N/A = not applicable.

Table 3
Linear correlation analysis between anatomic measurements and fractional flow reserve

n = 85	MLD (mm)		%DS		MLA (mm ²)		%AS	
	r Value	p Value	r Value	p Value	r Value	p Value	r Value	p Value
QCA	0.67	<0.01	-0.63	<0.01	N/A	N/A	N/A	N/A
CTA	0.47	<0.01	-0.52	<0.01	0.45	<0.01	-0.51	<0.01
IVUS	0.29	0.02	-0.22	0.09	0.25	0.04	-0.21	0.09

Table 4
Receiver operating characteristic analysis of quantitative coronary angiography, quantitative computed tomography angiography, and intravascular ultrasound derived anatomic measurements to predict obstructive fractional flow reserve <0.75

	Cut-point	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	Kappa	LR+	LR-
MLD (mm)										
QCA	1.15	0.96	95% (86%–100%)	82% (72%–91%)	64% (48%–81%)	98% (94%–100%)	85%	0.67	5.19	0.06
CTA	1.11	0.83	76% (58%–94%)	78% (67%–89%)	55% (37%–73%)	90% (82%–98%)	78%	0.48	3.46	0.31
IVUS	1.73	0.71	80% (55%–100%)	57% (44%–71%)	26% (10%–41%)	94% (86%–100%)	61%	0.2	1.88	0.35
%DS										
QCA	64%	0.91	90% (78%–100%)	83% (74%–93%)	66% (48%–83%)	96% (91%–100%)	85%	0.66	5.43	0.11
CTA	62%	0.85	81% (64%–98%)	75% (63%–86%)	53% (36%–70%)	92% (84%–99%)	76%	0.48	3.18	0.26
IVUS	44%	0.58	30% (1.6%–58%)	93% (86%–100%)	43% (62%–80%)	88% (79%–96%)	83%	0.26	4.05	0.76
MLA (mm ²)										
CTA	3.11	0.86	81% (64%–98%)	81% (71%–91%)	61% (43%–79%)	92% (85%–100%)	81%	0.56	4.34	0.23
IVUS	2.68	0.75	70% (42%–98%)	80% (69%–90%)	39% (16%–61%)	93% (86%–100%)	78%	0.37	3.44	0.38
%AS										
CTA	64%	0.86	90% (78%–100%)	75% (63%–86%)	56% (39%–73%)	96% (90%–100%)	79%	0.54	3.56	0.13
IVUS	69%	0.62	30% (1.6%–58%)	98% (95%–100%)	75% (33%–100%)	88% (80%–96%)	88%	0.37	16.2	0.71

LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; PPV = positive predictive value.

Table 5
Stepwise logistic multivariable regression for quantitative coronary angiography, computed tomography angiography, and intravascular ultrasound derived variables to predict obstructive fractional flow reserve 0.75

Modality	Variables	Odds Ratio	95% CI	p Value
QCA	MLD	0.0017	0.0001–0.0405	<0.001
CTA	%AS	1.09	1.0468–1.1363	<0.001
IVUS	MLA	0.28	0.1108–0.7171	0.008

CI = confidence interval.