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# Automated Quantification of Stenosis Severity on 64-Slice CT

## A Comparison With Quantitative Coronary Angiography

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OBJECTIVES This study sought to demonstrate the feasibility of a dedicated algorithm for automated quantification of stenosis severity on multislice computed tomography in comparison with quantitative coronary angiography (QCA).

BACKGROUND Limited information is available on quantification of coronary stenosis, and previous attempts using semiautomated approaches have been suboptimal.

METHODS In patients who had undergone 64-slice computed tomography and invasive coronary angiography, the most severe lesion on QCA was quantified per coronary artery using quantitative coronary computed tomography (QCCTA) software. Additionally, visual grading of stenosis severity using a binary approach (50% stenosis as a cutoff) was performed. Diameter stenosis (percentage) was obtained from detected lumen contours at the minimal lumen area, and corresponding reference diameter values were obtained from an automatic trend analysis of the vessel areas within the artery.

RESULTS One hundred patients (53 men; 59.8 ± 8.0 years) were evaluated, and 282 (94%) vessels were analyzed. Good correlations for diameter stenosis were observed for vessel-based ($n = 282$; $r = 0.83$; $p < 0.01$) and patient-based ($n = 93$; $r = 0.86$; $p < 0.01$) analyses. Mean differences between QCCTA and QCA were −3.0% ± 12.3% and −6.2% ± 12.4%. Furthermore, good agreement was observed between QCCTA and QCA for semiquantitative assessment of diameter stenosis (accuracy of 95%). Diagnostic accuracy for assessment of ≥50% diameter stenosis was higher using QCCTA compared with visual analysis (95% vs. 87%; $p = 0.08$). Moreover, a significantly higher positive predictive value was observed with QCCTA when compared with visual analysis (100% vs. 78%; $p < 0.05$). Although the visual approach showed a reduced diagnostic accuracy for data sets with moderate image quality, QCCTA performed equally well in patients with moderate or good image quality. However, in data sets with good image quality, QCCTA tended to have a reduced sensitivity compared with visual analysis.

CONCLUSIONS Good correlations were found for quantification of stenosis severity between QCCTA and QCA. QCCTA showed an improved positive predictive value when compared with visual analysis. (J Am Coll Cardiol Img 2010;3:699–709) © 2010 by the American College of Cardiology Foundation

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Multislice computed tomography (MSCT) has emerged as a promising noninvasive modality to detect coronary artery disease (CAD). High diagnostic accuracy for detection of significant CAD as compared with invasive coronary angiography has been reported in studies using 64-MSCT (1–3). Moreover, high negative predictive values have been reported in studies using 64-slice MSCT; as a result, MSCT is increasingly being used in the evaluation of CAD (1–3).

However, a major limitation of the technique is that at present, stenosis severity on MSCT can only be assessed visually; most frequently, a dichotomous score system with a cutoff value of 50% stenosis is used. A fully automated approach to quantify stenosis severity, similar to quantitative coronary angiography (QCA), would be preferred to further improve the diagnostic accuracy and reproducibility. However, such an automated quantitative approach is currently not available. In the majority of previous studies, attempts to quantify stenosis severity have used semimanual approaches rather than dedicated automated segmentation algorithms. Unfortunately, these semimanual approaches suffer from limited diagnostic accuracy and poor reproducibility; as a result, results were suboptimal in the majority of studies (4–7).

This study aimed to demonstrate the feasibility of employing a dedicated algorithm for automated quantification of stenosis severity in comparison with QCA.

**ABBREVIATIONS AND ACRONYMS**

**CAD** = coronary artery disease
**IVUS** = intravascular ultrasound
**MCA** = model-guided minimum cost approach
**MLA** = minimal lumen area
**MPR** = multiplanar reformatted
**MSCT** = multislice computed tomography
**QCCTA** = quantitative coronary computed tomography angiography
**QCA** = quantitative coronary angiography

## METHODS

**Study population.** The study population consisted of patients who underwent 64-slice CT and invasive coronary angiography sequentially within 4 months. Patients were clinically referred for MSCT because of known or suspected CAD. Known CAD was defined as a history of myocardial infarction, revascularization, or evidence of CAD on previous diagnostic tests.

No adverse cardiac events or hospitalizations were documented between MSCT and invasive coronary angiography. Patients underwent comprehensive imaging as part of an ongoing study registry addressing the value of MSCT in relation to other imaging modalities. Referral for invasive coronary angiography was made on the basis of clinical presentation and/or imaging results. Patients were excluded in case of atrial fibrillation, renal dysfunction (glomerular filtration rate <30 ml/min), documented iodine-containing contrast allergy, and pregnancy. Risk factors for CAD were derived from existing patient medical record data.

**Conventional invasive coronary angiography acquisition and analysis.** Conventional invasive coronary angiography was performed according to standard protocols. Quantitative analysis (QCA) was performed offline by an independent and blinded observer using a dedicated and validated software package (QAngioXA 7.1, Medis Medical Imaging Systems, Leiden, the Netherlands). Coronary arteries were evaluated according to the 17-segment model as previously described (8), and measurements were performed on a projection without superimposition of other coronary artery segments or cardiac structures and showing the stenosis in the tightest view. After catheter-based image calibration, side branches and coronary ostia were used as anatomic markers for accurate segment definition (17-segment model) (8). Image calibration was performed in 2 end-diastolic frames with a catheter diameter of 6F. Subsequently, the centerline was automatically defined, followed by automated detection of lumen contours and calculation of luminal diameter function. From these data, the reference diameter function was derived and reference contours were reconstructed. The reference diameter function was obtained from a linear regression fit on the lumen diameter function. This regression fit approximates best normal vessel tapering. Abnormal sections of a segment were excluded from the regression analysis by a user-interactive flagging procedure. At the site of minimal luminal diameter, the percentage diameter stenosis was calculated

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as: (1 − minimal luminal diameter/corresponding reference diameter) × 100% (9). Accordingly, in the current study, diameter stenosis refers to percentage diameter stenosis as previously described (9).

**MSCT examination. ACQUISITION.** The MSCT examinations were performed with a 64-slice CT scanner (Aquilion 64, Toshiba Medical Systems, Tokyo, Japan; or Lightspeed VR 64, GE Healthcare, Milwaukee, Wisconsin). Patients with elevated heart rates (≥65 beats/min) were administered metoprolol 50 or 100 mg orally, if not contraindicated. The contrast-enhanced helical scan was performed using a bolus of 95 to 130 ml of nonionic contrast medium (Iomeron 400, Bracco, Milan, Italy) followed by a bolus of saline flush (50 ml).

Before the helical scan, all patients underwent a nonenhanced electrocardiographic-gated scan to assess the coronary calcium score. For the 64-slice Lightspeed system (GE Healthcare), the following parameters were used for the coronary calcium scan: 4 × 3.0 mm or 2.5 mm, rotational time 350 to 500 ms, tube voltage 120 kV, and tube current 200 to 250 mA. The following parameters were used for the helical scan: collimation 64 × 0.625 mm, rotation time 350 ms, tube voltage 120 kV, and tube current 600 mA. Scan parameters for the Aquilion 64 CT scanner (Toshiba Medical Systems) have been published previously (3).

The electrocardiogram was obtained simultaneously for retrospective gating of the raw data. Images were reconstructed with a slice thickness of 0.5 mm and a reconstruction interval of 0.3 mm for the 64-slice Aquilion system (Toshiba Medical Systems). For the 64-slice Lightspeed system (GE Healthcare), data were reconstructed at an effective slice thickness of 0.625 mm.

**CORONARY ARTERY CALCIUM SCORE.** The nonhelical scans performed with the multislice Aquilion 64 system (Toshiba Medical Systems) or the 64-slice Lightspeed system (GE Healthcare) were analyzed using dedicated offline software (Vitrea 2 [Vital Images, Plymouth, Minnesota] and Advantage [GE Healthcare, Milwaukee, Wisconsin], respectively). An overall Agatston score was calculated for each patient (10).

**CT coronary angiography.** The MSCT angiography examinations were evaluated by an independent and experienced observer who was blinded to quantitative data derived from quantitative coronary computed tomography angiography (QCCTA) and QCA. Coronary arteries were divided into 17 segments according to the American Heart Association classification (8).

The most severely diseased segment per coronary artery was evaluated for the presence of significant (≥50% diameter stenosis) or nonsignificant (<50% diameter stenosis) diameter stenosis with the use of axial images and curved multiplanar reconstructions in at least 2 orthogonal planes.

Automated QCCTA was performed by an independent observer, blinded to QCA data, using dedicated software (QAngioCT 1.1, Medis Medical Imaging Systems). Using the 17-segment model (8), quantitative measurements were taken on the most severely diseased segment for each coronary artery, as defined with QCA. A single coronary stenosis was assigned per coronary segment. To ensure that similar segments were analyzed with QCA and QCCTA, accurate segment definition (defined with proximal and distal markers) was based on the 17-segment model. Side branches and coronary ostia were used as anatomic markers. Before automatic quantification, image quality of coronary segments was classified using the following scale: 1 = good image quality, 2 = moderate image quality, and 3 = poor image quality. Data sets with moderate image quality showed either motion artifacts or increased image noise. Data sets with poor image quality were nondiagnostic. In addition, atherosclerotic plaques were classified as noncalcified (lesions with lower density compared with contrast-enhanced lumen), mixed (lesions having elements of both noncalcified and calcified lesions), or calcified (lesions with high density).

Consecutively, automated quantification of diameter stenosis was performed. A fast vessel-tracking algorithm was used to obtain the 3-dimensional centerline (ranging from the proximal to distal marker) of the coronary artery. This vessel-tracking step consists of 1) a presegmentation of the vessel between the proximal and distal point and 2) a fastest path backtracking from distal to the proximal point through the center of the segmentation. Based on this centerline, a stretched multiplanar-reformatted (MPR) volume was created of the segment of interest. The MPR volumes allowed analysis of curved coronary arteries as straight vessels. Next, 4 longitudinal cross-sections were extracted from the MPR volume at 45° angular intervals. Subsequently, lumen borders in these 4 longitudinal images were detected by a model-guided minimum cost approach (MCA)

(11). A comprehensive overview of the whole coronary segment of interest was provided by these 4 longitudinal images and corresponding longitudinal contours. Consecutively, the lumen border contours were detected in each transversal slice of the MPR volume using MCA with a circular lumen model. The MCA method uses a combination of spatial first- and second-derivative gradient filters in combination with knowledge of the expected CT intensity values in the arteries. Therefore, the MCA method is insensitive to differences in attenuation values between data sets. During this step, the intersection points of each transversal slice with the earlier obtained longitudinal contours were used to guide the contour detection in each particular slice. Based on the cross-sectional area of the obtained transversal contours, a diameter function along the vessel course was derived using the formula for circular cross sections. Finally, from these data, the reference diameter function, minimal lumen diameter, and degree of stenosis were obtained, similar to the QCA method (Fig. 1). The minimal detectable diameter is approximately 0.25 mm with the currently used settings for coronary analyses in QCCTA. This is the image resolution at which the computed tomography angiography data set is resampled along the vessel within the stretched image. Automated quantitative processing steps were independent from the standard viewing settings (window level 1024, width 0). Only

**Table 1. Baseline Characteristics of Study Population (n = 100)**

| | |
|---|---|
| Men | 53 |
| Age (yrs) | 59.8 ± 8.0 |
| Heart rate (beats/min) | 61.1 ± 9.8 |
| Calcium score | 366 ± 728 |
| Suspected CAD | 93 |
| Known CAD | 7 |
| Previous coronary angioplasty | 4 |
| Indications of CAD on previous tests | 3 |
| Clinical presentation prior to MSCT | |
| Atypical angina pectoris | 70 |
| Typical angina pectoris | 24 |
| Cardiovascular risk factors | |
| Diabetes mellitus | 16 |
| Systemic hypertension | 65 |
| Hypercholesterolemia | 62 |
| Current smoking | 33 |
| Obesity | 23 |
| Positive family history | 36 |

Data are represented as mean ± SD or as number of patients.
CAD = coronary artery disease; MSCT = multislice computed tomography.

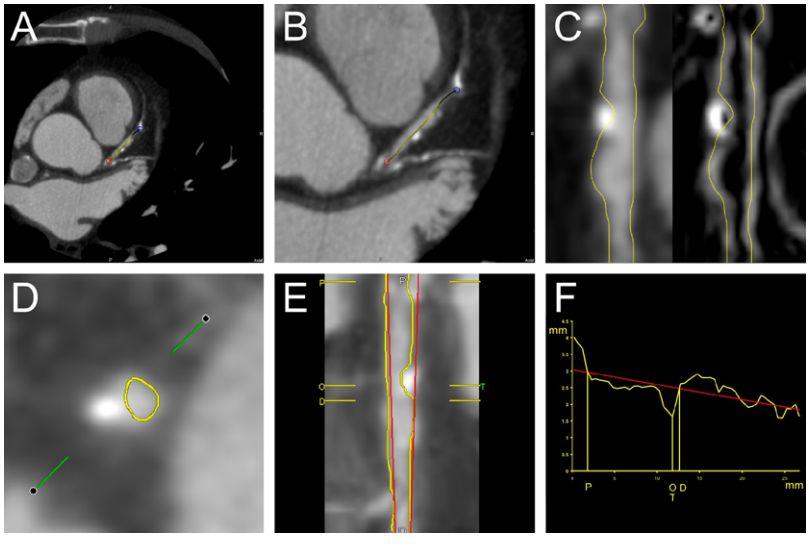


**Figure 1. Process of Automated Quantification of Stenosis Severity on 64-Slice CT**

Initially, accurate segment definition was performed using proximal and distal markers **(A and B)**. Automated contour detection was performed in longitudinal **(C)** and transversal **(D)** views. The longitudinal contours provide an initial approximation of the lumen border locations and are used to guide the automatic transversal contour detection. The right side of **Panel C** shows the gradient image, which is used to provide an intensity-independent border description. Lumen quantification is only based on the transversal contours. Finally, in **Panels E and F**, quantification of stenosis was based on differences between reference line **(red line)** and contour area **(yellow line)**. The reference line represented an estimate of normal tapering of the coronary artery. Diameter stenosis was 35.0% on QCCTA, which corresponded with 41.5% on QCA. MSCT = multislice computed tomography; QCA = quantitative coronary angiography; QCCTA = quantitative coronary computed tomography angiography.

**Table 2. Diameter Stenosis and Minimal Lumen Diameter Derived From QCCTA and QCA**

| | QCCTA | QCA |
|---|---|---|
| Diameter stenosis (%) | | |
| All vessels | 26.4 ± 19.4 | 29.4 ± 22.0* |
| Noncalcified lesions | 16.8 ± 11.9 | 20.1 ± 15.3* |
| Mixed lesions | 35.1 ± 21.5 | 38.5 ± 23.2* |
| Calcified lesions | 39.2 ± 19.0 | 40.9 ± 24.4 |
| Minimal lumen diameter (mm) | | |
| All vessels | 2.4 ± 0.8 | 2.2 ± 1.0* |
| Noncalcified lesions | 2.7 ± 0.7 | 2.5 ± 0.9* |
| Mixed lesions | 2.1 ± 0.9 | 1.9 ± 1.1* |
| Calcified lesions | 2.0 ± 0.7 | 1.7 ± 0.9* |

Data are represented as mean ± SD. *p < 0.05. All vessels (n = 282), noncalcified (n = 146), mixed (n = 81), and calcified lesions (n = 55).
QCA = quantitative coronary angiography; QCCTA = quantitative coronary computed tomography angiography.

limited manual input was used to improve the automated processing steps. Corrections could be made in the longitudinal contour detection to improve contour detection in a limited number of transversal slices (<5 min per patient). If indicated, coronary flagging of particular segments was performed to improve the luminal reference line (<1 min per patient).

Reproducibility of QCCTA was evaluated by assessment of interobserver and intraobserver variability. A second blinded observer performed QCCTA measurements in 20 patients (58 interpretable vessels) who were randomly identified. To assess intraobserver variability, measurements were performed twice by the same observer in a subset of 20 randomly selected patients (58 interpretable vessels).

**Statistical analysis.** Continuous data are presented as mean ± SD, and categoric data are presented as absolute numbers or percentages. The QCCTA and QCA were compared on a vessel and patient basis using Pearson linear regression analysis. Segments with the most severe lesion per coronary vessel were included in the vessel-based analysis, whereas segments with the most severe lesion per patient were included in the patient-based analysis. Additionally, a segment-based analysis on a subset of 10 randomly selected patients was performed to evaluate the performance of QCCTA in a wide range of stenosis and to avoid potential bias toward the most severe stenosis. For the segment-based analysis, each location of luminal narrowing per coronary segment was identified and analyzed using both quantitative approaches. Pearson linear regression analysis was used to compare QCCTA and QCA on a segment basis. Furthermore, separate analyses were performed for noncalcified, mixed, and calcified lesions. When appropriate, Wilcoxon signed rank tests were used to compare percentage diameter stenosis as derived from QCCTA and QCA.

Limits of agreement between QCCTA and QCA were calculated with Bland-Altman analyses showing the mean value of differences of each pair plotted against the average value of each pair. In addition, separate analyses were performed for noncalcified, mixed, and calcified lesions.

Diagnostic accuracy for assessment of significant coronary artery stenosis (≥50% diameter stenosis) was assessed for QCCTA and visual analysis. Corresponding sensitivity, specificity, and negative and positive predictive values were calculated. The 95% confidence intervals (CI) were calculated using the following formula: $p \pm 1.96 \times SE$, and the SE was estimated by $\sqrt{(p\,[1 - p]/n)}$. Agreement between quantitative and visual analyses was evaluated using Cohen kappa statistics, and k values were qualified as poor (<0.40), moderate (0.40 to 0.75), or good (>0.75) agreement. Interobserver and intraobserver variability were determined with Bland-Altman analyses (GraphPad Prism, version 5.01, GraphPad Software Incorporated, San Diego, California). Analyses were performed with statistical software (SPSS, version 16.0, SPSS Inc., Chicago, Illinois). A p value <0.05 was considered statistically significant.

**Table 3. Diagnostic Accuracy of QCCTA and Visual Analysis for Assessment of Significant Coronary Artery Stenosis (≥50% diameter stenosis) on a Patient Basis (n = 93)**

| | TN | TP | FN | FP | Se | Sp | NPV | PPV | Accuracy |
|---|---|---|---|---|---|---|---|---|---|
| Visual score | 56 | 25 | 5 | 7 | 83 | 89 | 92 | 78 | 87 |
| 95% CI | | | | | (70–97) | (81–97) | (85–99) | (64–93) | (80–94) |
| QCCTA | 63 | 25 | 5 | 0 | 83 | 100 | 93 | 100 | 95 |
| 95% CI | | | | | (70–97) | | (87–99) | | (90–99) |

CI = confidence intervals; FN = false negative; FP = false positive; NPV = negative predictive value; PPV = positive predictive value; QCCTA = quantitative coronary computed tomography angiography; Se = sensitivity; Sp = specificity; TN = true negative; TP = true positive.

**Table 4. Diagnostic Accuracy of QCCTA and Visual Analysis for Assessment of Significant Coronary Artery Stenosis (≥50% diameter stenosis) for Data Sets With Good (n = 62) or Moderate (n = 31) Image Quality**

| | TN | TP | FN | FP | Se | Sp | NPV | PPV | Accuracy |
|---|---|---|---|---|---|---|---|---|---|
| Visual analysis | | | | | | | | | |
| Good quality | 43 | 13 | 1 | 5 | 93 | 90 | 98 | 72 | 90 |
| 95% CI | | | | | (79–100) | (81–98) | (93–100) | (52–93) | (83–98) |
| Moderate quality | 13 | 12 | 4 | 2 | 75 | 87 | 76 | 86 | 81 |
| 95% CI | | | | | (54–96) | (70–100) | (56–97) | (67–100) | (67–95) |
| QCCTA | | | | | | | | | |
| Good quality | 48 | 11 | 3 | 0 | 79 | 100 | 94 | 100 | 95 |
| 95% CI | | | | | (57–100) | | (88–100) | | (90–100) |
| Moderate quality | 15 | 14 | 2 | 0 | 88 | 100 | 88 | 100 | 94 |
| 95% CI | | | | | (71–100) | | (73–100) | | (85–100) |

Abbreviations as in Table 3.

## RESULTS

**Study population and baseline results.** One hundred patients (53 men; 59.8 ± 8.0 years) who underwent 64-slice MSCT and invasive coronary angiography were enrolled retrospectively. The mean duration between both examinations was 38.0 ± 49.3 days. Baseline characteristics of the study population are listed in Table 1. Fifty patients underwent a 64-slice Aquilion (Toshiba Medical Systems) MSCT examination (Leiden University Medical Center, Leiden, the Netherlands), and 50 patients underwent a 64-slice Lightspeed (GE Healthcare) MSCT examination (Medical Center Haaglanden, the Hague, the Netherlands).

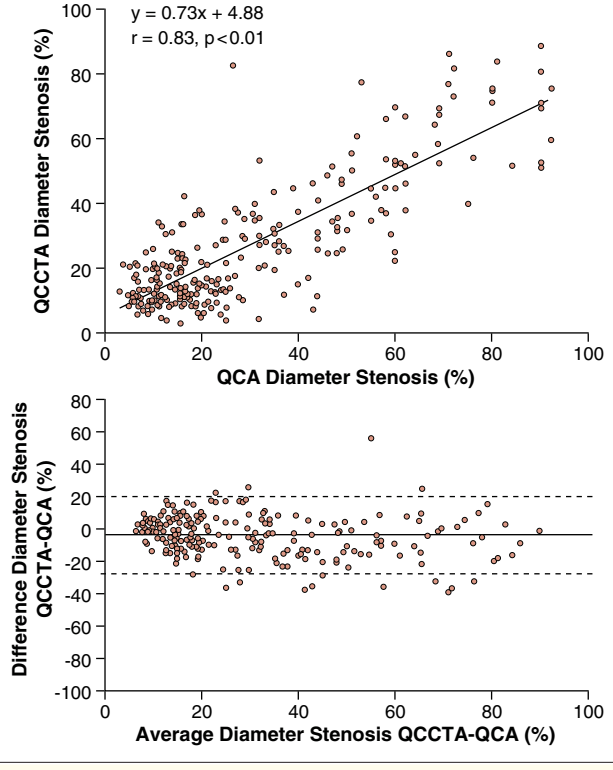


**Figure 2. Comparison Between QCCTA and QCA for Assessment of Diameter Stenosis on a Vessel Basis**

Linear regression **(upper panel)** and Bland-Altman **(lower panel)** analyses for diameter stenosis on a vessel basis (n = 282). The QCCTA and QCA showed good correlation and agreement for diameter stenosis. Abbreviations as in Figure 1.

In total, 282 (94%) vessels were included in the vessel-based analysis. Eighteen (6%) vessels from 18 patients were excluded because of poor image quality, including motion artifacts on MSCT (n = 7), reduced contrast arrival on MSCT (n = 7), or the presence of a total occlusion (n = 4). Good image quality was documented in 212 (71%) vessels, whereas moderate image quality was documented in 70 (23%) vessels. Mean values of diameter stenosis and minimal lumen diameter for vessel-based analysis are shown in Table 2.

On a patient basis, 93 (93%) patients were included; in 7 (7%) patients, the vessel with the most severe lesion was excluded because of poor image quality, including motion artifacts (n = 3) or total occlusion (n = 4). Of the 93 patients, good image quality was observed in 62 (62%) patients and moderate image quality in 31 (31%) patients.

**Agreement between visual analysis and QCA.** The agreement between visual analysis and QCA for semiquantitative assessment of significant coronary stenosis (using ≥50% diameter stenosis as a cutoff) was determined on a patient basis (Table 3). In total, 30 vessels were identified with significant stenosis on QCA, of which 25 were also classified as having significant stenosis on visual analysis (sensitivity 83%; 95% CI: 70% to 97%). Of the 63 vessels that were classified as nonsignificant using QCA,

visual analysis incorrectly classified 7 vessels as having significant stenosis (specificity 89%; 95% CI: 81% to 97%). The corresponding negative and positive predictive values were 92% (95% CI: 85% to 99%) and 78% (95% CI: 64% to 93%). The agreement between the visual analysis and QCA was 87% (95% CI: 80% to 94%), with a kappa value of 0.71 using ≥50% diameter stenosis as a cutoff for significant lesions.

In addition, further analysis of the agreement between visual analysis and QCA was performed in relation to image quality. In Table 4, corresponding sensitivity, specificity, and negative and positive predictive values are provided.

**Agreement between QCCTA and QCA.** Good correlations for diameter stenosis were observed between QCCTA and QCA on a vessel basis (n = 282; r = 0.83; p < 0.01) and a patient basis (n = 93; r = 0.86; p < 0.01) (Figs. 2 and 3). Additionally, the segment-based analysis that provided information regarding the performance of QCCTA in a wide range of percentage diameter stenosis showed a good correlation between QCCTA and QCA for diameter stenosis (n = 129; r = 0.82; p < 0.01).

In addition, limits of agreement between QCCTA and QCA for assessment of diameter stenosis were assessed. On a vessel basis, the mean value of differences ± SD was −3.0 ± 12.3% with 95% limits of agreement ranging from −27.1% to 21.0% (Fig. 2); on a patient basis, the mean value of differences ± SD was −6.2 ± 12.4% with 95% limits of agreement ranging from −30.5% to 18.1% (Fig. 3). For the segment-based analysis, the mean value of differences ± SD was −0.1 ± 8.2% with 95% limits of agreement ranging from −16.2% to 16.0%. Evaluation of interobserver and intraobserver variability revealed a mean value of differences ± SD of −1.4 ± 7.4% and −1.9 ± 7.2%, respectively.

The agreement between QCCTA and QCA for assessment of significant (≥50% diameter stenosis) or nonsignificant (<50% diameter stenosis) stenosis was calculated on a patient basis (Table 3). In 30 vessels, significant stenosis was identified on QCA, of which 25 vessels were classified similarly using QCCTA (sensitivity 83%; 95% CI: 70% to 97%). In 5 vessels, nonsignificant stenosis was identified with QCCTA, whereas QCA showed significant stenosis. Importantly, the majority of the lesions that were underestimated with QCCTA showed <70% stenosis on QCA (n = 4). Moreover, of the 63 nonsignificant lesions on QCA, 63 lesions were also classified as nonsignificant using QCCTA (specificity 100%). No lesions were overestimated on QCCTA compared with QCA, yielding an accuracy of 95% (95% CI: 90% to 99%) and a kappa value of 0.87. Using ≥50% diameter stenosis as a cutoff, corresponding negative and positive predictive values were 93% (95% CI: 87% to 99%) and 100%, respectively.

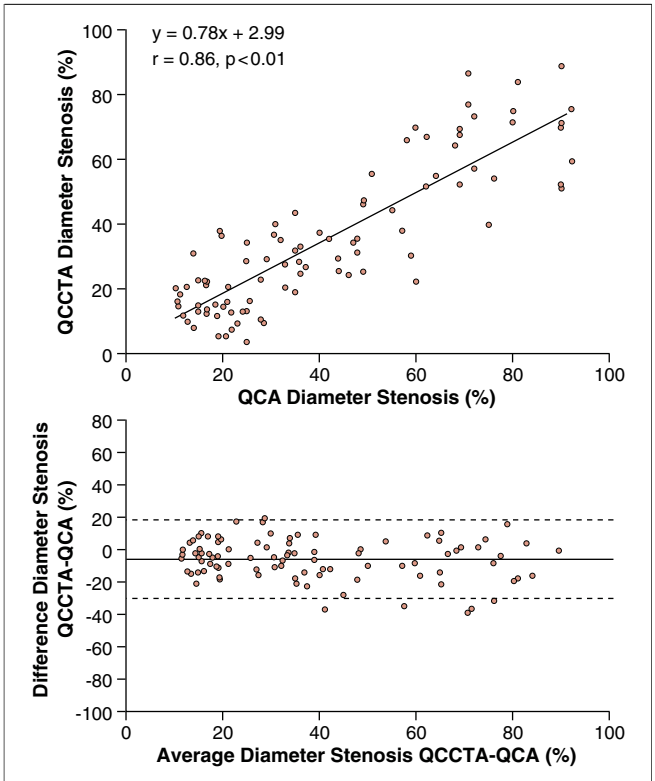


**Figure 3. Comparison Between QCCTA and QCA for Assessment of Diameter Stenosis on a Patient Basis**

Linear regression **(upper panel)** and Bland-Altman **(lower panel)** analyses for diameter stenosis on a patient basis (n = 93). The QCCTA and QCA showed good correlation and agreement for diameter stenosis. Abbreviations as in Figure 1.

Finally, further analysis of the agreement between QCCTA and QCA was performed in relation to image quality (Table 4). The QCCTA provided equally good results in patients with moderate or good image quality (diagnostic accuracy 94% vs. 95%; p = NS). However, compared with visual analysis, QCCTA tended to have reduced sensitivity in data sets with good image quality. Corresponding sensitivity, specificity, and negative and positive predictive values are shown in Table 4.

**Influence of plaque composition.** In addition, noncalcified, mixed, or calcified lesions were analyzed separately. Mean diameter stenosis and minimal lumen diameter for different plaque types are shown in Table 2. A good correlation for noncalcified (n =

146; r = 0.79; p < 0.01), mixed (n = 81; r = 0.80; p < 0.01), and calcified (n = 55; r = 0.77; p < 0.01) lesions was observed (Figs. 4 to 6). For noncalcified lesions, the mean value of differences ± SD was −3.2 ± 9.4% with 95% limits of agreement ranging from −21.6% to 15.1%. Furthermore, for mixed lesions, the mean value of differences ± SD was −3.5 ± 14.2% with 95% limits of agreement ranging from −31.3% to 24.4%. The mean value of differences ± SD for calcified lesions was −1.8 ± 15.7% with 95% limits of agreement ranging from −32.5% to 29.0% (Figs. 4 to 6).

## DISCUSSION

The main findings of this study are as follows: novel automated dedicated QCCTA software and QCA showed good correlations for quantification of stenosis severity on vessel- and patient-based analyses. In addition, QCCTA and QCA showed good agreement for semiquantitative assessment of stenosis severity (accuracy 95%; kappa = 0.87). Moreover, a tendency toward improved diagnostic accuracy was observed with QCCTA when compared with visual analysis of stenosis severity. Importantly, the positive predictive value was significantly higher with QCCTA when compared with visual analysis for the assessment of significant coronary artery stenosis.

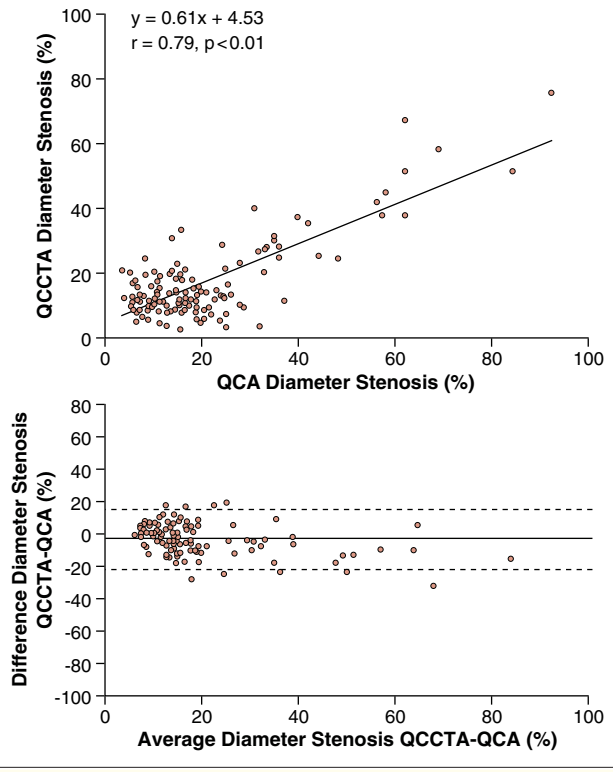


**Figure 4. Comparison Between QCCTA and QCA to Assess Diameter Stenosis of Segments With Noncalcified Lesions**

Linear regression **(upper panel)** and Bland-Altman **(lower panel)** analyses of diameter stenosis of segments with noncalcified lesions (n = 146). Good correlation and agreement were observed for assessment of diameter stenosis. Abbreviations as in Figure 1.

MSCT has appeared as a potent imaging technique for noninvasive evaluation of coronary atherosclerosis. Most of the studies have used visual, and moreover, binary approaches (≥50% luminal narrowing based on visual assessment) to identify significant stenoses with MSCT. However, quantification of stenosis severity may be preferred in terms of diagnostic accuracy and reproducibility. In addition, quantification of stenosis severity with an automated and robust approach may become particularly interesting when MSCT is used to evaluate progression of coronary atherosclerosis.

At present, however, limited evidence is available on quantification of stenosis severity with MSCT (5,7,13). Thus far, results of quantitative studies using a semiautomated CT approach for assessment of stenosis severity are lacking consistency. In addition, these semiquantitative approaches have resulted frequently in modest correlations between QCA and MSCT for the quantification of stenosis severity (5,7). An important study was performed by Leber et al. (5), who determined the diagnostic accuracy of 64-slice MSCT for quantification of stenosis severity in comparison with QCA. In 55 patients, 825 cardiac segments (15-segment model) could be visualized and analyzed using a semiautomated quantitative approach. Overall, moderate correlations were observed for stenosis severity between 64-slice MSCT and QCA (r = 0.54). Also, stenosis severity as assessed with intravascular ultrasound (IVUS) was moderately correlated with 64-slice MSCT (r = 0.61). Likewise, Raff et al. (4) evaluated the diagnostic accuracy of a semiautomated quantitative CT approach in comparison with invasive quantitative analyses in 70 patients with suspected CAD. Quantitative MSCT showed high diagnostic accuracy for the assessment of significant stenosis compared with QCA. Importantly, however, significant variability in stenosis severity was observed between QCA and quantitative MSCT. In particular, lesions of intermediate severity on QCA (30% to 70% diameter stenosis) showed high variability when compared with quantitative MSCT. Interestingly, Cheng et al. (14)

recently showed that a multitiered visual grading system was more accurate compared with semimanual quantification of MSCT.

A potential explanation for the limited accuracy observed for these semimanual quantification approaches may be the large variation that is introduced because of manual interference. For instance, in the study by Cheng et al. (14), manual input was required to assess the minimal luminal diameter at the site of stenosis (in addition to proximal and distal points). Furthermore, measurements were performed in a single longitudinal image. In the present study, however, an automated quantification algorithm was used for assessment of diameter stenosis in which only limited manual input was used to guide the automated processing steps. Manual input was limited to accurate segment definition using proximal and distal markers. In this respect, Marquering et al. (15) demonstrated that deviations were minimal in extracted centerlines when the position of placed proximal and distal markers was varied. In addition, the manual corrections made in the longitudinal contour detection were only used to improve the detected transversal contours in a limited number of locations in the transversal slice. Accordingly, quantification of stenosis severity was performed by an automated dedicated approach consisting of several consecutive programmed processing steps. Nevertheless, small corrections could also be made to improve the luminal reference line by flagging particular coronary segments, similar to that performed with QCA. Interestingly, this approach resulted in good correlations between QCCTA and QCA for assessment of diameter stenosis on vessel- and patient-based analyses.

In the study by Bruining et al. (16), an automated approach with limited manual interference was used to determine the diagnostic accuracy and reproducibility of coronary plaque measurements. Quantitative CT analysis was performed in 48 symptomatic patients who underwent invasive coronary angiography and IVUS. Measurements were performed by 2 independent observers using a coronary artery extraction method with computer-assisted quantitative volumetric analysis. Both observers found good correlations between MSCT and IVUS for lumen ($r = 0.76$ and $r = 0.95$) and plaque volumes ($r = 0.74$ and $r = 0.79$, respectively).

Another important finding of the present study was that no influence of plaque type was observed and that the algorithm performed equally well in noncalcified, mixed, and calcified lesions. In contrast, previous studies have reported that algorithms may quantify stenosis severity of noncalcified, mixed, and calcified plaques with variable accuracy (6,12,13). Overall, a tendency to underestimate stenosis severity of noncalcified lesions versus an overestimation of calcified lesions has been observed in many studies (6,12). In a previous study by Leber et al. (6), noncalcified and mixed-plaque volumes were significantly underestimated on quantitative MSCT (59.8 ± 76.6 $mm^3$ vs. 67.7 ± 67.9 $mm^3$ and 47.7 ± 87.5 $mm^3$ vs. 57.5 ± 99.4 $mm^3$; $p < 0.03$) compared with IVUS-derived plaque volumes, whereas calcified plaques were systematically overestimated (65.8 ± 110.0 $mm^3$ vs. 53.2 ± 90.3 $mm^3$; $p = 0.19$) on MSCT when compared with IVUS. In this study, a slight underestimation of stenosis severity using QCCTA for noncalcified and mixed plaques was found. Also, for calcified lesions, although the lowest mean value of differences is shown, a systematic underestimation of stenosis severity was observed in comparison with QCA. In contrast,

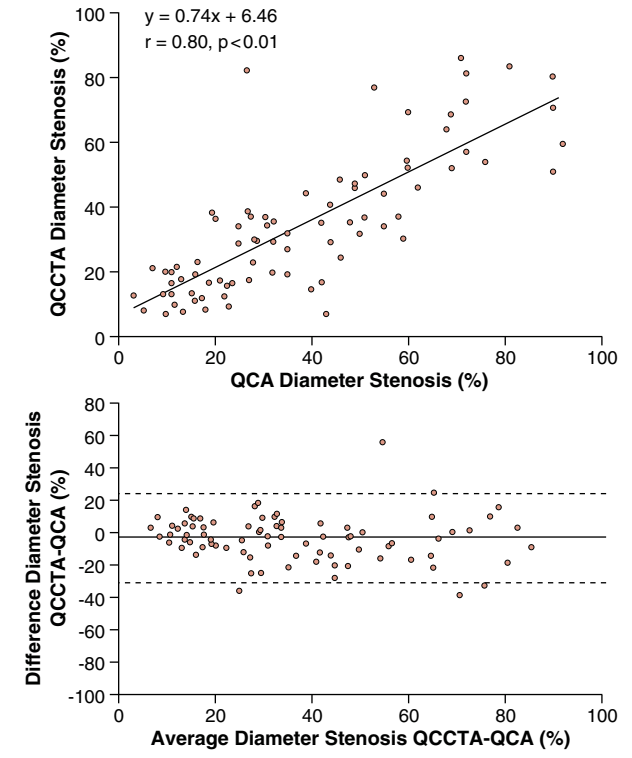


**Figure 5. Comparison Between QCCTA and QCA to Assess Diameter Stenosis of Segments With Mixed Lesions**

Linear regression **(upper panel)** and Bland-Altman **(lower panel)** analyses of diameter stenosis of segments with mixed lesions (n = 81). Good correlation and agreement were observed for assessment of diameter stenosis. Abbreviations as in Figure 1.

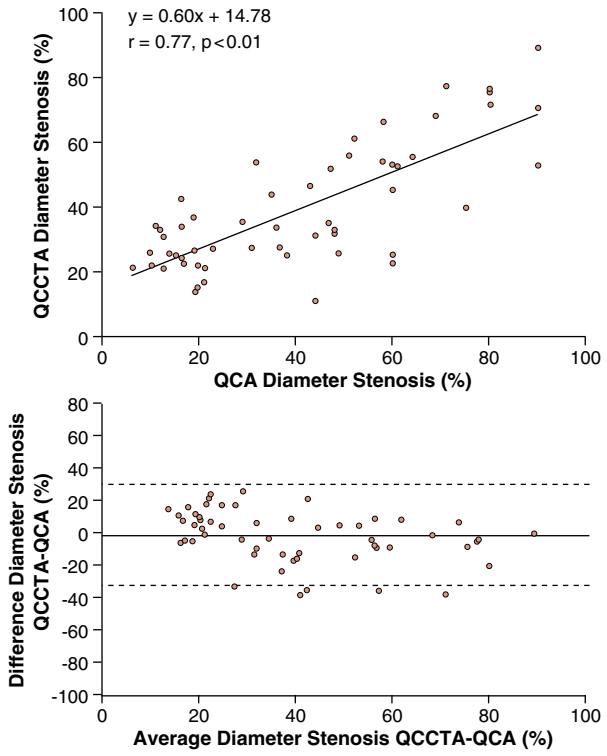


**Figure 6. Comparison Between QCCTA and QCA to Assess Diameter Stenosis of Segments With Calcified Lesions**

Linear regression **(upper panel)** and Bland-Altman **(lower panel)** analyses of diameter stenosis of segments with calcified lesions (n = 55). Good correlation and agreement were observed for assessment of diameter stenosis. Abbreviations as in Figure 1.

calcified lesions are usually overestimated with CT imaging possibly because of the blooming effect of calcium. With the use of an automatic quantification algorithm, however, the influence of blooming artifacts may be reduced, leading to a better estimate of stenosis severity.

In this study, results of the Bland-Altman analysis revealed smaller limits of agreement for vessel-based and patient-based analyses, compared with previously performed studies using semiquantitative measurements of coronary stenosis (7,13). These findings underline the feasibility of this novel, automated quantitative algorithm to assess stenosis severity, although further improvements are needed.

Moreover, semiquantitative assessment of the presence of significant coronary artery stenosis (≥50% diameter stenosis) revealed good agreement (overall agreement 95%). Only 5 lesions with ≥50% diameter stenosis on QCA were underestimated by QCCTA; the majority of these significant lesions were not severe and showed <70% diameter stenosis on QCA. Importantly, the current study showed a tendency toward improved diagnostic accuracy for assessment of significant lesions with QCCTA when compared with visual CT analysis (95% vs. 87%; $p = 0.08$). In particular, a significantly improved positive predictive value was observed using QCCTA compared with visual analysis (100% vs. 78%; $p < 0.05$).

In addition, the performance of QCCTA and visual analysis was analyzed in data sets with different image quality. Although the visual approach showed a reduced diagnostic accuracy for data sets with moderate image quality, QCCTA performed equally well in patients with moderate or good image quality. These findings demonstrate the feasibility of QCCTA for evaluation of coronary artery stenosis in data sets with variable image quality. Only in data sets with good image quality, sensitivity tended to be lower with QCCTA compared with visual analysis.

Finally, the present study demonstrated low interobserver and intraobserver variability for automated quantification of stenosis severity. This is an important finding because previous quantitative approaches were largely limited, owing to poor reproducibility (4–7,13) Accordingly, the current study provides important information on the use of automated quantification of stenosis severity with MSCT. Still, more studies are needed to elucidate the precise role of automated quantification in clinical cardiology.

**Study limitations.** The current study should be considered a feasibility study, validating a novel approach for automated quantification of stenosis severity. Integration of other plaque characteristics (remodeling index, plaque burden, eccentricity, and plaque length) would be preferred in evaluation of coronary atherosclerosis; however, the study was only designed to demonstrate feasibility of the new approach.

Further studies are needed to validate automated quantification of different plaque characteristics. In the present study, IVUS may have been a more reliable reference standard compared with QCA because IVUS is considered to be a true tomographic atherosclerosis imaging technique. However, conventional coronary angiography represents the validated standard for detection of coronary atherosclerosis in clinical cardiology. Finally, in the current study, the prevalence of significant CAD was relatively low, and the performance of QCCTA should be tested in more challenging

populations with higher disease prevalence as well.

## CONCLUSIONS

The novel automated QCCTA approach and QCA showed good correlation for quantification of stenosis severity on a vessel and patient basis. Good agreement was observed for semiquantitative assessment of the presence of significant coronary artery stenosis (≥50% diameter stenosis). The use of an automated quantification algorithm improves the positive predictive value of MSCT when compared with visual assessment of stenosis severity.

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## REFERENCES

1. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med 2008;359:2324–36.
2. Meijboom WB, Meijs MF, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. J Am Coll Cardiol 2008;52:2135–44.
3. Schuijf JD, Pundziute G, Jukema JW, et al. Diagnostic accuracy of 64-slice multislice computed tomography in the noninvasive evaluation of significant coronary artery disease. Am J Cardiol 2006;98:145–8.
4. Raff GL, Gallagher MJ, O'Neill WW, Goldstein JA. Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography. J Am Coll Cardiol 2005; 46:552–7.
5. Leber AW, Knez A, von ZF, et al. Quantification of obstructive and nonobstructive coronary lesions by 64-slice computed tomography: a comparative study with quantitative coronary angiography and intravascular ultrasound. J Am Coll Cardiol 2005; 46:147–54.
6. Leber AW, Becker A, Knez A, et al. Accuracy of 64-slice computed tomography to classify and quantify plaque volumes in the proximal coronary system: a comparative study using intravascular ultrasound. J Am Coll Cardiol 2006;47:672–7.
7. Dewey M, Rutsch W, Schnapauff D, Teige F, Hamm B. Coronary artery stenosis quantification using multislice computed tomography. Invest Radiol 2007;42:78–84.
8. Austen WG, Edwards JE, Frye RL, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation 1975;51:5–40.
9. Reiber JHC, Tuinenburg JC, Koning G, et al. Quantitative coronary arteriography. In: Oudkerk M, Reiser MF, editors. Coronary Radiology. 2nd edition. Berlin-Heidelberg, Germany: Springer-Verlag, 2009:41–65.
10. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.
11. van de Zwet PMJ, van Land CD, Loois G, Gerbrands JJ, Reiber JHC. An on-line system for the quantitative analysis of coronary arterial segments. Comp Cardiol 1990;19:157–60.
12. Otsuka M, Bruining N, Van Pelt NC, et al. Quantification of coronary plaque by 64-slice computed tomography: a comparison with quantitative intracoronary ultrasound. Invest Radiol 2008;43:314–21.
13. Husmann L, Gaemperli O, Schepis T, et al. Accuracy of quantitative coronary angiography with computed tomography and its dependency on plaque composition: plaque composition and accuracy of cardiac CT. Int J Cardiovasc Imaging 2008;24:895–904.
14. Cheng V, Gutstein A, Wolak A, et al. Moving beyond binary grading of coronary arterial stenoses on coronary computed tomographic angiography: insights for the imager and referring clinician. J Am Coll Cardiol Img 2009;1:460–71.
15. Marquering HA, Dijkstra J, de Koning PJ, Stoel BC, Reiber JH. Towards quantitative analysis of coronary CTA. Int J Cardiovasc Imaging 2005; 21:73–84.
16. Bruining N, Roelandt JR, Palumbo A, et al. Reproducible coronary plaque quantification by multislice computed tomography. Catheter Cardiovasc Interv 2007;69:857–65.

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