Quantitative CT Coronary Angiography: Does It Predict Functionally Significant Coronary Stenoses?

Rossi et al: Quantitative CTCA versus FFR

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Abstract

Background—Coronary lesions with a diameter narrowing ≥ 50% on visual CT coronary angiography (CTCA) are generally considered for referral to invasive coronary angiography (ICA). However, similarly to ICA, visual CTCA is often inaccurate in detecting functionally significant coronary lesions. We sought to compare the diagnostic performance of quantitative CTCA with visual CTCA for the detection of functionally significant coronary lesions using fractional flow reserve (FFR) as reference standard.

Methods and Results—CTCA and FFR measurements were obtained in 99 symptomatic patients. In total, 144 coronary lesions detected on CTCA were visually graded for stenosis severity. Quantitative CTCA measurements included lesion length, minimal area diameter (MLA), percentage area stenosis (%AS), minimal lumen diameter (MLD), percentage diameter stenosis (%DS) and plaque burden [(vessel area – lumen area)/vessel area*100]. Optimal cut-off values of CTCA-derived parameters were determined and their diagnostic accuracy for the detection of flow-limiting coronary lesions (FFR≤0.80) was compared to visual CTCA. FFR was ≤0.80 in 54/144 (38%) coronary lesions. Optimal cut-off values to predict flow-limiting coronary lesion were 10 mm for lesion length, 1.8 mm² for MLA, 73% for %AS, 1.5 mm for MLD, 48% for %DS and 76% for plaque burden. No significant difference in sensitivity was found between visual CTCA and quantitative CTCA parameters (p>0.05). Specificity of visual CTCA (42%; 95% CI: 32 to 52) was lower than that of MLA (68%; 95%CI: 57-77; p=0.001), %AS (76%, 95%CI: 65-84; p<0.001), MLD (67%; 95%CI: 55-76; p=0.001), %DS (72%, 95%CI: 62-80; p<0.001) and plaque burden (63%; 95%CI: 53-73; p=0.004). The specificity of lesion length was comparable to that of visual CTCA.

Conclusions—Quantitative CTCA improves the prediction of functionally significant coronary lesions compared to visual CTCA assessment but remains insufficient. Functional assessment is still needed in lesions of moderate stenosis to accurately detect impaired fractional flow reserve.

Key Words: non-invasive imaging, functionally significant coronary stenoses, quantitative CT coronary angiography, fractional flow reserve
Abbreviations list

CAD: Coronary Artery Disease
CTCA: Computed Tomography Coronary Angiography
ICA: Invasive Coronary Angiography
IVUS: Intravascular Ultrasound
FFR: Fractional Flow Reserve
MLA: Minimum Lumen Area
MLD: Minimum Lumen Diameter
%AS: Percentage Area Stenosis
%DS: Percentage Diameter Stenosis
RCA: Right Coronary Artery
LAD: Left Anterior Descending Coronary Artery
LCX: Left Circumflex Coronary Artery
ROC curves: Receiver Operating Characteristics Curves
CI: Confidence Intervals
Computed tomography coronary angiography (CTCA) is a reliable, non-invasive imaging modality to visualize coronary artery disease, with a high diagnostic accuracy compared to invasive coronary angiography (ICA)\textsuperscript{1-3}. In addition, CTCA can provide quantitative information of a coronary stenosis including similarly to intravascular ultrasound (IVUS), cross-sectional information and plaque burden. In daily practice, lesions with a diameter stenosis $\geq 50\%$ on visual CTCA are generally considered for referral to ICA. However, similarly to ICA, CTCA is an anatomical imaging technique, thus it may result in both underestimation and overestimation of a lesion's severity and is often inaccurate in identifying functionally significant coronary lesions which cause ischemia \textsuperscript{4-5}. Current guidelines suggest that treatment decisions based on the hemodynamic impact of a coronary lesion may improve clinical outcome \textsuperscript{6-8}. Therefore it would be relevant if quantitative parameters derived from CTCA could be optimized to predict the functional significance of a coronary stenosis.

The aim of this study was to compare the diagnostic performance of CTCA-derived quantitative parameters with visual CTCA in the detection of functionally significant coronary lesions using fractional flow reserve (FFR) as the reference standard.

**Methods**

**Study population**
We retrospectively included patients with stable angina who underwent both CTCA and ICA and a subsequent measurement of FFR in 2 teaching hospitals. The decision to measure FFR was based on the visual assessment of ICA and was made at the discretion of the interventional
cardiologist. Due to the potential hemodynamic interaction between 2 or more stenoses in series, we only included patients with a single coronary lesion per coronary vessel.

Exclusion criteria were impaired renal function (creatinine clearance < 60 ml/min), known allergy to iodine contrast material, calcium-score per vessel >400, left main coronary lesions, and poor image quality. Poor image quality was defined as severe motion artifacts or poor contrast opacification.

All patients gave written informed consent to undergo CTCA as part of research protocols approved by the institutional review boards of the participating institutions. FFR was carried out as part of routine clinical management.

CTCA acquisition

All patients received nitroglycerin (0.4 mg/ dose) sublingually just prior to the CT scan, provided there were no contraindications and patients with a heart rate above 65 beats per minute (bpm) received preparation with beta-blockers (50-100 mg metoprolol per os 1 hour prior to scanning or 1-30 mg metoprolol intravenously directly before scanning). The CT scan was performed using either a 64-slice dual source scanner (Somatom Definition, Siemens Medical Solutions, Forchheim, Germany) or a 128-slice second-generation dual source CT scanner (Somatom Definition Flash, Siemens Medical Solutions, Forchheim, Germany). First, all patients underwent an unenhanced scan for the calculation of the calcium score with the Agatston method (32 x 1.2 mm collimation, 120-kV tube voltage, 75 mAs tube current and 3-mm slice thickness with increment 1.5-mm). The CT angiographic scan parameters were: 1) for the 64-dual source CT scanner a gantry rotation time of 330 ms; 32x2x0.6 mm collimation with z-flying focal spot for both detectors, gantry rotation time 330 ms, tube voltage 120 kV and tube current of 320 to
412 mAs per rotation 2) for the 128-dual source CT scanner a gantry rotation time of 280 ms; 64x2x0.6 mm collimation with z-flying focal spot for both detectors, tube voltage 100 kV or 120 kV and tube current of 320 to 412 mAs per rotation. A bolus of iodinated contrast agent (370 mgI/mL, Ultravist; Schering, Berlin, Germany, or 300 mgI/ml, Omnipaque, GE Healthcare, Milwaukee, MI), which varied between 60 and 100 mL depending on the expected scan time, was injected intravenously at an injection rate of either 5.5ml/s or 7ml/s (depending on the type of contrast used) followed by a 45 mL saline chaser at the same injection rate. The iodine deliver rates achieved with both injection protocols were similar (2.0-2.1 gl/s). A bolus tracking technique was used to synchronize the start of image acquisition with the arrival of the iodinated contrast agent in the coronary arteries. With the 64-slice DSCT scanner, an ECG-gated spiral scan mode with ECG-pulsing was used for image acquisition. When scanning with the 128-slice DSCT either the prospectively ECG triggered sequential scan mode (‘step-and-shoot’) or the retrospective ECG-gated spiral scan mode with ECG-pulsing or a high pitch spiral scan mode were used, depending on the heart rate.

All CT images were reconstructed with a slice thickness of 0.75 mm and an increment of 0.4 mm. Images were analyzed using medium-to-smooth convolution kernels for non-calcified lesions and sharp convolution kernels for calcified lesions. More details about the CT protocol were previously described in detail 11.

**FFR measurements**

Fractional flow reserve was measured with a sensor-tipped 0.014-inch guidewire (Pressure Wire, Radi Medical Systems, Uppsala, Sweden). The pressure sensor was positioned just distal to the stenosis and maximal myocardial hyperemia was induced by a continuous intravenous infusion
of adenosine in a femoral vein (140 μg/kg/minute for a minimum of 2 min). FFR was calculated as the ratio of mean distal pressure measured by the pressure wire divided by the mean proximal pressure measured by the guiding catheter. A coronary stenosis with an FFR value ≤0.80 was considered functionally significant.

**CTCA image analysis**

First, the CTCA datasets were evaluated visually and the coronary lesion was graded as non-obstructive (<50% lumen narrowing), moderate (50% ≤ lumen narrowing ≤ 70%) and severe (≥ 70% lumen narrowing). Afterwards, all datasets were transferred to an offline workstation for analysis using semi-automated plaque analysis software (QAngioCT Research Edition v1.3.61, Medis Medical Imaging Systems, Leiden, The Netherlands). The location and the extent of the region of interest (ROI) were manually defined using proximal and distal markers as the coronary vessel region where the lumen diameter was reduced at least of 30% compared to the normal vessel. Planimetry of the inner lumen and outer vessel areas was performed following a stepwise approach as previously described. In summary, a centerline originating from the ostium was automatically extracted; then straightened multiplanar reformatted images were generated and the lumen and vessel borders were detected longitudinally on four different vessel views by the software; based on these longitudinal contours, cross-sectional images at 0.5 mm intervals were calculated in order to create transversal lumen and vessel wall contours, which were examined and, if necessary, adjusted by a single experienced observer. Based on the detected contours proximal and distal from the lesion region a reference area function is derived modeling the tapering of a healthy vessel. From these data the following cross-sectional CTCA-derived parameters were provided automatically by the software: lesion length, minimum lumen...
area (MLA), and percent area stenosis (%AS) at the level of the MLA defined by \[I-(MLA/corresponding\ reference\ lumen\ area)*100\]. In addition, minimum lumen diameter (MLD) and percent diameter stenosis (%DS) were provided as derived mathematically from the contour and reference area functions. Plaque burden was calculated for the whole coronary lesion by the following equation: \[(\text{vessel area} - \text{lumen area})/\text{vessel area}*100\], Figure 1.

**Statistical analysis**

Statistical analysis was performed using commercially available software (IBM SPSS Statistic, version 20). Results are reported in accordance with the STARD criteria. Continuous variables were presented as means ± standard deviation (SD) or medians with interquartile range (IQR) when not normally distributed and compared with the unpaired t-test or the Mann-Whitney test, respectively. Categorical variables were presented as frequencies and percentages and compared using the chi-square test.

The correlation between quantitative CTCA-derived parameters and FFR was assessed using linear regression analysis with non-linear predictors. Receiver operating characteristics (ROC) curves were used to assess the optimal cut-off values of quantitative CTCA-derived parameters to predict FFR ≤0.80. In the choice of the cut-off value we optimized the specificity, provided that sensitivity was at least 80%. Diagnostic performance of visual CTCA and quantitative CTCA-derived parameters for the detection of functionally significant lesions were evaluated on a per-lesion level and expressed as sensitivity, specificity, positive and negative predictive values and their corresponding 95% confidence intervals. A generalized estimating equation (GEE) model was used to account for the clustering between lesions in the same subject. The McNemar
test was used to compare the sensitivities and specificities of each quantitative CTCA-derived parameter versus visual CTCA.

Coronary lesions were divided into three groups based on visual assessment: non-obstructive (<50% lumen narrowing), moderate (50%≤lumen narrowing<70%) and severe (≥70% lumen narrowing). The cut-off values of quantitative CTCA-derived parameters derived from the ROC curves were used individually and in combination to investigate whether they could decrease the number of misclassified lesions in the three categories of lesions’ severity. When the combined approach was used a positive outcome was adjudicated if both quantitative CTCA-derived parameters were positive as defined by the optimal cut-off value. A misclassified lesion was defined as a mismatch between CTCA results and FFR measurements. Statistical significance was defined as p<0.05.

**Results**

**Study population**

In total 124 patients were considered for inclusion in the study. Twenty-five patients were excluded due to extreme calcifications (vessel calcium score> 400) in the target vessel (n =17), left main coronary lesions (n=2), and poor image quality (n=6). Therefore, 144 coronary lesions in 99 patients were finally included in the analysis. Baseline clinical characteristics and quantitative CTCA-derived parameters are shown in Table 1 and Table 2, respectively. The range of FFR values was between 0.24 and 1.00; 35% (35/99) of the patients had multi-vessel FFR measurements. The FFR was ≤ 0.80 in 54 lesions (38%). Coronary lesions with FFR ≤ 0.80 were longer lesions with smaller lumen area and diameter, more severe stenosis and higher plaque burden than those with FFR >0.80 (Table 2).
FFR versus cross-sectional CTCA-derived parameters

Non-linear regression analysis between quantitative CTCA-derived parameters and FFR demonstrated a significant curvilinear relation for %AS, %DS, MLA and MLD (Figure 2). Significant curvilinear relationship was also found for plaque burden ($R^2=0.302$, $p<0.001$) and lesion length ($R^2=0.148$, $p<0.001$). ROC analysis yielded an area under the curve (AUC) of 0.66 (0.57-0.75) for length, 0.82 (0.75-0.89) for MLA, 0.82 (0.75-0.89) for MLD, 0.83 (0.75-0.90) for %AS, 0.82 (0.74-0.89) for %DS and 0.80 (0.73-0.87) for plaque burden (Figure 3). Optimal cut-off values to predict the functional significance of coronary lesions were 10 mm for length, 1.8 mm$^2$ for MLA, 73% for %AS, 1.5 mm for MLD, 48% for %DS and 76% for plaque burden.

Diagnostic performance of visual CTCA and quantitative CTCA-derived parameters in predicting functionally significant coronary lesions

The diagnostic performance of visual CTCA and quantitative CTCA for the assessment of functionally significant coronary lesions ($FFR \leq 0.80$) is detailed in Table 3. No significant difference was found for sensitivity between visual CTCA and quantitative CTCA in terms of lesion length, MLA, %AS, MLD, %DS and plaque burden ($p=0.092$, $p=0.146$ and $p=0.092$, respectively). Specificity of MLA, %AS, MLD, %DS and plaque burden was significant higher than the specificity of visual CTCA ($p=0.001$, $p<0.001$ and $p=0.004$, respectively) for the detection of functionally significant coronary lesions. Lesion length had a comparable specificity than visual CTCA ($p=0.749$).

Moderate coronary lesions

Visual CTCA showed 42 (29%) non-obstructive lesions, 85 (59%) moderate lesions and 17 (12%) severe lesions. In the moderate lesion category 46 lesions were misclassified by visual
CTCA; the use of %AS and plaque burden in combination decreased the number of lesions incorrectly classified from 46/85 (54%) to 20/85 (24%) of which 15 lesions were incorrectly classified as non-functionally significant (Table 4).

Discussion

In this exploratory study we sought to investigate the ability of quantitative parameters derived by CTCA to predict the functional significance of coronary lesions using FFR as the reference standard.

The major findings of our study are the following: 1) the relationship between coronary lesion severity, as described by quantitative CTCA-derived parameters, and FFR is curvilinear; 2) the optimal cut-off values to predict the functional significance of coronary lesions were 10 mm, 1.8 mm², 73%, 1.5 mm, 48% and 76% for lesion length, MLA, %AS, MLD, %DS and plaque burden, respectively; 3) in the moderate lesion category the combined use of %AS and plaque burden decreased the number of lesions incorrectly classified from 46/85 (54%) to 22/85 (26%) of which 15 lesions were incorrectly classified as non-functionally significant lesions.

Relationship between quantitative CTCA-derived parameters and FFR

As shown in previous IVUS studies 17-18, MLA is important in determining coronary blood flow based on the Bernoulli equation. However, other important factors can affect coronary flow: the degree of diameter stenosis, lesion length, plaque burden, vessel size, lesion morphology, plaque characteristics, blood viscosity, collateral circulation, and supplied myocardium 19. Several of these parameters can be measured using CTCA 14. In our study, similarly to Kristensen et al. 20, a
curvilinear significant relationship was found between quantitative CTCA-derived parameters and FFR over a wide range of coronary lesion severity.

Several IVUS studies have validated an MLA of 3.0 mm² or 4.0 mm² as an anatomic predictor for physiological lesion significance 21-22. However, it has been shown that these cut-off values are not accurate; especially when applied in small vessels (diameter<2.5 mm) 17 a smaller cut-off value should be used. In our study, similarly to the finding reported by Kristensen et al. 20, we found an MLA CT-derived cut-off value of 1.8 mm² which is smaller compared to the IVUS-derived one reported by Kang et al. 17 This may be related to inherent differences between invasive and non-invasive imaging modalities. For instance, to avoid the induction of coronary spasm by the IVUS catheter, intracoronary nitrates are usually given before imaging at the dose of 100-200 μg causing a status of coronary vasodilation greater than the one induced by nitrates administered orally before the CTCA acquisition. In addition, IVUS does not assess severe coronary lesions due the large profile of the IVUS catheter which is unable to pass through small coronary lumen.

**CTCA-derived parameters in predicting flow-limiting coronary lesions**

Previous investigations have demonstrated that, similarly to ICA, the anatomical assessment of a coronary stenosis by CTCA correlates poorly with the functional significance of the stenosis defined by FFR 4-5. As previously shown in a study by Tonino et al., there was a high rate of non-functionally significant lesions in the range of angiographic severity 50% to 70% diameter stenosis 23. Similarly, in our study 54% of the coronary stenoses with an angiographic severity between 50% and 70% were not functionally significant. The use of quantitative CTCA decreased the number of misclassified lesions by half, mainly by reducing the number of lesions
incorrectly classified as functionally significant from 54% to 26%. However, 18% of these lesions were incorrectly classified as non-functionally significant, highlighting the fact that the increase in the specificity comes at the expense of a decrease in the sensitivity.

**Limitations**

This study has some limitations. Firstly it was a retrospective study performed in a relatively small number of patients; the possibility of a type II error should be considered. Secondly, due to the relative small number of positive observations we did not perform multivariate logistic regression to identify independent predictors of a positive FFR. Finally, we excluded vessels with poor image quality on CTCA; good image quality is a prerequisite for the reliable calculation of CT-derived cross-sectional parameters.

**Future directions**

The interest in overcoming the mismatch between anatomy and function in cardiac imaging has initiated intense research to assess the feasibility of new non-invasive diagnostic techniques. The safety and feasibility of stress myocardial CT perfusion imaging has been demonstrated in few experimental and human studies $^{24-28}$. The addition of stress myocardial CT perfusion imaging to the standard CTCA can provide complementary anatomical and functional information in a single examination. However, CT perfusion imaging involves increased patient radiation exposure, increased contrast volume and potential patient’s discomfort related to the administration of a pharmacological stress agent. In this study we determined whether the analysis of quantitative cross-sectional CTCA parameters could improve the prediction of functionally significant lesions without further irradiation, contrast or drug administration. In this
context, the possibility of a non-invasive FFR measurement, albeit still computationally difficult, has been shown with promising results 29.

Conclusion

CTCA cross-sectional quantitative parameters improve the prediction of flow-limiting lesions, compared to visual assessment, but remain insufficient. Functional assessment is still needed for lesions of moderate severity to accurately detect impaired fractional flow reserve.

Acknowledgements

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Disclosures

PK is employed by Medis medical imaging systems bv and has a research appointment at the Leiden University Medical Center.

References


<table>
<thead>
<tr>
<th>Table 1. Baseline clinical characteristics</th>
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<tr>
<td></td>
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<tr>
<td><strong>All</strong> (n=99)</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Age (yrs)</td>
</tr>
<tr>
<td>Risk factors</td>
</tr>
<tr>
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</tr>
<tr>
<td>Hypertension†</td>
</tr>
<tr>
<td>Dyslipidemia‡</td>
</tr>
<tr>
<td>Diabetes§</td>
</tr>
<tr>
<td>Family history of CAD†</td>
</tr>
<tr>
<td>Calcium score (Agatston)</td>
</tr>
</tbody>
</table>

Values are median (IQR) or n (percentage). *Comparison between fractional flow reserve (FFR)>0.80 versus FFR≤0.80.

† Blood pressure ≥ 140/90 mmHg or treatment for hypertension; ‡ Total cholesterol >180 mg/dl or treatment for hypercholesterolemia; § Treatment with oral anti-diabetic medication or insulin; † Family history of coronary artery disease having first- or second-degree relatives with premature CAD (age<55 years).
Table 2. Cross-sectional CT-derived parameters, vessel distribution and FFR

<table>
<thead>
<tr>
<th></th>
<th>All (n=144)</th>
<th>FFR&gt;0.80 (n=90)</th>
<th>FFR≤0.80 (n=54)</th>
<th>P-value*</th>
</tr>
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<tbody>
<tr>
<td>FFR</td>
<td>0.83 (0.75-0.90)</td>
<td>0.88 (0.84-0.93)</td>
<td>0.72 (0.68-0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>13 (9-19)</td>
<td>11 (8-17)</td>
<td>16 (11-25)</td>
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<tr>
<td>MLA (mm²)</td>
<td>1.8 (1.0-2.7)</td>
<td>2.3 (1.5-2.8)</td>
<td>1.0 (0.3-1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>%AS</td>
<td>71 (62-82)</td>
<td>67 (56-73)</td>
<td>84 (74-91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>1.5 (1.1-1.8)</td>
<td>1.7 (1.4-1.9)</td>
<td>1.1 (0.6-1.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>%DS</td>
<td>47 (39-58)</td>
<td>44 (35-49)</td>
<td>60 (49-71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plaque burden (%)</td>
<td>76 (71-79)</td>
<td>73 (69-77)</td>
<td>79 (76-82)</td>
<td>&lt;0.001</td>
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<tr>
<td>Vessel</td>
<td></td>
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<td></td>
<td>0.050</td>
</tr>
<tr>
<td>RCA</td>
<td>36 (25%)</td>
<td>24 (27%)</td>
<td>12 (22%)</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>76 (53%)</td>
<td>41 (46%)</td>
<td>35 (65%)</td>
<td></td>
</tr>
<tr>
<td>LCX</td>
<td>32 (22%)</td>
<td>25 (28%)</td>
<td>7 (13%)</td>
<td></td>
</tr>
<tr>
<td>Lesion location</td>
<td></td>
<td></td>
<td></td>
<td>0.121</td>
</tr>
<tr>
<td>Proximal</td>
<td>76 (53%)</td>
<td>43 (48%)</td>
<td>33 (61%)</td>
<td></td>
</tr>
<tr>
<td>Mid</td>
<td>68 (47%)</td>
<td>47 (52%)</td>
<td>21 (39%)</td>
<td></td>
</tr>
</tbody>
</table>

Values are median (IQR) or n (percentage). * Comparison between fractional flow reserve (FFR)>0.80 versus FFR≤0.80.

MLA = Minimal Lumen Area; %AS = Percentage Area Stenosis; RCA = Right Coronary Artery; LAD = Left Anterior Descending Coronary Artery; LCX = Left Circumflex Coronary Artery
Table 3. Diagnostic accuracy of visual CTCA and optimal cut-off values of lesion length, MLA, %AS, MLD, %DS, and %DS derived from quantitative CTCA in the detection of flow-limiting coronary lesions as defined by a FFR ≤ 0.80

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
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</thead>
<tbody>
<tr>
<td>Visual assessment</td>
<td>50</td>
<td>38</td>
<td>52</td>
<td>4</td>
<td>93 (82-97)</td>
<td>42 (31-54)</td>
<td>49 (38-60)</td>
<td>91 (77-96)</td>
</tr>
<tr>
<td>Length (mm)</td>
<td>44</td>
<td>35</td>
<td>55</td>
<td>10</td>
<td>82 (69-90)</td>
<td>39 (28-51)</td>
<td>44 (34-56)</td>
<td>78 (63-88)</td>
</tr>
<tr>
<td>MLA (mm²)</td>
<td>43</td>
<td>61</td>
<td>29</td>
<td>11</td>
<td>80 (67-88)</td>
<td>68 (57-77)**</td>
<td>60 (46-72)</td>
<td>85 (75-91)</td>
</tr>
<tr>
<td>%AS</td>
<td>43</td>
<td>68</td>
<td>22</td>
<td>11</td>
<td>80 (65-89)</td>
<td>76 (65-84)**</td>
<td>66 (53-77)</td>
<td>86 (76-92)</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>44</td>
<td>60</td>
<td>30</td>
<td>10</td>
<td>82 (69-90)</td>
<td>67 (55-76)**</td>
<td>60 (46-72)</td>
<td>86 (76-92)</td>
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<tr>
<td>%DS</td>
<td>43</td>
<td>65</td>
<td>25</td>
<td>11</td>
<td>80 (65-89)</td>
<td>72 (62-80)**</td>
<td>63 (50-74)</td>
<td>86 (75-92)</td>
</tr>
<tr>
<td>Plaque Burden (%)</td>
<td>43</td>
<td>57</td>
<td>33</td>
<td>11</td>
<td>80 (66-89)</td>
<td>63 (52-73)**</td>
<td>57 (43-69)</td>
<td>84 (72-91)</td>
</tr>
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</table>

CTCA = CT Coronary Angiography; FFR = Fractional Flow Reserve; MLA = Minimal Lumen Area; %AS = Percentage Area Stenosis; MLD = Minimal Lumen Diameter; %DS = Percentage Diameter Stenosis; AUC = area under the curve; TP = true positive; TN = true negative; PPV = positive predictive value; NPV = negative predictive value.

* AUC corresponds to the performance of the optimal cut-off value of each quantitative CTCA-derived parameter.

** p<0.05 derived from McNemar comparing the specificities of lesion length, MLA, %AS, MLD, %DS and plaque burden with the specificity of visual assessment.
Table 4. Diagnostic performance of quantitative CTCA parameters to predict functionally significant lesions (FFR≤0.80)

<table>
<thead>
<tr>
<th>Visual assessment</th>
<th>Non-obstructive stenoses</th>
<th>Moderate stenoses</th>
<th>Severe stenoses</th>
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<tbody>
<tr>
<td>(n=42)</td>
<td>(n=85)</td>
<td>(n=17)</td>
<td></td>
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<tr>
<td>FFR&gt;0.80</td>
<td>38</td>
<td>46</td>
<td>6</td>
</tr>
<tr>
<td>FFR≤0.80</td>
<td>4</td>
<td>39</td>
<td>11</td>
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</table>

<table>
<thead>
<tr>
<th>MLA (mm²)</th>
<th>&gt;1.8</th>
<th>≤1.8</th>
<th>&gt;1.8</th>
<th>≤1.8</th>
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<th>≤1.8</th>
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<tbody>
<tr>
<td>FFR&gt;0.80</td>
<td>28</td>
<td>10</td>
<td>29</td>
<td>17</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>FFR≤0.80</td>
<td>1</td>
<td>3</td>
<td>10</td>
<td>29</td>
<td>0</td>
<td>11</td>
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<table>
<thead>
<tr>
<th>AS (%)</th>
<th>&lt;73</th>
<th>≥73</th>
<th>&lt;73</th>
<th>≥73</th>
<th>&lt;73</th>
<th>≥73</th>
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<td>FFR&gt;0.80</td>
<td>33</td>
<td>5</td>
<td>31</td>
<td>15</td>
<td>4</td>
<td>2</td>
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<tr>
<td>FFR≤0.80</td>
<td>1</td>
<td>3</td>
<td>10</td>
<td>29</td>
<td>0</td>
<td>11</td>
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<table>
<thead>
<tr>
<th>Plaque burden (%)</th>
<th>&lt;76</th>
<th>≥76</th>
<th>&lt;76</th>
<th>≥76</th>
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<td>FFR&gt;0.80</td>
<td>27</td>
<td>11</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>FFR≤0.80</td>
<td>1</td>
<td>3</td>
<td>10</td>
<td>29</td>
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<tr>
<th>MLA (mm²) and Plaque Burden (%)</th>
<th>MLA&gt;1.8 PB&lt;76</th>
<th>MLA&lt;1.8 PB≥76</th>
<th>MLA&gt;1.8 PB&lt;76</th>
<th>MLA&lt;1.8 PB≥76</th>
<th>MLA&gt;1.8 PB&lt;76</th>
<th>MLA&lt;1.8 PB≥76</th>
</tr>
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<tbody>
<tr>
<td>FFR&gt;0.80</td>
<td>35</td>
<td>3</td>
<td>36</td>
<td>10</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>FFR≤0.80</td>
<td>1</td>
<td>3</td>
<td>15</td>
<td>24</td>
<td>0</td>
<td>11</td>
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<thead>
<tr>
<th>AS (%) and Plaque Burden (%)</th>
<th>AS&lt;73 PB&lt;76</th>
<th>AS≥73 PB≥76</th>
<th>AS&lt;73 PB&lt;76</th>
<th>AS≥73 PB≥76</th>
<th>AS&lt;73 PB&lt;76</th>
<th>AS≥73 PB≥76</th>
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<tbody>
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<td>FFR&gt;0.80</td>
<td>36</td>
<td>2</td>
<td>41</td>
<td>5</td>
<td>4</td>
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<tr>
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<td>3</td>
<td>15</td>
<td>24</td>
<td>0</td>
<td>11</td>
</tr>
</tbody>
</table>
Values are numbers.

For each CT parameter and for each stenosis category: upper left cell = true negative; upper right cell = false positive; lower left cell = false negative; lower right cell = true positive. Yellow cells show the number of misclassified coronary lesions in the moderate stenosis category.

CTCA = CT Coronary Angiography; FFR = Fractional Flow Reserve; MLA = Minimal Lumen Area; %AS = Percentage Area Stenosis; PB = Plaque Burden.
Figure Legends

Figure 1. Quantitative CT coronary angiography (CTCA) and fractional flow reserve (FFR) measurement in a moderate coronary lesion.

Example of a patient with a moderate (50-70% lumen narrowing by visual CTCA) coronary lesion due a partly calcified plaque in the left descending coronary artery (LAD). Panel A shows the screenshot of the quantitative CTCA analysis using dedicated software. The lesion was assessed as moderate by visual CTCA. Lumen (yellow) and wall (orange) contours were semi-automatically detected. At the level of the minimal lumen area (yellow line), lumen area, percentage area stenosis and plaque burden were measured as 1.6 mm², 83% and 91%, respectively. The FFR was 0.68 (panel B).

Figure 2. Curvilinear relationship between FFR and MLA, %AS, MLD and %DS.
MLA = Minimal Lumen Area; %AS = Percentage Area Stenosis; MLD = Minimal Lumen Diameter; %DS = Percentage Diameter Stenosis.

Figure 3. ROC curves of MLA, %AS, MLD and %DS.
MLA = Minimal Lumen Area; %AS = Percentage Area Stenosis; MLD = Minimal Lumen Diameter; %DS = Percentage Diameter Stenosis.
Quantitative CT Coronary Angiography: Does It Predict Functionally Significant Coronary Stenoses?


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