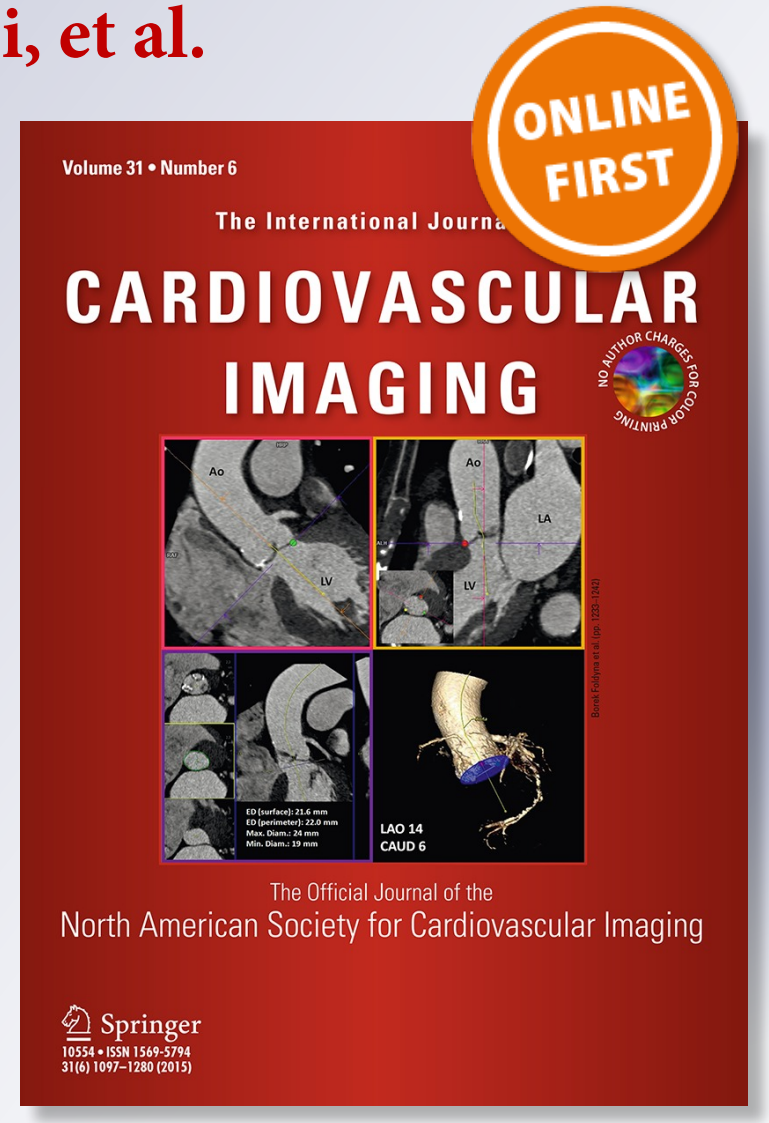
Diagnostic performance of quantitative coronary computed tomography angiography and quantitative coronary angiography to predict hemodynamic significance of intermediate-grade stenoses

Olivier Ghekiere, Willem Dewilde, Michel Bellekens, Denis Hoa, Thierry Couvreur, Julien Djekic, Tim Coolen, Isabelle Mancini, et al.

The International Journal of Cardiovascular Imaging
X-Ray Imaging, Echocardiography, Nuclear Cardiology Computed Tomography and Magnetic Resonance Imaging

ISSN 1569-5794

Int J Cardiovasc Imaging
DOI 10.1007/s10554-015-0748-1



Springer

Int J Cardiovasc Imaging
DOI 10.1007/s10554-015-0748-1

ORIGINAL PAPER

Diagnostic performance of quantitative coronary computed tomography angiography and quantitative coronary angiography to predict hemodynamic significance of intermediate-grade stenoses

Olivier Ghekiere[1,2,3] · Willem Dewilde[4] · Michel Bellekens[5] · Denis Hoa[6] · Thierry Couvreur[1] · Julien Djekic[1] · Tim Coolen[7] · Isabelle Mancini[1] · Piet K. Vanhoenacker[8] · Paul Dendale[3,9] · Alain Nchimi[10]

Received: 20 June 2015 / Accepted: 17 August 2015

Abstract Fractional flow reserve (FFR) during invasive coronary angiography has become an established tool for guiding treatment. However, only one-third of intermediate-grade coronary artery stenosis (ICAS) are hemodynamically significant and require coronary revascularization. Additionally, the severity of stenosis visually established by coronary computed tomography angiography (CCTA) does not reliably correlate with the functional severity. Therefore, additional angiographic morphologic descriptors affecting hemodynamic significance are required. To evaluate quantitative stenosis analysis and plaque descriptors by CCTA in predicting the hemodynamic significance of ICAS and to compare it with quantitative catheter coronary angiography (QCA). QCA was performed in 65 patients (mean age 63 ± 9 years; 47 men) with 76 ICAS (40–70 %) on CCTA. Plaque descriptors were determined including circumferential extent of calcification, plaque composition, minimal lumen diameter (MLD) and area, diameter stenosis percentage (Ds %), area stenosis percentage and stenosis length on CCTA. MLD and Ds % were also analyzed on QCA. FFR was measured on 52 ICAS lesions on CCTA and QCA. The diagnostic values of the best CCTA and QCA descriptors were calculated for ICAS with FFR $\leq$ 0.80. Of the 76 ICAS on CCTA, 52 (68 %) had a Ds % between 40 and 70 % on QCA. Significant intertechnique correlations were found between CCTA and QCA for MLD and Ds % ($p < 0.001$). In 17 (33 %) of the 52 ICAS lesions on QCA, FFR values were $\leq$0.80. Calcification circumference extent ($p = 0.50$) and plaque composition assessment ($p = 0.59$) did not correlate with the hemodynamic significance. Best predictors for FFR $\leq$ 0.80 stenosis were $\leq$1.35 mm MLD (82 % sensitivity, 66 % specificity), and $\leq$2.3 mm^2 minimal lumen area (88 % sensitivity, 60 % specificity) on CCTA, and $\leq$1.1 mm MLD (59 % sensitivity, 77 % specificity) on QCA. Quantitative CCTA and QCA poorly predict hemodynamic significance of ICAS, though CCTA seems to have a better sensitivity than QCA. In this range of stenoses, additional functional evaluation is required.

Electronic supplementary material The online version of this article (doi:10.1007/s10554-015-0748-1) contains supplementary material, which is available to authorized users.

✉ Olivier Ghekiere
olivierghekiere@gmail.com

[1] Department of Radiology, Centre Hospitalier Chrétien (CHC), Rue de Hesbaye 75, Liège 4000, Belgium

[2] Department of Radiology, Jessa Ziekenhuis, Stadsomvaart 11, Hasselt 3500, Belgium

[3] Faculty of Medecine and Life Sciences, Hasselt University, Martenlarenlaan 42, Hasselt 3500, Belgium

[4] Department of cardiology, Amphia Ziekenhuis, Molengracht 21, 4818 CK Breda, The Netherlands

[5] Department of cardiology, Centre Hospitalier Chrétien (CHC), Rue de Hesbaye 75, Liège 4000, Belgium

[6] Department of Radiology, Clinique du Parc, 50 rue Emile Combes, 34170 Castelnau-le-Lez, France

[7] Department of Radiology, Université Libre de Bruxelles (ULB), Route de Lennik 808, Bruxelles 1070, Belgium

[8] Department of Radiology, OLV ziekenhuis Aalst, Moorselbaan 164, Aalst 9300, Belgium

[9] Department of Cardiology, Jessa Ziekenhuis, Stadsomvaart 11, Hasselt 3500, Belgium

[10] Department of Radiology, University Hospital Sart-Tilman Liège (ULg), GIGA cardiovascular diseases, Domaine universitaire du Sart Tilman, Rue de l'hôpital 1, Liège 4000, Belgium

Published online: 01 September 2015

Keywords Intermediate-grade coronary artery stenosis · Quantitative coronary computed tomography angiography (CCTA) · Quantitative coronary angiography (QCA) · Fractional flow reserve (FFR) · Plaque descriptors · Hemodynamic significance

Introduction

About 7,4 million deaths were due to coronary heart disease in 2012 [1]. Catheter coronary angiography (CCA) is the standard of reference for the evaluation of patients with high pre-test probability for coronary artery disease (CAD), where relevant coronary artery stenosis (CAS) is defined as a diameter reduction ≥50 %. Nevertheless, CCA is invasive and cannot be recommended as the sole diagnostic test, especially in patients with low-to-intermediate probability for CAD. For these patients, coronary computed tomography angiography (CCTA) is a highly accurate diagnostic alternative, with regards to its correlation with CCA and its high negative predictive value to exclude ≥50 % stenosis [2, 3]. Meanwhile, to determine the likelihood for lesions' functional significance, the use of a discrete threshold lacks sensitivity, specificity or both [4, 5]. A range of stenosis beyond and above which hemodynamic significance is highly unlikely and likely, respectively, is therefore used in practice. Minimal diameter reduction in the 40–70 % range, the so-called intermediate-grade CAS, is not an uncommon finding on CCA, as it may account for up to 90 % of lesions assuming a Gaussian distribution [6, 7]. Because their visual assessment poorly predicts their functional significance, these lesions require additional workup, including, in some cases, pressure-wire fractional flow reserve (FFR) measurement, the standard Refs. [4, 5, 8, 9].

Other techniques, such as quantitative coronary angiography (QCA), reportedly provide key anatomical properties of these stenoses, potentially helping decision-making and predicting hemodynamic significance [10]. Interestingly, the same findings can be obtained non-invasively on CCTA [11]. However, the incremental value and influence on the need for functional evaluation or FFR assessment in case of intermediate-grade CAS have received only little attention in the literature. Although a statistical correlation exists between CCTA stenosis descriptors and FFR value, their diagnostic value to predict FFR ≤ 0.80 coronary stenoses was moderate. Furthermore, plaque descriptors such as calcification extent and plaque composition assessment providing a potential advantage of CCTA over QCA were either excluded or not investigated [12–14].

In summary, additional angiographic morphologic descriptors affecting hemodynamic significance are required. Therefore, the purpose of this study was to compare the diagnostic performance of CCTA using all stenosis and plaque descriptors to that of QCA in predicting hemodynamic significance of intermediate-grade CAS.

Materials and methods

Patients and study design

This study protocol was approved by the hospital Ethics Committee and all patients gave written informed consent after CCTA diagnosis of at least one intermediate-grade coronary stenosis. The study fully complied with our facility guidelines for cardiovascular disease requiring that vessel stenosis significance should be based on an "intention to treat" decision tree [15]. This implies that: (1) reported CAS is quantitatively assessed; (2) all stenoses above 70 % diameter reduction on QCA are considered significant and amenable to treatment; (3) Intermediate CAS should not be considered significant until proven using FFR.

Between September 2009 and November 2012, all patients undergoing CCTA in our institution for intermediate pre-test probability for CAD [16] based on cardiovascular risk factors, clinical examination, ECG, echocardiography and/or exercise ECG, having one or more coronary segment(s) >2 mm in diameter with an intermediate-grade CAS were eligible for this prospective study. All patients were more than 18 years and had no contraindications to X-ray exposure and iodinated contrast agent administration. In addition, they were requested to have no heart rhythm disease and no contraindication to the administration of beta-blockers if their resting HR was >65 beats/min. Figure 1 shows the flowchart of this study. In total, 123 patients were eligible; exclusion criteria were refusal to participate (n = 32), previous stress imaging testing (exercise stress or dobutamine echocardiography, vasodilator or dobutamine MRI, vasodilator or stress exercise stress scintigraphy) in the work up for the symptoms to avoid inclusion bias (n = 21), and unreported myocardial infarct at CCTA (n = 5).

CCTA technique and evaluation

CCTA was performed with a 64-detector CT-scanner (LightSpeed VCT or Discovery CT 750 high-definition, GE Healthcare, Milwaukee, USA). Patients with baseline HR > 65 beats per min (bpm) were given 5 mg of bisoprolol (Emconcor mitis, Merck, Overijse, Belgium) orally the evening before and the morning of the examination. For the patients with HR remaining >65 bpm an IV bolus of 5–15 mg of metoprolol (Seloken, AstraZeneca, Brussels, Belgium) was given prior to examination.

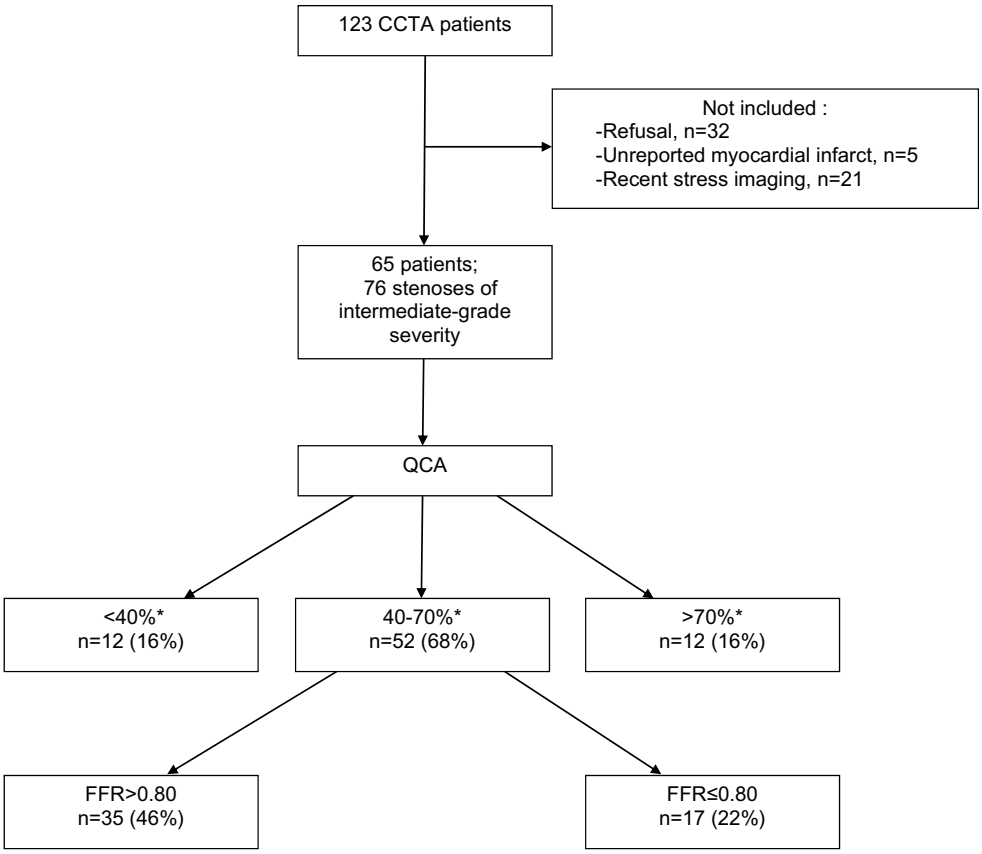


Fig. 1 Study flowchart. Numbers between parentheses are the percentages. *Asterisk* Reported percentages refer to minimal diameter stenosis. *CCTA* coronary computed tomography angiography, stenosis; *QCA* quantitative coronary angiography, *FFR* fractional flow reserve

After placement of an 18-gauge catheter into an antecubital vein, HR and arterial pressure check, the patient was placed on the scan table in dorsal decubitus, chest electrodes were placed and the quality of ECG signal was checked for optimal synchronization. HR was checked again for 2 min. HR variability was defined as the sum of absolute differences between two consecutive heartbeats divided by the number of heartbeats and expressed as mean interbeat difference. Scout imaging was performed and 0.4 mg of sublingual nitroglycerin was administered. Approximately 2 min later, CCTA was acquired during a bolus injection of 70–90 mL of iodinated contrast material (Iomeron 400 mg/mL, Bracco, Milan, Italia) depending on patient's body mass index (BMI), and followed by a saline chaser of 40 mL at a rate of 4.5–6 mL/s. The appropriate time-window for CCTA acquisition was determined using a stationary sequential axial scanning of 5 mm thickness every 3 s using 40 mA and 100 kV, to detect the contrast bolus arrival at the level of the ascending aorta (SmartPrep; GE Healthcare Milwaukee, USA). CCTA was performed in a craniocaudal direction with a Gantry rotation time of 350 ms, and a 64×0.625 mm collimation, allowing a 40 mm coverage per rotation. The tube voltage and the tube current were automatically set between 100 and 120 kV and 400 and 600 mA, respectively, to ensure a diagnostic image quality with the lowest dose, depending on the patient's BMI.

In patients with HR < 65 bpm and mean interbeat difference <10, a prospective ECG-triggered CCTA was performed ($n = 53$), allowing radiation dose reduction through a sequential acquisition of 4 consecutive transverse sections with tube-current switched "on" only during the 75 %-phase of the 4 RR cycles. Padding of the "tube-on" time was used to allow an adaptation to minor HR variations during acquisitions and modify retrospectively the reconstruction window to ensure an identical cardiac phase from one transverse section to another. The padding value was chosen by the operator on the basis of HR fluctuations prior to CCTA, and ranged from 50 ms in patients with stable HR to 100 ms in patients with HR variability close to 10.

In patients with >10 mean interbeat difference and/or HR ≥ 65 bpm ($n = 12, 18.5$ %), CCTA was acquired using a retrospective ECG-triggered technique and consisted of a helical scanning across all phases of the cardiac cycle, with a continuous table movement and small pitch to ensure multisegment reconstruction of each phase of the cardiac cycle. ECG-controlled tube current modulation was used in all patients, with the peak tube current in mid-diastole and 80 % reduction in systole. The pitch was determined automatically by the system, ranging from approximately 0.2 to 0.3, depending on the HR. Average dose-length product (DLP) and the estimated effective radiation dose (conversion of

k = 0.014 × DLP) for prospective (n = 53, 81.5 %), and retrospective (n = 12, 18.5 %) ECG-gated scanning was 219 mGy.cm; 3.07 mSv (range, 108–377 mGy.cm; 1.51–5.28 mSv) and 630 mGy.cm; 8.82 mSv (range, 444–1021 mGy.cm; 6.22–14.29 mSv), respectively.

In all patients, an initial reconstruction was performed at 75 % of the RR interval. The section thickness was 0.625 mm and the increment 0.625 mm with the use of a small- or medium-sized cardiac field of view. In case of motion artifacts on this phase, multiphase reconstructions were obtained for the data acquired with prospective and retrospective ECG triggering techniques, respectively with 5 and 10 % steps, in the ranges of 65–85 and 0–100 % of the RR intervals. Images were reconstructed using a standard reconstruction algorithm.

CCTA image interpretation

Visually, image quality allowed stenosis quantification in all patients. All reconstructed data were evaluated independently by 2 blinded readers (O.G. and A.N.) with >4-year experience in CCTA imaging. The volumetric data displaying the best image quality for each coronary segment was evaluated on a dedicated workstation (AW Volumeshare; GE Healthcare) equipped with software (CardIQ Xpress; GE Healthcare) enabling automatic centerline tracking of all coronary segments. When needed, small manual corrections were made on the centerline and coronary segments were subsequently displayed along their long and short axes. Then a review was performed to evaluate the atherosclerotic plaque on longitudinal and orthogonal reconstructions, with the window and width levels set to approximately 240 and 1200 for lumen and calcification detection. In case of severe calcifications, an additional sharp kernel reconstruction (High spatial resolution kernel, GE Healthcare) was performed to limit blooming artifacts of calcium. In all affected segments, the minimal lumen diameter (MLD) and minimal lumen area (MLA), measured manually using calipers and contour tracing on orthogonal reformations, were reported to the average between proximal and distal diameters and areas to the plaque, in order to define respectively minimal diameter and area stenosis percentages (Ds % and As %) (Fig. 2). In ostial lesions, only the distal reference site was used. Stenosis length (Ls) was measured on longitudinal reformations, from the start to the end of the narrowing. A semi-quantitative plaque composition assessment was performed using a 4-point scale: (1) soft (no calcification); (2) mixed with predominant soft component, (3) mixed with predominant calcified component, and (4) completely

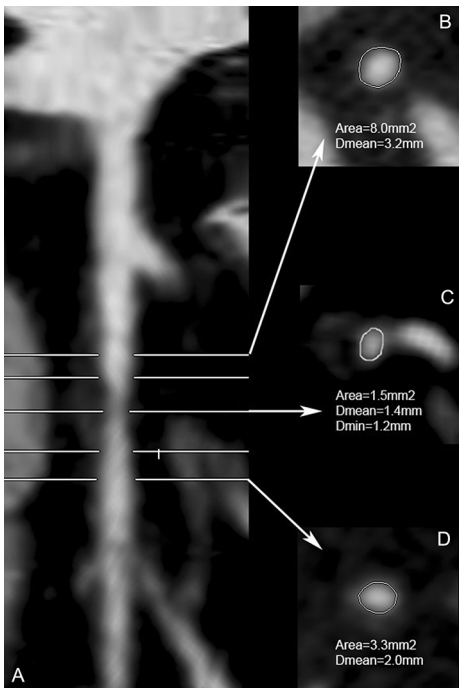


Fig. 2 Stenosis quantification on CCTA. An intermediate-grade coronary artery stenosis of the mid segment of the *left anterior* descending artery is displayed along its long axis (*A*). The length of the stenosis is measured from the proximal to the distal reference points where the vessel respectively starts to narrow or returns to its normal dimension. *B–D* are orthogonal transverse sections at both reference points and the maximal narrowing, showing vessel contours, areas and diameters. *CCTA* Coronary computed tomography angiography

Table 1 Patient demographics and cardiovascular risk factors

Patient characteristic	All patients (n = 65)
Age (years), mean ± SD [range]	62 ± 9 [44–82]
BMI (kg/m^2), mean ± SD [range]	28 ± 4 [21–42]
Heart rate on clinical examination (beats per minute), mean ± SD [range]	67 ± 10 [51–100]
Familial History of heart disease, n (%)	19 (29)
Personal History of heart disease, n (%)	8 (12)
Diabetes mellitus, n (%)	14 (22)
Smoking, n (%)	24 (37)
Hyperlipidemia, n (%)	44 (68)
Hypertension, n (%)	44 (68)

Table 2 Morphologic descriptors of 76 intermediate coronary artery stenosis [Mean ± SD (range)] and interobserver agreement on CCTA

Measurement	Reader 1	Reader 2	Intraclass correlation*
Reference diameter (mm)	3.21 ± 0.59 [1.90–5.10]	3.23 ± 0.60 [2.10–5.10]	0.94
MLD (mm)	1.43 ± 0.31 [0.80–2.30]	1.44 ± 0.33 [0.80–2.60]	0.88
Ls (mm)	8.76 ± 4.42 [3.00–28.00]	8.17 ± 4.58 [2.00–28.00]	0.84
Ds %	55.47 ± 6.40 [41.00–70.00]	55.59 ± 5.75 [42.00–69.00]	0.79
Reference area (mm^2)	8.44 ± 3.38 [2.70–19.30]	8.52 ± 3.62 [2.70–22.00]	0.96
MLA (mm^2)	2.50 ± 1.07 [1.00–6.60]	2.56 ± 1.23 [0.80–7.50]	0.91
As %	69.38 ± 8.43 [49.00–85.00]	69.07 ± 8.82 [50.00–86.00]	0.84

* All p values <0.001

SD standard deviation, *MLD* minimal lumen diameter, *Ds* diameter stenosis, *MLA* minimal lumen area, *As* area stenosis, *Ls* stenosis length, *CCTA* coronary computed tomography angiography

Table 3 Coronary plaque composition and calcification circumference extent of the 76 coronary artery stenoses of intermediate severity on CCTA and inter-observer variability

Lesion characteristics	Reader 1 n (%)	Reader 2 n (%)
Plaque composition grade		
i	16 (21)	16 (21)
ii	26 (34)	29 (38)
iii	30 (40)	28 (37)
iv	4 (5)	3 (4)
	kappa = 0.92	
Circumferential extent of calcification		
None	16 (21)	16 (21)
Low	19 (25)	19 (25)
Mild	20 (26)	22 (29)
High	16 (21)	15 (20)
Very high	5 (7)	4 (5)
	kappa = 0.88	

CCTA coronary computed tomography angiography

calcified. Orthogonal reformations were used to grade the highest coronary segment calcification circumference as: low (<25 % of the circumference), mild (<50 % of the circumference), high (<75 % of the circumference) and very high (> 75 % of the circumference). To compare CCTA with QCA, the average quantitative data of both readings were used for MLD, MLA, Ds %, As %, reference diameter and area, and Ls, while consensus readings were performed to resolve all discordant qualitative findings (plaque composition and calcification circumference extent).

QCA and pressure wire-derived FFR

CCA was performed after catheterization of a common femoral artery using a 7-French catheter, after 100–200 μg intracoronary nitroglycerin infusion, with at least 2 orthogonal projections for all segments as described in the AHA guidelines (3). All cineangiographies (Hexabrix 320 mgI/mL, Guerbet, Aulnay-Sous-Bois, France) were recorded on digital supports. A registry was made of the material used like catheters, guides, balloons, stents, and pressure guides, if applicable. QCA was performed with the Xcelera R3.1L1 system (Philips Medical Systems, Best, The Netherlands).

Intracoronary pressure wire-derived FFR was measured using a 0.014 inch pressure wire with a pressure-sensing guidewire system (FloWire® Doppler Guide Wire image Volcano Corporation). After placement of the pressure sensor tipped coronary angioplasty guide wire across the coronary stenosis, the absolute distal pressure was recorded at rest and at maximal myocardial hyperemia, i.e. 30–60 s after intracoronary injection of 15–20 mg of papaverine (papaverine STEROP 100 mg/3 mL).

The data provided by both QCA and FFR for the selected intermediate-grade stenosis include the diameter of reference, MLD at peak stenosis, Ds % and the FFR value.

Statistical analysis

Continuous data were expressed as mean ± standard deviation (SD). Cohen's Kappa and intraclass correlation (ICC) statistics were used to assess the readers' concordance for plaque composition and calcification circumference extent and quantitative measurements on CCTA, respectively. Bland–Altman statistics were used to assess the concordance between CCTA and QCA assessment of the MLD and Ds %. Fischer and Wilcoxon Rank Sum test were used to evaluate the respective distribution of qualitative and non qualitative variables according to hemodynamic significance. Receiver operator characteristics (ROC) statistics were used to determine the diagnostic performance of CCTA and QCA descriptors in predicting FFR $\leq$ 0.8 stenosis. A p value of less than 0.05 was considered to express a statistically significant difference.

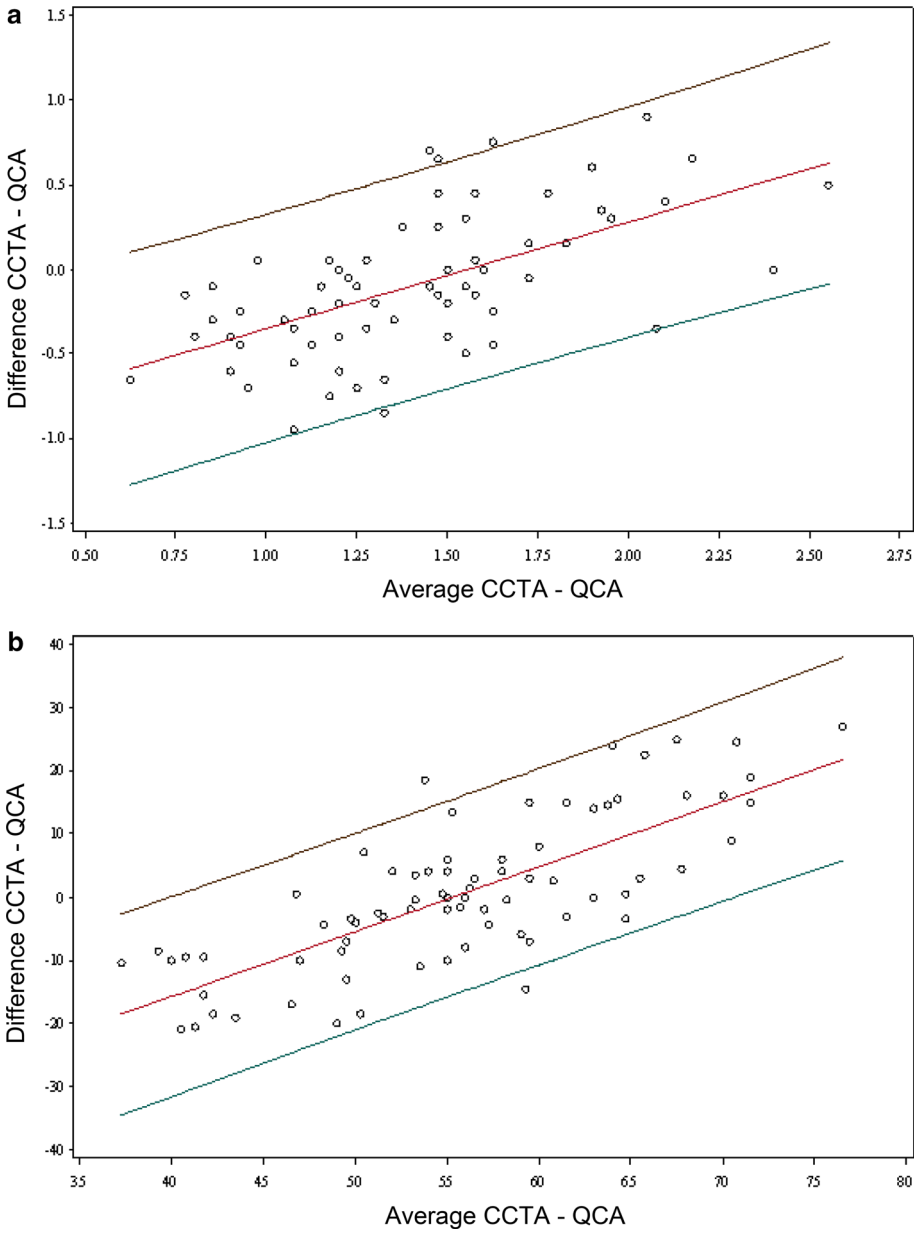


Fig. 3 **a** 95 % Confidence interval Bland–Altman plot of MLD on CCTA versus QCA. The average inter-technique difference show bias, as it increases significantly with the stenosis percentage ($p < 0.001$). *MLD* minimal lumen diameter, *CCTA* coronary computed tomography angiography, *QCA* quantitative coronary angiography. **b** 95 % Confidence interval Bland–Altman plot of Ds % on CCTA versus QCA. The average inter-technique difference show bias, as it increases significantly with the stenosis percentage ($p < 0.001$). Ds % = minimal diameter stenosis percentage; *MLD* minimal lumen diameter, *CCTA* coronary computed tomography angiography, *QCA* quantitative coronary angiography

Table 4 Distribution of lesion location, plaque type and calcification extent on CCTA with regard to the stenosis grade on QCA

Lesion characteristics	Stenosis grade on CCTA			
	<40 % stenosis (n = 12)	40–70 % stenosis (n = 52)	>70 % stenosis (n = 12)	*p* value (Fischer)
Entirely soft plaque, n (%)	3 (25)	10 (19)	3 (25)	0.85
High to very high calcification circumference, n (%)	3 (25)	11 (21)	5 (42)	0.33
Ostium (bi-tri-furcation) lesion, n (%)	3 (25)	9 (17)	4 (33)	0.44
At least one of the above, n (%)	7 (58)	28 (54)	10 (83)	0.17

CCTA coronary computed tomography angiography, *QCA* quantitative coronary angiography

Table 5 Distribution of lesion determinants in 52 lesions with regard to significance after FFR assessment

Lesion characteristics	Non-significant (n = 35)	Hemodynamic significant (n = 17)	*p* value
Reference diameter (mm)	3.28 ± 0.64	3.06 ± 0.42	0.20*
MLD (mm)	1.46 ± 0.31	1.28 ± 0.13	0.03*
Ls (mm)	7.08 ± 3.31	9.58 ± 4.52	0.14*
Minimal Ds (%)	55.30 ± 5.52	57.74 ± 4.18	0.11*
Reference area (mm^2)	8.91 ± 3.98	7.49 ± 2.02	0.24*
MLA (mm^2)	2.80 ± 1.28	1.98 ± 0.43	0.01*
As (%)	67.83 ± 7.74	71.97 ± 8.52	0.07*
QCA MLD (mm)	1.39 ± 0.44	1.13 ± 0.32	0.03*
QCA minimal Ds %	54.63 ± 6.70	58.18 ± 7.72	0.13*
Plaque composition grade			
i	7 (16)	3 (38)	0.59**
ii	17 (39)	3 (38)	
iii	18 (41)	2 (24)	
iv	2 (4)	0 (0)	
Circumferential extent of calcification			
None	7 (16)	3 (38)	0.50**
Low	11 (25)	2 (24)	
Mild	15 (34)	3 (38)	
High	9 (20)	0 (0)	
Very high	2 (4)	0 (0)	
Ostial (bi- or trifurcation) lesion	7 (16)	2 (25)	0.61**
Proximal lesion	14 (32)	3 (38)	1.00**

Numbers between parentheses are the percentages

MLD minimal lumen diameter, *Ds* diameter stenosis, *MLA* minimal lumen area, *As* area stenosis, *Ls* stenosis length, *CCTA* coronary computed tomography angiography, *FFR* fractional flow reserve, *QCA* quantitative coronary angiography

* Wilcoxon Rank-Sum test

** Fischer test

Results

In total, 65 patients (mean age 63 ± 9, range 44–82 years; 47 males) were included; their demographics and cardiovascular risk factors are given in Table 1. Seven and two patients had 2 and 3 segments with intermediate-grade CAS, respectively, resulting in a total of 76 intermediate-grade CAS at different segment locations, including 16 (21 %) ostial lesions (See additional table). No more than 1 intermediate to high-grade stenosis was present on the same coronary segment.

Mean/SD and range for measurements and frequency/percentage for plaque composition and calcification circumference extent of all 76 lesions on CCTA are given for both readers in Tables 2 and 3, respectively; the inter-reader concordances (kappa values range; 0.88–0.92) and correlations (ICC range; 0.79–0.96) were excellent. Plotting MLD and Ds % on CCTA using QCA as the standard of reference showed an excellent inter-technique correlation. However, average inter-technique difference increased significantly for MLD (Fig. 3a) and Ds % (Fig. 3b) ($p < 0.001$).

On QCA, 12/76 (16 %) lesions were above the 70 % Ds % threshold (average 78.2 ± 5.1 %), and 12/76 (16 %) below the 40 % Ds % threshold (average 34.9 ± 2.4 %). The respective rate of entirely soft lesions, highly to very highly calcified lesions and ostial lesions did not vary significantly among appropriately graded, undergraded and overgraded CAS on CCTA (Table 4).

Prediction of hemodynamic significance

FFR values were ≤0.80 (hemodynamically significant) in 17 (33 %) and >0.80 in 35 (67 %) of the 52 intermediate-grade CAS on QCA; their characteristics are given in Table 5. Lesion location, calcification circumference, plaque composition sub-categorization, reference diameter, reference area, Ds %, As %, and Ls distributions were not statistically different between the two groups (all *p* values >0.05) while CCTA-based MLD ($p = 0.030$) and MLA

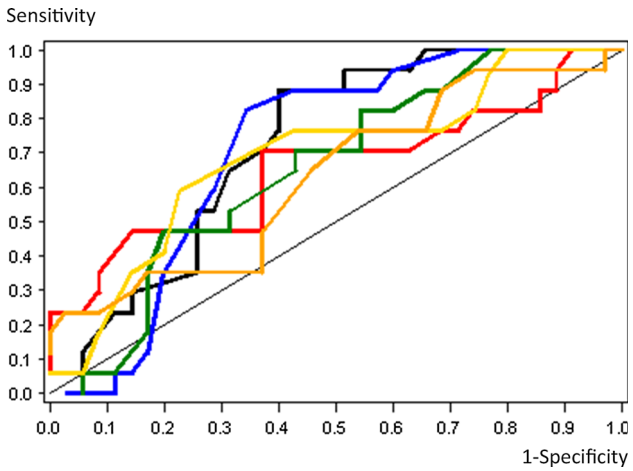


Fig. 4 Receiver Operator Characteristic curves predicting hemodynamic significance among 52 intermediate-grade lesions for: MLD (*blue curve*), MLA (*black curve*), Ds % (*green curve*) and As % (*red curve*) on CCTA, and MLD (*yellow curve*) and Ds % (*brown curve*) on QCA. Areas under curve values and their 95 % confidence intervals are respectively 0.71 [0.56–0.87], 0.72 [0.57–0.88], 0.65 [0.49–0.82], 0.65 [0.49–0.82], 0.69 [0.53–0.85] and 0.63 [0.46–0.80]. *CCTA* coronary computer tomography angiography, *MLD* minimal lumen diameter, *Ds %* minimal diameter stenosis percentage, *MLA* minimal lumen area; *As %* area stenosis percentage

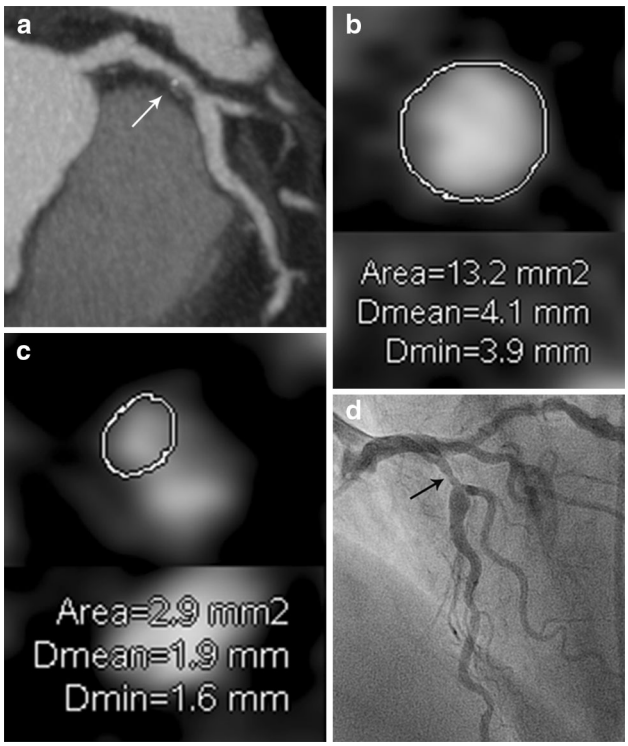


Fig. 5 A 62-year-old man with QCA-proven intermediate-grade coronary artery stenosis of the proximal segment of the left anterior descending artery on curvilinear reformation of CCTA (*arrow* in **a**) and CCA (*arrow* in **d**). The minimal lumen diameter (MLD) and minimal lumen area (MLA) at the level of the stenosis were respectively 1.6 mm and 2.9 mm^2 (**c**) on orthogonal reformats, resulting in a 59 % diameter narrowing when reported to the proximal reference diameter (**b**), while FFR value was 0.61. *CCTA* coronary computed tomography angiography; stenosis, *QCA* quantitative coronary angiography, *CCA* catheter coronary angiography, *FFR* fractional flow reserve

($p = 0.008$) were significantly lower in hemodynamic significant stenoses (all p values <0.05). Ls was ≤15 mm in all lesions, except one (25 mm). QCA-based MLD was also significantly lower in hemodynamic significant lesions ($p = 0.027$), unlike QCA-based Ds % ($p = 0.134$).

ROC curves for each of the CCTA and QCA lesion descriptors, with regard to the diagnostic threshold of FFR ≤ 0.8 are displayed in Fig. 4. The area under curves (AUC) ranged between 0.63 and 0.72. The best cut-off points on CCTA were ≤1.35 mm MLD [(14/17) 82 % sensitivity, (23/35) 66 % specificity] and ≤2.3 mm^2 MLA [(15/17) 88 % sensitivity, (21/35) 60 % specificity]; and ≤1.1 mm MLD [(10/17) 59 % sensitivity, (27/35) 77 % specificity] on QCA. All combinations of stenosis and plaque descriptors on CCTA and QCA did not result in higher diagnostic values (areas under ROC curves). Figures 5 and 6 represent the false-negative and false-positive cases of CCTA, respectively, using these MLD and MLA cut-offs.

Discussion

Generally thought, CCTA has a high negative predictive value in excluding significant CAS using a 50 % threshold [17, 18]. Paradoxically, when it comes to stenosis grade correlation with QCA, quantitative CCTA is often subject to both over- and underestimation [4, 12]. Our data were consistent with these data, with a total number of 24/76 (32 %) stenoses out of the intermediate severity range on QCA, with a good balance between overestimation (12/24 with <40 % stenosis) and underestimation (12/24 with >70 % stenosis). The respective advantages of CCA over CCTA and vice versa may theoretically cause these stenosis grade discrepancies. Of note, the spatial resolution of CCTA is lower as compared to CCA, especially in case of calcified lesions [19–21], but CCTA is superior to CCA for assessing eccentric, ostial or tortuous lesions [5]. Nevertheless, we found no convincing effect of the distribution of calcified plaques, ostial and angulated lesions on the rate of misclassified and correctly classified lesions. An explanation for the poor intertechnique categorical stenosis grade agreement came from the continuous lesion descriptors (such as MLD and Ds %) agreement assessment. Although some studies reported only moderate [22] or weak [23] correlations between CCTA and QCA, we found significant correlations between both techniques similarly to Meijboom et al. [4] and Voros et al. [24]. In addition, the inter-technique difference increased

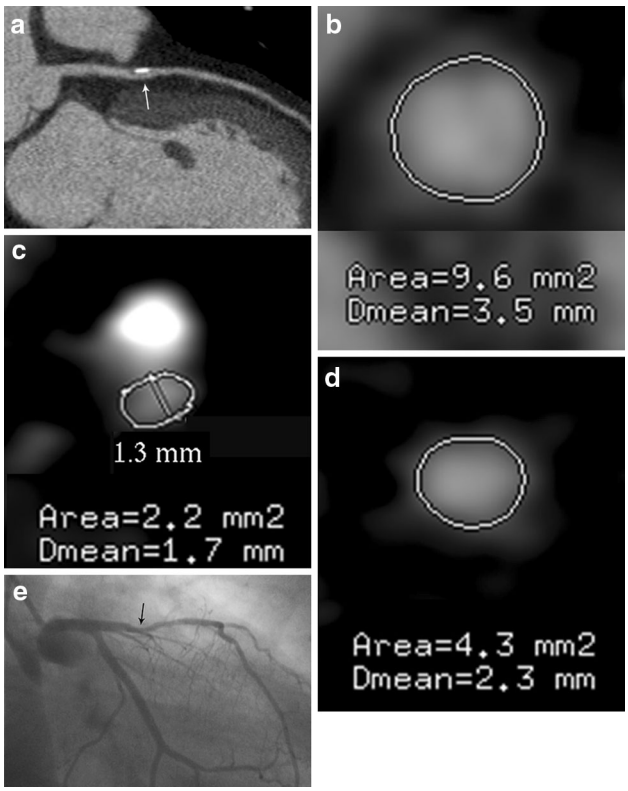


Fig. 6 A 66-year-old female with intermediate-grade coronary artery stenosis of the mid segment of the *left anterior* descending artery on curvilinear reformation of CCTA (*arrow* in **a**) and CCA (*arrow* in **e**). The minimal lumen diameter (MLD) and minimal lumen area (MLA) at the level of the stenosis were respectively 1.3 mm and 2.2 mm^2 (**c**) at CCTA on orthogonal reformats, resulting in a 55 % diameter narrowing when reported to the average between the proximal (**b**) and distal (**d**) vessel diameters, while FFR value was 0.83. *CCTA* coronary computed tomography angiography, stenosis; *QCA* quantitative coronary angiography, *CCA* catheter coronary angiography, *FFR* fractional flow reserve

significantly with the percentage stenosis as a result of a stenosis range bias between CCTA and QCA, meaning that stenoses at the limits of the range on CCTA would be automatically underestimated or overestimated on QCA.

As we observed, the corollary of a good intertechnique correlation for MLD and Ds % is that CCTA shares the known limitations of QCA in the prediction of hemodynamic significance using these descriptors [4, 9], meanwhile there was a slightly higher sensitivity for quantitative CCTA as compared to QCA. The ability to evaluate plaque composition and length, degree of calcification, MLA and As % are other potential advantages of CCTA over QCA; given these advantages, this study did not show any increment of the prediction of hemodynamic significance using these variables even with a combination of different descriptors. In addition, the cut-off values of quantitative imaging descriptors for hemodynamic significance are vessel-size dependent and therefore, highly variable according to the location and the vasotone [24, 25]. For example, in our study, 2.3 mm^2 MLA was the best predictor of FFR $\leq$ 0.8, with a sensitivity and specificity of 88 and 60 % respectively. Our cut-off value, though similar to the 2.2 mm^2 reported by Doh et al. [13], is slightly higher to the 1.8 mm^2 reported by Kristensen et al. [26], and lower than the 3.0 mm^2 reported by Opolski et al. [14].

The lesion rate of FFR $\leq$ 0.8 was 17/52 (33 %). This is within the range reported in previous studies assessing specifically intermediate-grade CAS on CCA [27, 28] and on CCTA [13]. However, our reported prevalence was substantially higher than the rate of 18 % (10/56) reported by Kristensen et al. [26] but lower than the rate of 45 % reported by Rossi et al. [12]. This difference in prevalence is mainly due to differences in FFR cut-off, patient selection and the mode of stenosis assessment (visual or quantitative) on CCTA. With regard to the increasing use of CCTA in patients with low to intermediate pre-test probability for CAD [29], the observed test-positive rate places increasing pressure on the diagnostic strategies for hemodynamic significance.

A limitation of this study may be the relatively low number of patients included. Our few data missed some challenging but not uncommon lesions, such as long (>15 mm) or multiple successive stenoses. However, in our study, patients with intermediate-grade CAS were enrolled in a guideline-compliant clinical decisional algorithm to determine the hemodynamic significance outcome of these lesions based on stenosis and plaque descriptors analyses from both quantitative CCTA and QCA. Indeed, the 181 and 71 coronary artery lesions reported in the prospective study of Doh et al. [13] and Opolski et al. [30]. respectively, were included on the basis of a visual analysis of CCA and CCTA. The 85 lesions recently described by Rossi et al. [12] resulted from a retrospective assessment. Because of our study design, no FFR assessment was available in 24/76 lesions. However, this study was undertaken in accordance with clinical practice guidelines defining the need for coronary revascularization in lesions with minimal diameter stenosis $\geq$70 % or positive FFR assessment [15]. In current practice, CCTA morphological descriptors of lesion stenosis are daily used to determine the likelihood for a coronary lesion to be of hemodynamic significance. Although CCTA may perform well to determine the likelihood of hemodynamic significance in high- and low-grade stenoses, our work adds to the current knowledge that this may be untrue in the intermediate-severity range. Furthermore, this also applies to QCA, as CCTA seems to perform slightly better. In addition, we used a specific manufacturer workstation and could not guarantee that other workstations would provide strictly identical results. Lastly, we did not assess

the clinical and cost effectiveness of the strategies in the workup for intermediate-grade CAS on CCTA, which will require further investigations.

Conclusions

Quantitative CCTA and QCA poorly predict the hemodynamic significance of intermediate CAS, though CCTA seems to have a better sensitivity than QCA. In this range of stenoses, additional functional evaluation is required. New clinical and cost effective functional evaluation strategies and guidelines are needed, especially with regard to the increasing use of CCTA in patients with low-to-intermediate probability for CAD.

Acknowledgments The authors would like to thank Dr John Patrick Garvey, who recently passed away, for his assistance in linguistic reviewing the manuscript. We also thank GE Healthcare for the trial support.

Compliance with ethical standards

Conflict of interest None.

References

1. WHO. Cardiovascular diseases (CVDs) 2015
2. Vanhoenacker PK, Heijenbrok-Kal MH, Van Heste R, Decramer I, Van Hoe LR, Wijns W, Hunink MG (2007) Diagnostic performance of multidetector CT angiography for assessment of coronary artery disease: meta-analysis. Radiology 244:419–428
3. Sun Z, Lin C, Davidson R, Dong C, Liao Y (2008) Diagnostic value of 64-slice CT angiography in coronary artery disease: a systematic review. Eur J Radiol 67:78–84
4. Meijboom WB, Van Mieghem CA, van Pelt N, Weustink A, Pugliese F, Mollet NR, Boersma E, Regar E, van Geuns RJ, de Jaegere PJ, Serruys PW, Krestin GP, de Feyter PJ (2008) Comprehensive assessment of coronary artery stenoses: computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. J Am Coll Cardiol 52:636–643
5. Tobis J, Azarbal B, Slavin L (2007) Assessment of intermediate severity coronary lesions in the catheterization laboratory. J Am Coll Cardiol 49:839–848
6. Rensing BJ, Hermans WR, Deckers JW, de Feyter PJ, Tijssen JG, Serruys PW (1992) Lumen narrowing after percutaneous transluminal coronary balloon angioplasty follows a near gaussian distribution: a quantitative angiographic study in 1445 successfully dilated lesions. J Am Coll Cardiol 19:939–945
7. Patil CV, Beyar R (2000) Intermediate coronary artery stenosis: evidence-based decisions in interventions to avoid the oculostenotic reflex. Int J Cardiovasc Intervent 3:195–206
8. Kern MJ, Lerman A, Bech JW, De Bruyne B, Eeckhout E, Fearon WF, Higano ST, Lim MJ, Meuwissen M, Piek JJ, Pijls NH, Siebes M, Spaan JA (2006) Physiological assessment of coronary artery disease in the cardiac catheterization laboratory: a scientific statement from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. Circulation 114:1321–1341
9. Sarno G, Decraemer I, Vanhoenacker PK, De Bruyne B, Hamilos M, Cuisset T, Wyffels E, Bartunek J, Heyndrickx GR, Wijns W (2009) On the inappropriateness of noninvasive multidetector computed tomography coronary angiography to trigger coronary revascularization: a comparison with invasive angiography. JACC Cardiovasc Intervent 2:550–557
10. Waksman R, Legutko J, Singh J, Orlando Q, Marso S, Schloss T, Tugaoen J, DeVries J, Palmer N, Haude M, Swymelar S, Torguson R (2013) FIRST: fractional flow reserve and intravascular ultrasound relationship study. J Am Coll Cardiol 61:917–923
11. Natsumeda M, Nakazawa G, Murakami T, Torii S, Ijichi T, Ohno Y, Masuda N, Shinozaki N, Ogata N, Yoshimachi F, Ikari Y (2015) Coronary angiographic characteristics that influence fractional flow reserve. Circ J 79:802–807
12. Rossi A, Papadopoulou SL, Pugliese F, Russo B, Dharampal AS, Dedic A, Kitslaar PH, Broersen A, Meijboom WB, van Geuns RJ, Wragg A, Ligthart J, Schultz C, Petersen SE, Nieman K, Krestin GP, de Feyter PJ (2014) Quantitative computed tomographic coronary angiography: does it predict functionally significant coronary stenoses? Circ Cardiovasc Imaging 7:43–51
13. Doh JH, Koo BK, Nam CW, Kim JH, Min JK, Nakazato R, Silalahi T, Prawira H, Choi H, Lee SY, Namgung J, Kwon SU, Kwak JJ, Lee WR (2014) Diagnostic value of coronary CT angiography in comparison with invasive coronary angiography and intravascular ultrasound in patients with intermediate coronary artery stenosis: results from the prospective multicentre FIGURE-OUT (Functional Imaging criteria for GUiding REview of invasive coronary angiOgraphy, intravascular Ultrasound, and coronary computed Tomographic angiography) study. Eur Heart J Cardiovasc Imaging 15:870–877
14. Opolski MP, Kepka C, Achenbach S, Pregowski J, Kruk M, Staruch AD, Kadziela J, Ruzyllo W, Witkowski A (2014) Advanced computed tomographic anatomical and morphometric plaque analysis for prediction of fractional flow reserve in intermediate coronary lesions. Eur J Radiol 83:135–141
15. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA (2009) ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness criteria for coronary revascularization: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology: Endorsed by the American Society of Echocardiography, The Heart Failure Society of America, and The Society of Cardiovascular Computed Tomography. Circulation 119:1330–1352
16. Hendel RC, Patel MR, Kramer CM, Poon M, Carr JC, Gerstad NA, Gillam LD, Hodgson JM, Kim RJ, Lesser JR, Martin ET, Messer JV, Redberg RF, Rubin GD, Rumsfeld JS, Taylor AJ, Weigold WG, Woodard PK, Brindis RG, Douglas PS, Peterson ED, Wolk MJ, Allen JM (2006) ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. J Am Coll Cardiol 48:1475–1497
17. Raff GL, Gallagher MJ, O'Neill WW, Goldstein JA (2005) Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography. J Am Coll Cardiol 46:552–557

18. Herzog C, Zwerner PL, Doll JR, Nielsen CD, Nguyen SA, Savino G, Vogl TJ, Costello P, Schoepf UJ (2007) Significant coronary artery stenosis: comparison on per-patient and per-vessel or per-segment basis at 64-section CT angiography. Radiology 244:112–120
19. Otero HJ, Steigner ML, Rybicki FJ (2009) The "post-64" era of coronary CT angiography: understanding new technology from physical principles. Radiol Clin North Am 47:79–90
20. Yong AS, Ng AC, Brieger D, Lowe HC, Ng MK, Kritharides L (2011) Three-dimensional and two-dimensional quantitative coronary angiography, and their prediction of reduced fractional flow reserve. Eur Heart J 32:345–353
21. Leber AW, Knez A, von Ziegler F, Becker A, Nikolaou K, Paul S, Wintersperger B, Reiser M, Becker CR, Steinbeck G, Boekstegers P (2005) 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 46:147–154
22. Feuchtner G, Loureiro R, Bezerra H, Rocha-Filho JA, Sarwar A, Pflederer T, Marwan M, Petranovic M, Raffel CO, Brady TB, Jang IK, Achenbach S, Cury RC (2012) Quantification of coronary stenosis by dual source computed tomography in patients: a comparative study with intravascular ultrasound and invasive angiography. Eur J Radiol 81:83–88
23. Joshi SB, Okabe T, Roswell RO, Weissman G, Lopez CF, Lindsay J, Pichard AD, Weissman NJ, Waksman R, Weigold WG (2009) Accuracy of computed tomographic angiography for stenosis quantification using quantitative coronary angiography or intravascular ultrasound as the gold standard. Am J Cardiol 104:1047–1051
24. Koo BK, Yang HM, Doh JH, Choe H, Lee SY, Yoon CH, Cho YK, Nam CW, Hur SH, Lim HS, Yoon MH, Park KW, Na SH, Youn TJ, Chung WY, Ma S, Park SK, Kim HS, Tahk SJ (2011) Optimal intravascular ultrasound criteria and their accuracy for defining the functional significance of intermediate coronary stenoses of different locations. JACC Cardiovasc Intervent 4:803–811
25. Decramer I, Vanhoenacker PK, Sarno G, Van Hoe L, Bladt O, Wijns W, Parizel PM (2008) Effects of sublingual nitroglycerin on coronary lumen diameter and number of visualized septal branches on 64-MDCT angiography. AJR Am J Roentgenol 190:219–225
26. Kristensen TS, Engstrom T, Kelbaek H, von der Recke P, Nielsen MB, Kofoed KF (2010) Correlation between coronary computed tomographic angiography and fractional flow reserve. Int J Cardiol 144:200–205
27. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, Maccarthy PA, Van't Veer M, Pijls NH (2010) Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol 55:2816–2821
28. Nam CW, Yoon HJ, Cho YK, Park HS, Kim H, Hur SH, Kim YN, Chung IS, Koo BK, Tahk SJ, Fearon WF, Kim KB (2010) Outcomes of percutaneous coronary intervention in intermediate coronary artery disease: fractional flow reserve-guided versus intravascular ultrasound-guided. JACC Cardiovasc Intervent 3:812–817
29. Einstein AJ, Elliston CD, Arai AE, Chen MY, Mather R, Pearson GD, Delapaz RL, Nickoloff E, Dutta A, Brenner DJ (2010) Radiation dose from single-heartbeat coronary CT angiography performed with a 320-detector row volume scanner. Radiology 254:698–706
30. Opolski MP, Pregowski J, Kruk M, Staruch AD, Witkowski A, Demkow M, Hryniewiecki T, Michalek P, Ruzyllo W, Kepka C (2014) The prevalence and characteristics of intra-atrial right coronary artery anomaly in 9284 patients referred for coronary computed tomography angiography. Eur J Radiol 83:1129–1134