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ORIGINAL PAPER

The evolution and investigation of native coronary arteries in patients after coronary stent implantation: a study by 320-detector CT angiography

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Abstract To study the role of 320-detector coronary computed tomography angiography (CTA) in assessing native coronary arteries in patients treated with coronary stents. 123 patients with coronary stenting received both CTA and conventional coronary angiography (CCA) within 1 day. The clinical parameters, coronary calcium scoring, CTA and CCA were analyzed to determine the prevalence of significant stenosis of native coronary arteries (SSNCA), the predictive value of CTA and the factors correlating with SSNCA and newly developed SSNCA after stenting (NDSSNCAS), with CCA as the standard of reference, using both vessel-based analysis (VBA) and patient-based analysis (PBA). Both the source and the reconstructed images were analyzed by CTA. All native coronary arteries were interpretable independent of cardiac motion. CTA showed a sensitivity/specificity of 93.5 %/97.3 % and 92.5 %/92.5 % in diagnosing SSNCA in VBA and PBA, respectively. The significant factors related to SSNCA were higher calcium scores ($P = 0.003$), a higher serum glucose level ($P = 0.048$), a greater number of vessels without previous stent placement ($P = 0.003$) and fewer stents implanted within the vessels ($P = 0.003$). The risk factors showed no significant correlation from PBA on SSNCA or from NDSSNCAS on either VBA or PBA. CTA demonstrates excellent correlation with CCA. The prevalence of SSNCA is significantly correlated with the presence of higher calcium scores in the arteries, a higher serum glucose level, a greater number of vessels without previous stent placement and fewer stents implanted within the vessels; PBA on SSNCA and NDSSNCAS on both VBA and PBA showed no significance.

Keywords Coronary artery stenosis · Coronary computed tomography angiography · Calcium score · Coronary stents · Native coronary artery

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Introduction

Stenting of coronary arteries is the most common revascularization procedure for treating patients with coronary artery disease (CAD) and is becoming increasingly popular [1]. Recurrent CAD may occur in any native coronary artery [2]. The prevalence of significant stenosis of native coronary arteries (SSNCA) in patients after stent implantation has been reported to be similar to that of in-stent restenosis with more than 1 year after stent placement [3–7]. Conventional coronary angiography (CCA) is the gold standard for diagnosing recurrent CAD [8], but it poses the potential risk of complications and patient discomfort [8, 9]. Therefore, there is a need to search for less invasive methods to detect SSNCA after stent placement.

Multidetector computed tomographic coronary angiography (CTA) is increasingly used for non-invasive imaging in the identification or exclusion of significant CAD using 64-detector computed tomography (CT) [10–12]. The technological development of coronary CTA is evidenced by the

320-detector CTA with a longitudinal coverage of 16 cm, which enables the completion of an entire cardiac scan within a single heartbeat [under controlled heart rate (HR)], thereby providing a comparable diagnosis with a reduction in radiation dosage and the number of un-interpretable segments due to HR variability [8, 12–14]. To our knowledge, previous studies have focused primarily on patients with coronary arterial bypass grafting or variability in HR and arrhythmia [8, 13]; very few have used 320-detector CT to assess SSNCA [13]. This is the first report to describe the role of 320-detector CT in assessing native coronary arteries and analyzing the correlating factors of SSNCA and newly developed SSNCA after stenting (NDSSNCAS).

Materials and methods

Patient selection

Between September 2010 and January 2012, this prospective research study included a total of 123 patients (aged from 36 to 79 years, with a mean age of 56.99; 106 patients were male) who were asymptomatic but had previous coronary arterial stenting performed at a single medical center. Patients were excluded from this study if they refused to participate, or if they had any known contraindications to the contrast medium, any allergy to contrast medium and beta-blockers, or a history of renal insufficiency or hemodynamic instability. The institutional review board approved this study, and informed consent was obtained from all patients. Patient characteristics and clinical information (smoking, diabetes mellitus, hyperlipidemia) and the other coronary risk factors—including time elapsed since stent placement, laboratory data (baseline glucose and cholesterol levels)—are also reviewed and collected. Diabetes mellitus is recorded if there is documentation of its existence or two episodes of fasting glucose >125 mg/dl in the chart. Hyperlipidemia is recorded if there is documented hyperlipidemia or hypercholesterolemia.

Coronary calcium scoring and CTA

All patients underwent Agatston coronary calcium scoring (CS) and subsequent CTA using a 320-detector CT (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) with 320 detector rows, each 0.5 mm wide, and a gantry rotation time of 0.35 s with craniocaudal or z-axial coverage of up to 160 mm. Tube voltages (kVp) and currents (mAs) were selected according to the manufacturer's suggestions and were primarily based on patients' body mass index (BMI). Kernel setting FC12 was used for CS and FC03 and FC05 were used for CTA. All patients received subsequent CCA within 1 day of CTA.

Patient preparation

Patients' blood glucose levels and cholesterol profiles were recorded. Vital signs and clinical information were recorded on the day of CTA, including age, gender, body height, body weight, BMI, chest circumference, waist circumference and baseline blood pressure. Patients were given one to four tablets of β-blocker Inderal (10 mg propranolol in each tablet, AstraZeneca UK Limited, Cheshire, United Kingdom) half an hour to 1 hour before the scan if their HR was ≥65 beats per minute (bpm). Alternatively, in cases of persistent HR over 65 bpm, esmolol (esmolol HCL Injection, 10 mg/mL, 0.05 mL/Kg, JenYa Biotech Incor. Limited, Hsing Chu, Taiwan) was administered intravenously at a dosage of 0.5 mg/Kg, under electrocardiography (ECG) monitoring. A tablet of Nitrostat (each tablet containing 0.6 mg of nitroglycerin, Pfizer Pharmaceuticals LLC, Puerto Rico, USA) was administered sublingually three minutes prior to scanning to improve coronary artery imaging.

Scanning parameters

CS was routinely performed and scores were assessed and recorded by workstation software (Vitrea FX, Vital Images, Minnetonka, MN, USA). The scan was also used as a reference to tailor scan length. Slice thickness was set as 3 mm, with the coverage area extending from the pulmonary trunk down to the diaphragm. All CTA procedures were performed under prospective ECG-gated scans. If a patient's HR was ≤65 bpm, a one-heartbeat acquisition and half-scan reconstruction was used at mid-diastolic phase (65–85 %). Patients with HRs from 66 to 79 and ≥80 bpm were scanned with either two- or three-heartbeat acquisitions, respectively, with alternative adjustment to a wider phase window (35–85 %) as necessary.

For vascular enhancement, a bolus of contrast medium (Iohexol; Omnipaque 350, Amersham Health, Co, Cork or Ireland, GE Healthcare) was administered intravenously, with a volume of 60 mL for patients with BMI ≤28 and 70 mL for those with BMI >28 at a rate of 5 mL/s through the antecubital vein using a power injector (Mallinckrodt LF OptiVantage DH V8402, USA); this was followed by 40 mL of saline chasing at a rate of 5 mL/s. CT scanning was started manually when contrast medium reached the peak in the left ventricle.

Image quality analysis

CS and CTA images were analyzed retrospectively in consensus by two radiologists (with 7 and 31 years of experience, respectively) who were blinded to the CCA results.

The total calcium score was measured (using workstation software) as a total amount from the four major native coronary vessels with the side branches considered part of their corresponding main vessel. Calcium scores in each major coronary artery were also recorded for analysis. Due to the difficulty in differentiating the stent from calcium plaques, those coronary segments with calcium covered by the stent were excluded from measurement.

With regard to CTA, the source images as well as the reconstructed images were analyzed, including an axial view, two oblique views, spider views, global views with maximum intensity projections, curved multiplanar reconstruction, a tree view, and 3-D volume rendering. Since a large number (85.5 %) of stents had been deployed in the proximal and middle segments of the coronary artery, and it was difficult to accurately quantify the extent of stent coverage with several stents covering more than one segment, the study performed both patient-based and vessel-based analysis (VBA) for both CS and CTA analysis. Segment-based analysis was not performed. The VBA included examination of the coronary arteries in the context of the four major arteries: left main coronary (LM), left anterior descending coronary (LAD), left circumflex coronary (LCX) and right coronary (RCA); while all side-branches were considered part of their corresponding main coronary arteries. As previously mentioned, the coronary segments with calcium covered by the stent were excluded from measurement. SSNCA was defined as luminal diameter reduction of the native artery by $\geq$50 %.

Both vessel-based and patient-based analyses were performed to evaluate the diagnostic accuracy per patient for detecting SSNCA. The patient was identified as having SSNCA if there was a presence of at least one vessel with SSNCA. The effective radiation dose in mSv was estimated by multiplying the dose-length product (DLP) with a conversion factor of 0.014 mSv/mGy cm [8, 15] for both men and women.

CCA protocol

Aspirin (300 mg) and clopidogrel (300 mg) were given orally before angiography. The femoral or radial artery was punctured using the standard Seldinger technique after adequate local anesthesia. Six French Judkins left and Judkins right (Cordis Corporation, Miami, FA, USA) catheters were used for left and RCA angiography, separately. Heparin 3000 U was administered if the coronary angiography was performed from radial access. Coronary angiography was performed in true left anterior oblique (LAO); right anterior oblique (RAO); RAO caudal, in

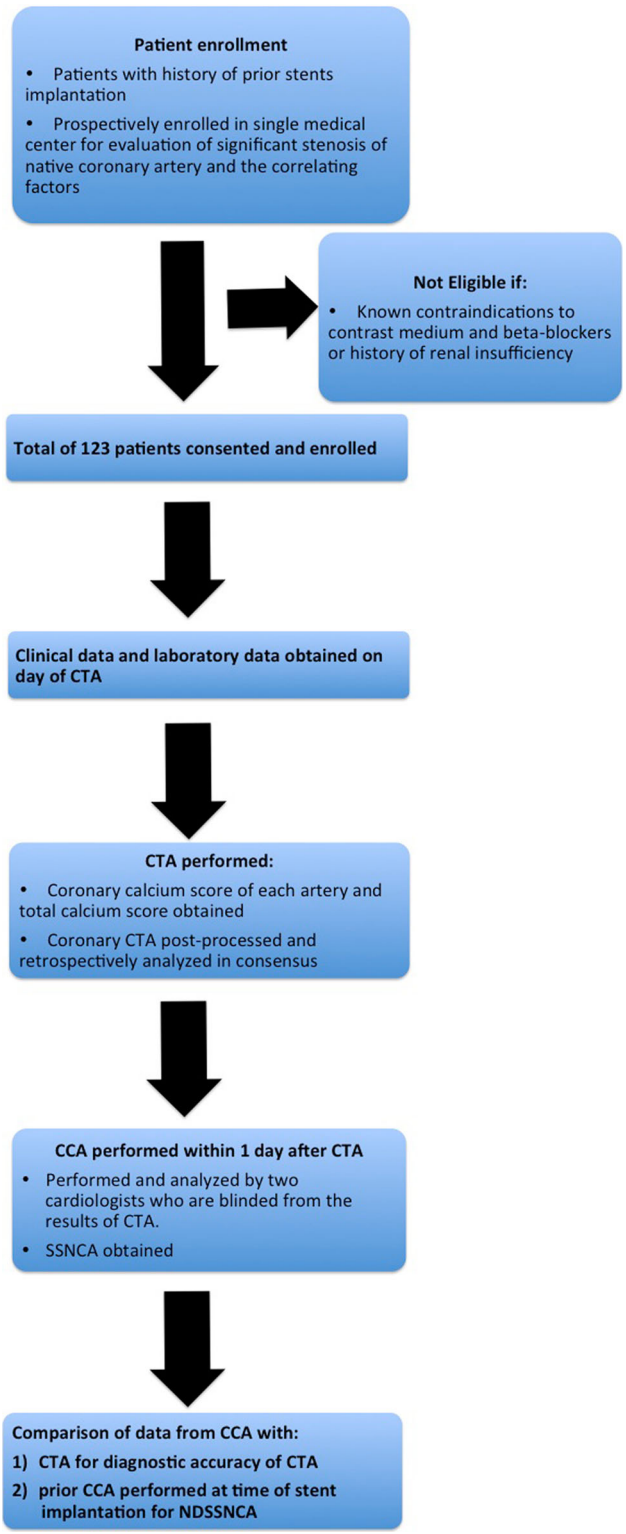

Fig. 1 Flow-chart showing the process in patient inclusion, exclusion, images data collection and image analysis. *CTA* computed tomographic angiography, *SSNCA* significant stenosis of native coronary artery, *CCA* conventional coronary angiography, *NDSSNCA* newly developed SSNCA after stenting

which the LAO cranial view was performed for both LCX and LAD; and RAO view for RCA. All the images were recorded at 15 frames/s by a monoplane X-ray angiogram (AXIOM-Artis, Siemens, Forchheim, Germany) at a resolution of 512 × 512 pixels. Quantitative coronary angiographic data for coronary stenosis was analyzed using a quantitative analysis software package (Scientific QCA Analysis, Siemens). The CCAs were performed and analyzed by two experienced cardiologists (C.C.C. and I.C.H.) blinded by the CTA data.

Two CCA datasets were analyzed in each patient with the same manner, including the current CCA after the CTA and a retrospective search for the previous CCA performed during the time of stent implantation. The presence of NDSSNCAS was defined as SSNCA, which was not present during the prior CCA performed at the time of stent placement, but was newly developed at the CCA performed after the CTA. The factors correlating with the development of NDSSNCAS were also analyzed. Significant stenosis was defined as a luminal diameter reduction of ≥50 %. Both vessel-based and patient-based analyses were performed to evaluate the correlating factors of SSNCA and NDSSNCAS. The patient was identified as having SSNCA if there was the presence of at least one vessel with SSNCA. The important workflow in the process of patient selection, exclusion, image acquisition and analysis was denoted in Fig. 1.

Statistical analysis

Continuous variables were expressed as mean ± SD. Categorical data were compared using Chi square testing or Fisher's exact test when appropriate; the Mann–Whitney U test was used to compare differences in continuous variables between groups. A two-sided *P* value less than 0.05 was considered statistically significant. The diagnostic accuracy of 320-detector CTA to detect SSNCA was compared to ICA as the reference standard and expressed as accuracy, sensitivity, specificity, positive predictive value and negative predictive value. Statistical analysis was performed using SPSS software (version 17; SPSS Inc., Chicago, IL, USA).

Results

General information

All 123 patients successfully completed the CTA and CCA without complications. Patients' demographic data were summarized in Table 1. The average time of examination after stenting was 4–81 (12.66 ± 13.53) months. Although stents were placed in all four major coronary arteries, the majority were deployed in the LAD (52.4 %, 109/211). The HR during scanning was 58.4 ± 10.59 bpm, while Beta-blocker was administered whenever necessary. Under this HR, no native coronary arteries were considered uninterpretable due to motion artifact. Only six patients (4.9 %) required a two-heartbeat scan; all other patients were scanned with a one-heartbeat scan. The DLP for CTA was 447.16 ± 273.78 mGy cm with an effective radiation dose of 6.26 ± 3.83 mSv. The DLP for CS acquired during the scanning was 146.89 ± 27.79 mGy cm with a calculated effective radiation dose of 2.06 ± 0.39 mSv.

Table 1 Summary of demographic data from 123 patients

Category	Values (mean ± SD)
Chest circumference (cm)	96.47 ± 8.68
Waist circumference (cm)	93.59 ± 11.19
Body mass index (kg/m^2)	26.57 ± 3.77
Blood pressure (mmHg)	
Systolic	137.56 ± 20.50
Diastolic	78.09 ± 10.33
Risk factors for coronary artery disease	
Diabetes mellitus	37 (30.1 %)
Hypertension	65 (52.8 %)
Smoking	14 (11.4 %)
Obesity	52 (42.3 %)
Hyperlipidemia	26 (21.1 %)

Prevalence of SSNCA and diagnostic value of CTA

The prevalence of significant stenosis in CTA and CCA, and the predictive value of CTA compared with CCA using VBA, are summarized in Table 2. There was a significant correlation between CTA and CCA with a high sensitivity and specificity in differentiating SSNCA from non-significant stenosis of native coronary arteries (NSSNCA) (Fig. 2). The highest prevalence of SSNCA was found in LCX, with the same figure of 26.8 % in both CTA and CCA. The lowest prevalence of CAD (16.3 %) was found in LAD. The best correlation and predictive value was observed for RCA.

With regard to patient-based analysis (PBA), a total of 56 patients (45.5 %) were diagnosed as having SSNCA by CCA, while 67 patients (54.5 %) were considered to have NSSNCA. In contrast to VBA, CTA showed similar prevalence of SSNCA (46.3 %, 57/123 patients) as compared with CCA. Among those with SSNCA, 38 (30.9 %) had single-vessel SSNCA, 15 (12.2 %) had two-vessel SSNCA and 3 had three-vessel SSNCA (2.4 %).

The causes of false positives and false negatives are summarized in Table 3, with blooming artifacts being the major cause of false positives. It is notable that all

Table 2 Prevalence of significant stenosis of native coronary artery (SSNCA) and diagnostic value of computed tomographic angiography (CTA) versus CCA on VBA

	RCA ($n = 123$)	LAD ($n = 123$)	LCX ($n = 123$)	Total ($n = 492$)
Number and percentage of vessels with SSNCA in CTA	24 (19.5 %)	25 (20.3 %)	33 (26.8 %)	83 (16.9 %)
Number and percentage of vessels with SSNCA in CCA	24 (19.5 %)	20 (16.3 %)	33 (26.8 %)	77 (15.7 %)
Accuracy (%)	98.4	94.3	95.1	96.7
Sensitivity (%)	95.8	95	90.9	93.5
Specificity (%)	99	94.2	96.7	97.3
Positive predictive value (%)	95.8	76	90.9	86.7
Negative predictive value (%)	99	99	96.7	98.8

The correlations between CTA and CCA could not be computed and compared in the left main artery as no SSNCA was found by CCA. *RCA* right coronary artery, *LAD* left anterior descending coronary artery, *LCX* left circumflex artery

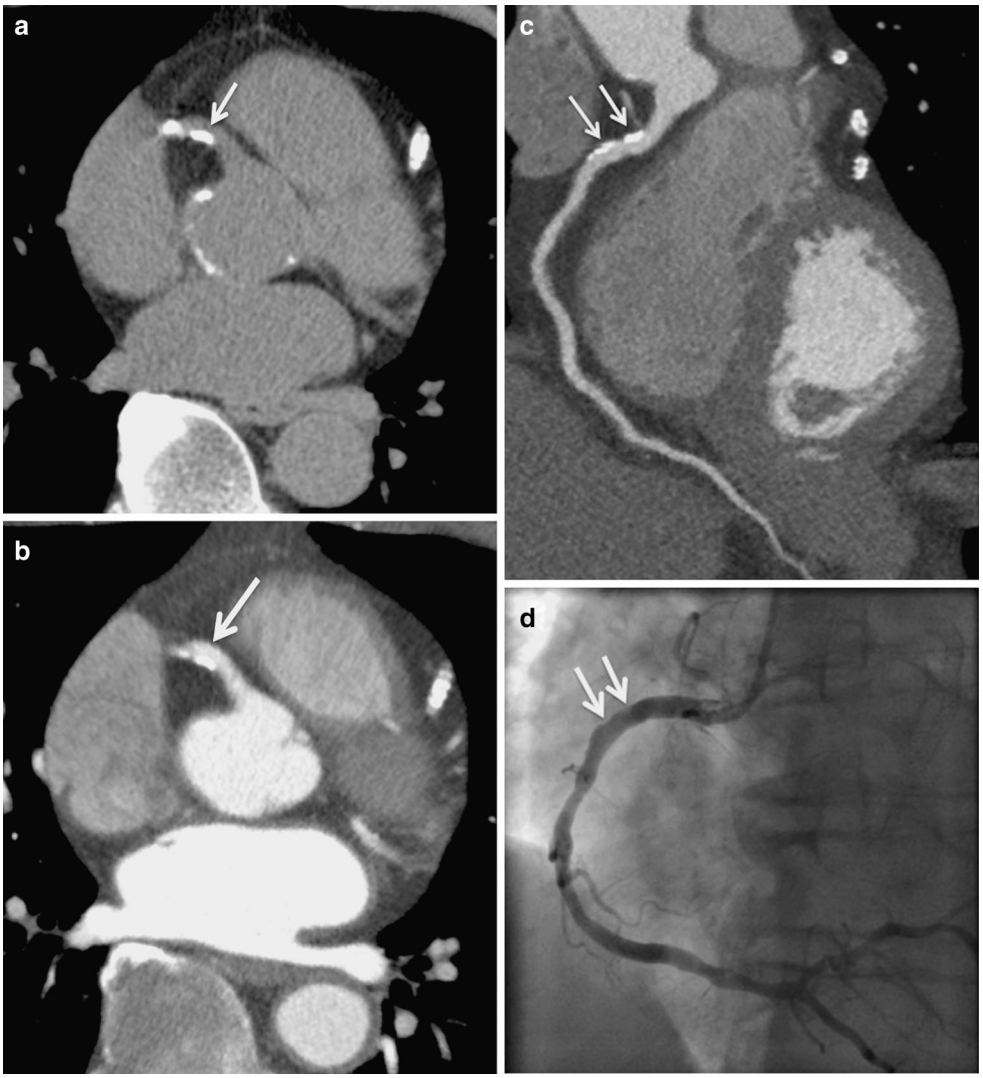

Fig. 2 A 70-year-old male underwent coronary CT angiography with a total calcium score of 350. **a** Non-contrast enhanced axial CT revealed two calcified plaques in proximal RCA artery (*arrow*). Post-contrast enhanced axial CT (**b**) and curved multiplanar reformation (**c**) showed no significant stenosis caused by the calcified plaques (*arrows*). **d** CCA confirmed no significant stenosis (*arrows*)

Table 3 Summary of the causes of disagreements between computed tomographic angiography (CTA) and CCA

Disagreements	Percentage (number of cases)
False positives	
Heavy blooming artifacts causing overestimate of stenosis severity	66.67 % (6/9): all in LAD or its diagonal branch
Mixed plaques with overestimated stenosis severity	33.33 % (3/9): 2 in LCX, 1 in RCA
False negatives	
Narrowing over orifice or proximal segment of branch artery, not detected by CTA	60 % (3/5): 1 in each of D1, OM1 and LCX
Total stenosis in distal branch of artery with collaterals adjacent vessel, not detected in CTA	20 % (1/5): distal PDA with collateral from distal LAD
Soft plaque with underestimated stenosis severity by CTA	20 % (1/5): middle LCX

RCA right coronary artery, *LAD* left anterior descending artery, *LCX* left circumflex artery, *D1* first diagonal branch of LAD, *OM1* first obtuse marginal branch of LCX, *PDA* posterior descending coronary artery

blooming artifacts resulting in false positive results for SSNCA were found in LAD (Fig. 3). The false negative results included a case of unrecognized total occlusion of the distal posterior descending artery (PDA) with good collaterals from the distal LAD (Fig. 4). No significant stenosis of the left main artery (LM) was found in CCA. As for PBA, a similar significant correlation was also established between CTA and CCA ($P = 0.000$, $n = 123$). CTA had an overall sensitivity of 92.9 % and a specificity of 92.5 % in differentiating SSNCA from NSSNCA.

Factors significantly correlated with SSNCA

Table 4 summarized the factors significantly correlating with SSNCA, while Table 5 included those without significant correlation. There was a significantly higher prevalence of SSNCA in vessels without previous stent placement or with fewer stents implanted within the vessels. The calcium scores from each artery, as well as serum glucose level, also differed significantly between vessels with and without SSNCA.

Prevalence of NDSSNCAS

The prevalence of NDSSNCAS was 8.3 % (41/492) on VBA. The highest prevalence of NDSSNCAS was found in LCX (13.0 %, 16/123), followed by LAD (10.6 %, 13/123) and RCA (9.8 %, 12/123). No NDSSNCAS was found in the LM.

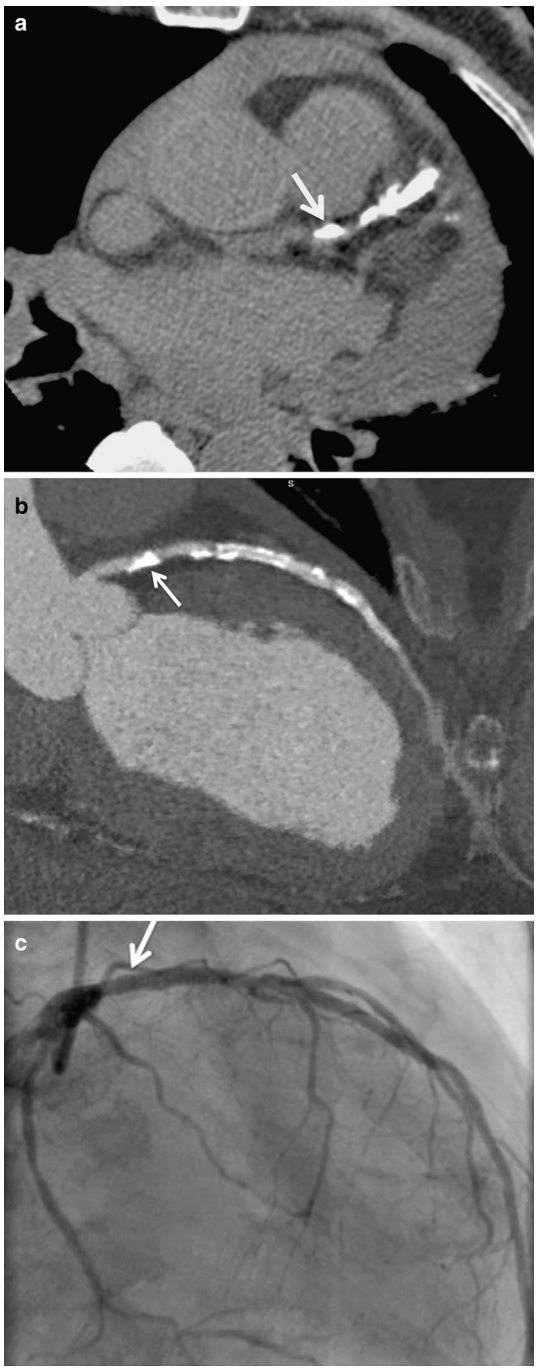

Fig. 3 A 70-year-old male had three stent placements 12 months ago in the proximal to middle thirds of the left anterior descending artery (LAD). He underwent coronary CT angiography (CTA) with a total calcium score of 1,720. **a** Non-contrast enhanced axial CT revealed heavy calcified plaque in the proximal LAD with stents in the proximal to middle thirds of the LAD. (*arrow*) **b** Post-contrast enhanced CT with curved multiplanar reformation revealed heavy calcified plaque in the proximal LAD with high-grade occlusion of the arterial lumen (*arrow*). **c** CCA from a RAO cranial view demonstrated no significant stenosis (*arrow*), suggesting a false positive result of the CTA due to blooming artifact

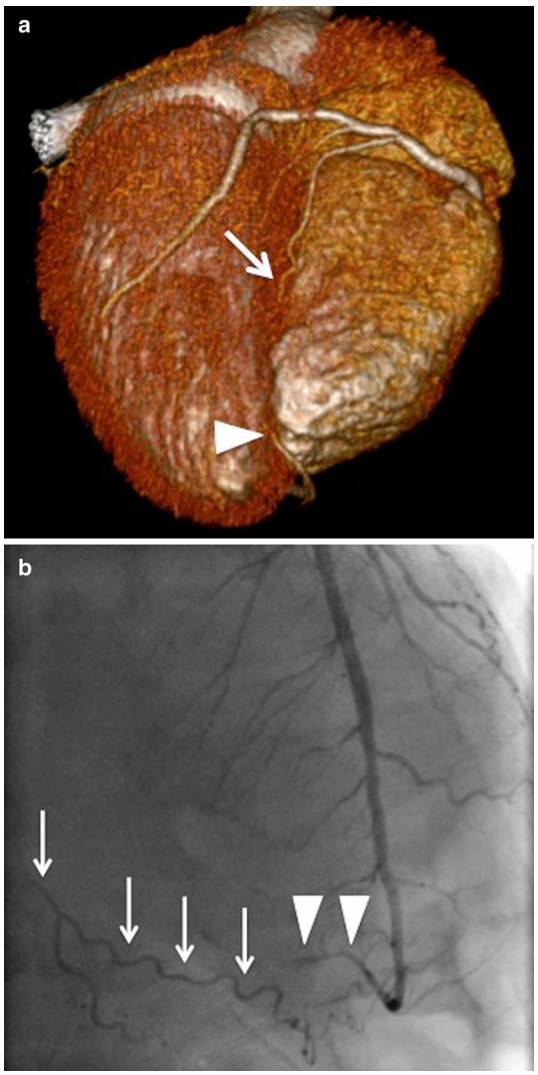

Fig. 4 A 45-year-old female received stent placement in the middle third of the left anterior descending coronary artery (LAD) 8 months ago and underwent coronary CT angiography (CTA). **a** CTA with 3D-volume rendering reformation revealed shortening of the posterior descending coronary artery (PDA, *arrow*) and excessively long distal LAD extending to the posterior interventricular sulcus (*arrowhead*), suggesting total occlusion of the PDA with non-visualized collateral from the LAD. **b** CCA from a RAO cranial view confirms an excessively long LAD extending to the posterior interventricular sulcus (*arrowheads*) with collateral supply to the PDA (*arrows*)

Factors significantly correlated with NDSSNCAS

Table 6 summarizes those factors with and without significant correlations with NDSSNCAS. No risk factors are found to be significantly correlated with the presence of NDSSNCAS.

Table 4 Comparison of correlating and non-correlating factors of significant stenosis of native coronary artery (SSNCA) with CCA between vessel-based and patient-based analyses

Factors	Vessel-based	Patient-based
Presence of stent placement ($n = 492$)	$P = 0.003$*	Not compared because all patients had stent placement
SSNCA with stent	14/160 (8.8 %)	
SSNCA without stent	63/332 (19.0 %)	
Number of stents versus SSNCA ($n = 492$)	$P = 0.003$*	$P = 0.298$
With SSNCA	$n = 77$, 0.22 ± 0.50	$n = 56$, 1.57 ± 0.931
Without SSNCA	$n = 415$; 0.46 ± 0.72	$n = 67$, 1.79 ± 1.112
Calcium scores ($n = 492$)	$P < 0.001$*	$P = 0.108$
Vessels with SSNCA	$n = 77$, 141.25 ± 257.26	$n = 56$, 321.82 ± 479.88
Vessels without SSNCA	$n = 415$, 48.96 ± 107.18	$n = 67$, 198.0 ± 314.96
Baseline serum glucose level (mg/dL)	$P = 0.048$*	$P = 0.224$
With SSNCA	$n = 77$, 117.39 ± 45.947	$n = 56$, 114.32 ± 42.56
Without SSNCA	$n = 415$, 108.68 ± 36.82	$n = 67$, 106.46 ± 34.84

* Denotes data with statistical significance

Discussion

Calcium score

The CS is related to myocardial ischemia and prognosis in patients without prior stent placement [16, 17], provides important information for risk management, and may help to improve lifestyle modification and medication [17, 18]. Although much emphasis has been placed on the application of CS in atherosclerotic vessels, little is known about its association with SSNCA in post-stent placement. The stented segments have been excluded during the calculation of the CS in our study. Although this may result in an underestimation of the overall atherosclerotic burden, CS measurements were eliminated in the stented segments for several reasons: First, the focus of this study is on the assessment of SSNCA and NSSNCA, which do not occur in stented segments; thus the measurement of CS in these segments may not reflect the atherosclerotic burden of the

Table 5 Non-correlating factors of the significant stenosis of native coronary artery (SSNCA) with CCA in both vessel-based and patient-based analyses

Factors	Vessel-based	Patient-based
Gender	$P = 0.555$, $n = 492$	P = 0.151, $n = 123$
Male	68/424 (16.0 %)	51/106 (48.1 %)
Female	9/68 (13.2 %)	5/17 (29.0 %)
Time after stent placement	$P = 0.265$, $n = 205$	$P = 0.972$, $n = 123$
Time <1 year	37/174 (21.3 %)	45/99 (45.5 %)
Time 1–5 years	3/21 (14.3 %)	8/18 (44.4 %)
Time >5 years	4/10 (40 %)	3/6 (50 %)
Smoking	$P = 0.629$, $n = 492$	$P = 0.134$, $n = 123$
Smoking	10/56 (17.9 %)	9/14 (64.3 %)
Non-smoking	67/436 (15.4 %)	47/109 (43.1 %)
Body mass index (kg/m^2)	$P = 0.831$, $n = 492$	$P = 0.953$, $n = 123$
With SSNCA	$n = 77$, 26.38 ± 3.76	$n = 56$, 26.50 ± 3.951
Without SSNCA	$n = 415$, 26.61 ± 3.76	$n = 67$, 26.64 ± 3.63
Obesity (body mass index ≥30)	$P = 0.387$, $n = 492$	$P = 0.627$, $n = 123$
Obesity	36/208 (17.3 %)	25/52 (48.1 %)
Non-Obesity	41/284 (14.4 %)	31/71 (43.7 %)
Diabetes Mellitus	$P = 0.299$, $n = 492$	$P = 0.395$, $n = 123$
DM	27/148 (18.2 %)	19/37 (51.4 %)
Non-DM	50/344 (14.5 %)	37/86 (43.0 %)
Hypertension	$P = 0.566$, $n = 492$	$P = 0.610$, $n = 123$
Hypertension	43/260 (16.5 %)	31/65 (47.7 %)
Non-hypertension	34/232 (14.7 %)	25/58 (43.1 %)
Blood pressure (BP)(mmHg)		
Systolic BP ($n = 492$)	$P = 0.668$	$P = 0.698$
With SSNCA	$n = 77$, 138.78 ± 20.43	$n = 56$, 138.55 ± 20.37
Without SSNCA	$n = 415$, 137.33 ± 20.46	$n = 67$, 136.73 ± 20.73
Diastolic (BP) ($n = 492$)	$P = 0.193$	$P = 0.815$
With SSNCA	$n = 77$, 76.82 ± 10.38	$n = 56$, 77.84 ± 10.78
Without SSNCA	$n = 415$, 78.33 ± 10.28	$n = 67$, 78.30 ± 10.02
Hyperlipidemia	$P = 0.933$, $n = 492$	$P = 0.710$, $n = 123$
Hyperlipidemia	16/104 (15.4 %)	11/26 (42.3 %)
Non-hyperlipidemia	61/388 (15.7 %)	45/97 (46.4 %)
Cholesterol levels (mg/dL)		
Total cholesterol:	$P = 0.860$	$P = 0.933$
With SSNCA	$n = 77$, 148.94 ± 51.56	$n = 56$, 147.88 ± 48.12
Without SSNCA	$n = 415$, 144.26 ± 37.62	$n = 67$, 142.58 ± 32.36
Low density lipoprotein	$P = 0.229$	$P = 0.338$
With SSNCA	$n = 77$, 85.99 ± 48.45	$n = 56$, 84.59 ± 45.55
Without SSNCA	$n = 415$, 78.38 ± 34.14	$n = 67$, 75.37 ± 27.38
High density lipoprotein	$P = 0.583$	$P = 0.374$
With SSNCA	$n = 77$, 38.71 ± 8.81	$n = 56$, 38.27 ± 8.69
Without SSNCA	$n = 415$, 39.29 ± 9.73	$n = 67$, 39.99 ± 10.33
Low density/high density lipoprotein	$P = 0.310$	$P = 0.311$
With SSNCA	$n = 77$, 2.33 ± 1.54	$n = 56$, 2.32 ± 1.51
Without SSNCA	$n = 415$, 2.36 ± 5.18	$n = 67$, 2.00 ± 0.92
Triglyceride	$P = 0.139$	$P = 0.284$
With SSNCA	$n = 77$, 134.68 ± 141.06	$n = 56$, 144.16 ± 162.04
Without SSNCA	$n = 415$, 141.89 ± 121.80	$n = 67$, 137.93 ± 84.30

Table 6 Factors without significant correlation to newly developed significant stenosis of the native coronary artery after stent placement (NDSSNCAS), using both vessel-based and patient-based analyses

Factors	Vessel-based	Patient-based
Gender	$P = 1.000$, $n = 492$	$P = 0.778$, $n = 123$
Male	35/424 (8.3 %)	30/106 (28.3 %)
Female	6/68 (8.8 %)	4/17 (23.5 %)
Time after stent placement	$P = 0.570$, $n = 205$	$P = 0.234$, $n = 123$
Time <1 year	20/154 (11.5 %)	30/99 (30.3 %)
Time 1–5 years	2/21 (9.5 %)	2/18 (11.1 %)
Time >5 years	2/10 (20.0 %)	2/6 (33.3 %)
Presence of stent placement ($n = 492$)	$P = 0.224$	Not compared because all patients had stent placement
NDSSNCAS with stent	17/160 (10.6 %)	
NDSSNCAS without stent	24/332 (7.2 %)	
Number of stented vessels versus NDSSNCAS ($n = 492$)	$P = 0.217$, $n = 492$	$P = 0.209$, $n = 123$
With NDSSNCAAS	$n = 41$, 0.54 ± 0.75	$n = 34$, 1.82 ± 1.00
Without NDSSNCAS	$n = 451$, 0.41 ± 0.69	$n = 89$, 1.63 ± 1.05
Smoking	$P = 0.207$, $n = 492$	$P = 0.346$, $n = 123$
Smoking	2/56 (3.6 %)	2/14 (14.3 %)
Non-smoking	39/436 (8.9 %)	32/109 (29.4 %)
Body mass index (kg/m^2)	$P = 0.677$, $n = 492$	$P = 0.819$, $n = 123$
With NDSSNCAS	$n = 41$, 26.45 ± 4.16	$n = 34$, 58.26 ± 10.07
Without NDSSNCAS	$n = 451$, 26.58 ± 3.72	$n = 89$, 56.51 ± 9.28
Obesity (body mass index ≥ 30)	P = 1.000, $n = 492$	P = 0.879, $n = 123$
Obesity	17/208 (8.2 %)	14/52 (26.9 %)
Non-obesity	24/284 (8.5 %)	20/71 (28.2 %)
Diabetes Mellitus (DM)	$P = 0.479$, $n = 492$	$P = 0.327$, $n = 123$
DM	10/148 (6.8 %)	8/37 (21.6 %)
Non-DM	31/344 (9.0 %)	26/86 (30.2 %)
Calcium scores ($n = 492$)	$P = 0.061$	$P = 0.147$
Vessels with NDSSNCAS	$n = 41$, 142.00 ± 217.91	$n = 34$, 384.29 ± 506.28
Vessels without NDSSNCAS	$n = 451$, 56.26 ± 134.69	$n = 89$, 204.72 ± 344.25
Baseline serum glucose level	$P = 0.341$	$P = 0.248$
With NDSSNCAS	$n = 41$, 112.34 ± 49.75	$n = 34$, 108.29 ± 43.25
Without NDSSNCAS	$n = 451$, 109.83 ± 37.34	$n = 89$, 110.71 ± 36.89
Hypertension	$P = 0.626$, $n = 492$	$P = 0.990$, $n = 123$
Hypertension	20/260 (7.7 %)	18/65 (27.7 %)
Non-hypertension	21/232 (9.1 %)	16/58 (27.6 %)
Blood pressure (BP)(mmHg)		
Systolic BP ($n = 492$)	P = 0.898	P = 0.336
With NDSSNCAS	$n = 41$, 138.88 ± 22.74	$n = 34$, 141.09 ± 22.25
Without NDSSNCAS	$n = 451$, 137.44 ± 20.24	$n = 89$, 136.21 ± 19.76
Diastolic BP ($n = 492$)	P = 0.283	P = 0.078
With NDSSNCAS	$n = 41$, 79.83 ± 8.92	$n = 34$, 80.74 ± 9.41
Without NDSSNCAS	$n = 451$, 77.93 ± 10.41	$n = 89$, 77.08 ± 10.54
Hyperlipidemia	$P = 0.558$, $n = 492$	$P = 0.280$, $n = 123$
Hyperlipidemia	7/104 (6.7 %)	5/26 (19.2 %)
Non-hyperlipidemia	34/388 (8.8 %)	29/97 (29.9 %)
Cholesterol levels		
Total cholesterol:	$P = 0.693$	$P = 0.368$
With NDSSNCAS	$n = 41$, 153.07 ± 64.28	$n = 34$, 147.59 ± 55.95

Table 6 continued

Factors	Vessel-based	Patient-based
Without NDSSNCAS	$n = 451$, 144.26 ± 37.15	$n = 89$, 144.00 ± 32.63
Low density lipoprotein	$P = 0.876$	$P = 0.730$
With NDSSNCAS	$n = 41$, 87.10 ± 58.42	$n = 34$, 81.24 ± 48.35
Without NDSSNCAS	$n = 451$, 78.88 ± 34.18	$n = 89$, 78.93 ± 31.79
High density lipoprotein	$P = 0.872$	$P = 0.790$
With NDSSNCAS	$n = 41$, 38.61 ± 6.80	$n = 34$, 38.74 ± 7.01
Without NDSSNCAS	$n = 451$, 39.26 ± 9.81	$n = 89$, 39.38 ± 10.47
Low density/high density lipoprotein	$P = 0.771$	$P = 0.890$
With NDSSNCAS	$n = 41$, 2.35 ± 1.72	$n = 34$, 2.18 ± 1.44
Without NDSSNCAS	$n = 451$, 2.36 ± 4.98	$n = 89$, 2.13 ± 1.14
Triglyceride	$P = 0.174$	$P = 0.068$
With NDSSNCAS	$n = 41$, 125.29 ± 92.68	$n = 34$, 124.24 ± 98.97
Without NDSSNCAS	$n = 451$, 142.17 ± 127.39	$n = 89$, 147.08 ± 133.92

native vessels. Second, differentiation between calcium and the stents is very difficult and cannot be performed objectively using the workstation software. Lastly, these segments are rather protected by the deployed stents from further atherosclerotic narrowing. In this study, the CS showed significant correlation with the development of SSNCA. The radiation dosage associated with CS was similar to that of previous studies [17]. We believe the above-mentioned benefits might justify the additional radiation dose administered for the measurement of calcium score in post-stent patients. Further study is required to clarify the clinical applications of CS in predicting SSNCA.

CTA

The CS has previously been proposed as a risk-prediction tool [16, 17]; however, it is not suggested to be used as a sole indicator for patients with known coronary disease, previous myocardial infarction, revascularization or clinical symptoms [17]. CTA offers incremental information for cardiac coronary CS, cardiac magnetic resonance imaging and echocardiography, including information on coronary anatomy, plaque characteristics and the severity of stenosis [10, 17]. The role of 64-detector CTA in diagnosing CAD was demonstrated through two large studies, including ACCURACY [19] and core-64 [12]. The corresponding figures for sensitivity and specificity were 95/85 and 83/90 %, respectively. In VBA focusing on HR variability, 320-detector CT had an accuracy of 90 %, a sensitivity of 77 %, a specificity of 94 %, a PPV of 76 % and an NPV of 94 %, respectively, in detecting CAD. No significant difference in diagnostic accuracy was found when comparing patients with normal sinus rhythm and those with high HR or arrhythmia [13].

Although this study did not measure inter-observer agreements, a previous study using 64-detector CTA demonstrated excellent inter-observer agreement in the interpretation of CTA (Cohen's kappa = 0.93 and 0.84 per subject and per segment analysis, respectively) [20, 21]. In this study, CTA had an overall higher diagnostic value or accuracy of 96.7 % in detecting SSNCA than that of previous studies [12, 13, 19]. Similar studies analyzing patients with post coronary artery bypass grafting using 320-detector CT revealed a similar diagnostic accuracy in assessing graft, recipient vessels and non-grafted vessel occlusion (96, 92 and 100 %, respectively) [8].

Hsiao et al. [14] in 2010 compared the 320-detector CT scanner with 64-detector CT scanners. The advantages of the 320-detector CT include elimination of stair-step and misalignment artifacts, reduction of radiation dose exposure, and reduction of the amount of contrast media administered. A major benefit of 320-detector CT is its wide z-axial coverage of 16 cm [14], which generates significantly reduced motion artifacts and allows the imaging of the heart within one cardiac cycle if HR is properly controlled. An initial study consisting of 40 patients using 320-detector CT by Rybicki et al. [22] found that 89 and 99 % of all coronary segments were of excellent and diagnostic quality, respectively. A study of patients with post coronary artery bypass graftings using 320-detector CT found that only 2 % of the segments were considered uninterpretable [8]. To our knowledge, this is the first study to evaluate native coronary arteries in post-stented patients, and no native coronary arteries were found to be uninterpretable. The clinical use of CTA with 320-detector CT could be encouraged due to the significantly improved ability to assess coronary arteries.

Cutlip et al. [21] reported that the prevalence of SSNCA in patients after stents placement is 18.3 % in the first year,

1.7 % during the second to fifth year, and 53.6 % after the fifth year. However, our study found no significant difference when comparing the event rates of these years (Table 5). This could be due to the small number of cases in our cohort. Further studies in this field could provide greater insight into the true relevance of this correlation.

As mentioned above, the highest prevalence of SSNCA and NDSSNCAS were found in LCX, while the lowest prevalence of CAD was found in the LAD. This finding could be partly explained by the fact that more than half of the stents were deployed in the LAD. Blooming artifact, as shown in this study and others [14], was the major cause of false positive findings. Underestimation of the severity of stenosis near coronary orifices was the major cause of false negative results, a finding that may prompt the development of new reconstruction methods to assist with better visualization of the orifice. The use of spider or global views enabled us to better delineate the coronary arterial origins and proximal coronary arteries, and their clinical implications should be further elaborated and studied. Another cause of false negative results is non-visualization of short segmental total occlusion in distal coronary arteries with good collaterals [23].

Risk factors for SSNCA and NDSSNCAS

It is proposed that several conventional risk factors are related to coronary artery stenosis, including age, CS, male gender, diabetes mellitus, serum baseline glucose, LDL and triglyceride levels [2, 21, 24]. This study revealed that four factors were correlated with the development of SSNCA: higher calcium scores in each coronary artery, higher serum glucose level, fewer vessels with stent placement, and a smaller number of deployed stents in the vessels. These findings could be attributed to the fact that higher calcium scores may imply a greater probability of calcified plaques and increased number of SSNCA. As mentioned earlier, a large proportion of stents have been implanted in the proximal and middle parts of the coronary arteries. The correlation of SSNCA with the absence of, or smaller number of, previously stented vessels implies that fewer numbers or segments of native vessels are protected by the stented segments, and thus more vessels are vulnerable to progression of atherosclerosis. Higher serum glucose levels may imply progression of atherosclerosis due to poor diabetic control; this corresponds with the findings of previous studies that emphasized baseline serum glucose as the strongest significant cardiovascular risk factor for disease progression [2, 24]. Although the other non-significant conventional risk factors in this study have been shown to correlate to the formation of SSNCA [2], other studies have demonstrated some of these risk factors to be non-significant during follow-up evaluation with angiography, or when compared with the presence of myocardial ischemia [16, 25]. We would encourage further studies to investigate the risk factors of SSNCA to clarify the discrepancies between reported findings.

Limitations

There are several limitations to this study. First, this study focused mainly on the diagnostic accuracy of 320-detector CT on SSNCA in patients after coronary stents placement, as well as the investigation into correlating factors for SSNCA. Second, as the title of this work implies, the evaluation of in-stent restenosis is beyond the scope of vision in this study. Third, CTA was not performed prior to CCA when stents were deployed; thus, this study was also limited by its lack of comparison of the accuracy of CTA in detecting the progression of significant arterial stenosis, particularly in the case of patients who had CCAs and stent deployment several times in different time periods. Fourth, drug and related treatments can also affect the prevalence of SSNCA; however, a wide variety of medications may be used for these patients, depending on their conditions and other comorbidities. Such factors are too complicated to analyze in this study, and we believe that this topic can be discussed in further studies pertaining to individual drug effects and SSNCA.

In conclusion, four factors have been correlated with higher prevalence of SSNCA, including higher calcium scores in each coronary artery, higher serum glucose levels, fewer vessels with stent placement, and a smaller number of deployed stents in the vessels. CTA shows excellent correlation with CCA in diagnosing SSNCA. Further studies based on a large cohort are needed to verify our preliminary findings.

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Conflict of interest None.

References

1. Schroeder S, Achenbach S, Bengel F, Burgstahler C, Cademartiri F, de Feyter P, George R, Kaufmann P, Kopp AF, Knuuti J, Ropers D, Schuijf J, Tops LF, Bax JJ, Working Group Nuclear C, Cardiac CT, European Society of C, European Council of Nuclear C (2008) Cardiac computed tomography: indications, applications, limitations, and training requirements: report of a Writing Group deployed by the Working Group Nuclear Cardiology and Cardiac CT of the European Society of Cardiology and the European Council of Nuclear Cardiology. Eur Heart J 29(4):531–556

2. Moulias A, Alexopoulos D (2011) Long-term outcome of percutaneous coronary intervention: the significance of native coronary artery disease progression. Clin Cardiol 34(10):588–592
3. Cutlip DE, Chhabra AG, Baim DS, Chauhan MS, Marulkar S, Massaro J, Bakhai A, Cohen DJ, Kuntz RE, Ho KK (2004) Beyond restenosis: five-year clinical outcomes from second-generation coronary stent trials. Circulation 110(10):1226–1230
4. Leon MB, Allocco DJ, Dawkins KD, Baim DS (2009) Late clinical events after drug-eluting stents: the interplay between stent-related and natural history-driven events. JACC Cardiovasc Interv 2(6):504–512
5. Chacko R, Mulhearn M, Novack V, Novack L, Mauri L, Cohen SA, Moses J, Leon MB, Cutlip DE (2009) Impact of target lesion and nontarget lesion cardiac events on 5-year clinical outcomes after sirolimus-eluting or bare-metal stenting. JACC Cardiovasc Interv 2(6):498–503
6. Alexopoulos D, Xanthopoulou I, Davlouros P, Damelou A, Mazarakis A, Chiladakis J, Hahalis G (2010) Mechanisms of nonfatal acute myocardial infarction late after stent implantation: the relative impact of disease progression, stent restenosis, and stent thrombosis. Am Heart J 159(3):439–445
7. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW, Investigators P (2011) A prospective natural-history study of coronary atherosclerosis. N Engl J Med 364(3):226–235
8. de Graaf FR, van Velzen JE, Witkowska AJ, Schuijf JD, van der Bijl N, Kroft LJ, de Roos A, Reiber JH, Bax JJ, de Grooth GJ, Jukema JW, van der Wall EE (2011) Diagnostic performance of 320-slice multidetector computed tomography coronary angiography in patients after coronary artery bypass grafting. Eur Radiol 21(11):2285–2296
9. Elhendy A, van Domburg RT, Bax JJ, Nierop PR, Valkema R, Geleijnse ML, Kasprzak JD, Liqui-Lung AF, Cornel JH, Roelandt JR (1998) Dobutamine-atropine stress myocardial perfusion SPECT imaging in the diagnosis of graft stenosis after coronary artery bypass grafting. J Nucl Cardiol 5(5):491–497
10. de Azevedo CF, Hadlich MS, Bezerra SG, Petriz JL, Alves RR, de Souza O, Rati M, Albuquerque DC, Moll J (2011) Prognostic value of CT angiography in patients with inconclusive functional stress tests. JACC Cardiovasc Imaging 4(7):740–751
11. Meijboom WB, Meijs MF, Schuijf JD, Cramer MJ, Mollet NR, van Mieghem CA, Nieman K, van Werkhoven JM, Pundziute G, Weustink AC, de Vos AM, Pugliese F, Rensing B, Jukema JW, Bax JJ, Prokop M, Doevendans PA, Hunink MG, Krestin GP, de Feyter PJ (2008) Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. J Am Coll Cardiol 52(25):2135–2144
12. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, Paul N, Clouse ME, Shapiro EP, Hoe J, Lardo AC, Bush DE, de Roos A, Cox C, Brinker J, Lima JA (2008) Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med 359(22):2324–2336
13. Uehara M, Takaoka H, Kobayashi Y, Funabashi N (2013) Diagnostic accuracy of 320-slice computed-tomography for detection of significant coronary artery stenosis in patients with various heart rates and heart rhythms compared with conventional coronary-angiography. Int J Cardiol 167(3):809–815
14. Hsiao EM, Rybicki FJ, Steigner M (2010) CT coronary angiography: 256-slice and 320-detector row scanners. Curr Cardiol Rep 12(1):68–75
15. Valentin J, International Commission on Radiation P (2007) Managing patient dose in multi-detector computed tomography (MDCT). ICRP Publication 102. Ann ICRP 37(1):1–79 iii
16. Lai HM, Holtzman D, Aronow WS, DeLuca AJ, Ahn C, Matayev S, Belkin RN (2012) Association of coronary artery calcium with severity of myocardial ischemia in left anterior descending, left circumflex, and right coronary artery territories. Clin Cardiol 35(1):61–63
17. Hamilton-Craig CR, Friedman D, Achenbach S (2012) Cardiac computed tomography–evidence, limitations and clinical application. Heart Lung Circ 21(2):70–81
18. Taylor AJ, Bindeman J, Feuerstein I, Le T, Bauer K, Byrd C, Wu H, O'Malley PG (2008) Community-based provision of statin and aspirin after the detection of coronary artery calcium within a community-based screening cohort. J Am Coll Cardiol 51(14):1337–1341
19. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, Scherer M, Bellinger R, Martin A, Benton R, Delago A, Min JK (2008) Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (assessment by coronary computed tomographic angiography of individuals undergoing invasive coronary angiography) trial. J Am Coll Cardiol 52(21):1724–1732
20. Hoffmann U, Nagurney JT, Moselewski F, Pena A, Ferencik M, Chae CU, Cury RC, Butler J, Abbara S, Brown DF, Manini A, Nichols JH, Achenbach S, Brady TJ (2006) Coronary multidetector computed tomography in the assessment of patients with acute chest pain. Circulation 114(21):2251–2260
21. Choi EK, Choi SI, Rivera JJ, Nasir K, Chang SA, Chun EJ, Kim HK, Choi DJ, Blumenthal RS, Chang HJ (2008) Coronary computed tomography angiography as a screening tool for the detection of occult coronary artery disease in asymptomatic individuals. J Am Coll Cardiol 52(5):357–365
22. Rybicki FJ, Otero HJ, Steigner ML, Vorobiof G, Nallamshetty L, Mitsouras D, Ersoy H, Mather RT, Judy PF, Cai T, Coyner K, Schultz K, Whitmore AG, Di Carli MF (2008) Initial evaluation of coronary images from 320-detector row computed tomography. Int J Cardiovasc Imaging 24(5):535–546
23. Laynez-Carnicero A, Estornell-Erill J, Trigo-Bautista A, Valle-Munoz A, Nadal-Barange M, Romaguera-Torres R, Planas del Viejo A, Corbi-Pascual M, Paya-Serrano R, Ridocci-Soriano F (2010) Non-invasive assessment of coronary artery bypass grafts and native coronary arteries using 64-slice computed tomography: comparison with invasive coronary angiography. Rev Esp Cardiol 63(2):161–169
24. Schoenenberger AW, Jamshidi P, Kobza R, Zuber M, Stuck AE, Pfisterer M, Erne P (2010) Progression of coronary artery disease during long-term follow-up of the Swiss Interventional Study on Silent Ischemia Type II (SWISSI II). Clin Cardiol 33(5):289–295
25. Borges JC, Lopes N, Soares PR, Góis AF, Stolf NA, Oliveira SA, Hueb WA, Ramires JA (2010) Five-year follow-up of angiographic disease progression after medicine, angioplasty, or surgery. J Cardiothorac Surg 26(5):91