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Cardiac Imaging

Computed Tomography Angiography and Myocardial Computed Tomography Perfusion in Patients With Coronary Stents

Prospective Intraindividual Comparison With Conventional Coronary Angiography

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Objectives This study sought to determine whether adding myocardial computed tomography perfusion (CTP) to computed tomography angiography (CTA) improves diagnostic performance for coronary stents.

Background CTA of coronary stents has been limited by nondiagnostic studies caused by metallic stent material and coronary motion.

Methods CTA and CTP were performed in 91 consecutive patients with stents before quantitative coronary angiography, the reference standard for obstructive stenosis (≥50%). If a coronary stent or vessel was nondiagnostic on CTA, adenosine stress CTP in the corresponding myocardial territory was read for combined CTA/CTP.

Results Patients had an average of 2.5 ± 1.8 coronary stents (1 to 10), with a diameter of 3.0 ± 0.5 mm. Significantly more patients were nondiagnostic for stent assessment by CTA (22%; mainly due to metal artifacts [75%] or motion [25%]) versus CTP (1%; $p < 0.001$; severe angina precluded CTP in 1 case). The per-patient diagnostic accuracy of CTA/CTP for stents (87%, 95% confidence interval [CI]: 78% to 93%) was significantly higher than that of CTA alone (71%, 95% CI: 61% to 80%; $p < 0.001$), mainly because nondiagnostic examinations were significantly reduced ($p < 0.001$). In the analysis of any coronary artery disease, diagnostic accuracy and nondiagnostic rate were also significantly improved by the addition of CTP ($p < 0.001$). CTA/CTP (7.9 ± 2.8 mSv) had a significantly lower effective radiation dose than angiography (9.5 ± 5.1 mSv; $p = 0.005$). The area under the receiver-operating characteristic curve for CTA/CTP (0.82, 95% CI: 0.69 to 0.95) was superior to that for CTA (0.69, 95% CI: 0.57 to 0.82; $p < 0.001$) in identifying patients requiring stent revascularization.

Conclusions Combined coronary CTA and myocardial CTP improves diagnosis of CAD and in-stent restenosis in patients with stents compared with CTA alone. (Coronary Artery Stent Evaluation With 320-Slice Computed Tomography—The CArS 320 Study [CARS-320]; NCT00967876) (J Am Coll Cardiol 2013;62:1476–85) © 2013 by the American College of Cardiology Foundation

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Stent implantation has become a routine procedure, resulting in greater freedom from angina than medical therapy does (1), and stents are used in about 90% of all percutaneous interventions, with about 528,000 procedures per year in the United States and 854,000 in Europe (2,3). Computed tomography angiography (CTA) is not recommended in patients with coronary stents because of high rates of nondiagnostic stents (4), mainly due to artifacts resulting from the metallic material of stent struts and fast coronary artery motion. High and irregular heart rates enhance artifacts caused by metal stents (5). Magnetic resonance angiography is hampered by signal loss in the stent, and patency can only be assessed distal to stents (6).

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The increasing use of stents in small vessels (7) makes it even more difficult to reliably depict coronary in-stent restenosis (ISR) by CTA (8). Strategies to improve CT can be classified into those improving spatial and temporal resolution (9), and those providing additional functional information (10). State-of-the-art CT can combine volumetric coverage and reduced radiation for coronary angiography (9) with myocardial computed tomography perfusion (CTP) in a single examination (10).

We conducted a prospective study of CTA and CTP using 320 detector rows for identifying coronary ISR or any coronary artery disease (CAD).

Methods

Study design. The CARS-320 (Coronary Artery Stent Evaluation with 320-Row Computed Tomography) study is a prospective study for detecting coronary ISR using quantitative coronary angiography (QCA) as the reference standard. In this intention-to-diagnose study, all patients and stents were included regardless of type, size, or number of stents and duration since implantation, even if a study or a vessel segment was nondiagnostic, to avoid overestimating diagnostic accuracy (11). The 25 criteria of the Standards for Reporting of Diagnostic Accuracy statement (12) are given in Online Figure 1.

CT was performed ≤14 days before conventional coronary angiography (CCA) to avoid differential verification and disease progression bias (13). The study protocol was approved by the Charité ethics board (EA1/133/08) and the Federal Office for Radiation Protection (BfS Z5-22462/2-2008-057).

Study population. Consecutive patients with clinically suspected coronary ISR referred to Charité for CCA were included if they were at least 40 years and had sinus rhythm. Exclusion criteria are listed in Figure 1. Patients were enrolled between April 2, 2009, and November 23, 2011, and all gave written informed consent.

Preparation for CT. Seventy-six patients were on chronic oral beta-blocker medications (84%), and 73 received additional oral beta-blockade medications (71 ± 44 mg atenolol, Tenormin, AstraZeneca, Wedel, Germany) 1 h before CTA. Immediately before CTA, intravenous beta-blockers (mean: 44 ± 103 mg esmolol, Brevibloc, Baxter, Unterschleissheim, Germany) were given in 16 patients (18%) with heart rates above 60 beats/min and all patients received 0.8 mg glycerol trinitrate sublingually (Nitrolingual N Spray, Pohl-Boskamp, Hohenlockstedt, Germany) (14).

Abbreviations and Acronyms

CCA = conventional coronary angiography
CI = confidence interval(s)
CT = computed tomography
CTA = computed tomography angiography
CTP = computed tomography perfusion
ISR = in-stent restenosis
QCA = quantitative coronary angiography
ROC = receiver-operating characteristic

Coronary CTA and CTP. Data were acquired on 320-row CT (0.5-mm detector collimation and 350-ms gantry rotation time; Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) as recently described (9). Noncontrast CT was acquired using prospective triggering to assess coronary calcium (120 kV, 150 mA) and define the anatomical range for subsequent CTA/CTP (15). For CTA and CTP, a nonionic contrast agent (50 to 70 ml of iomeprol, Iomeron 400, 400 mg iodine/ml, Bracco Imaging, Milan, Italy) was injected into an antecubital vein of the right arm (except for 2 patients each in whom injection was done at the back of the hand and forearm). The amount and flow of contrast agent was adjusted to body weight (16). For CTA, we used prospective triggering with scanner settings of 120 kV and tube currents adjusted to the body mass index, as described (16).

CTP was performed with a delay of at least 20 min after nitroglycerin as described (16); another contrast agent injection followed 4 min after the beginning of intravenous infusion of adenosine in the antecubital fossa of the left arm (140 μg/kg/min; Adenosin Life Medical, Carinopharm GmbH, Gronau/Leine, Germany), except for 4 and 2 patients in whom adenosine infusion was done at the back of the hand and forearm, respectively. Adenosine infusion was continued until completion of contrast agent injection. For CTP, we used the target mode with scanner settings of 120 kV and tube currents adjusted to body mass index (16).

CTA and CTP were initiated when bolus tracking detected an absolute increase of 200 Hounsfield units in the descending aorta following identical amounts of contrast agent (16). Using a conversion factor of 0.014 mSv/mGy cm (17), the effective dose was estimated for CT.

CTA and CTP reconstruction and evaluation. CT data were reconstructed with validated beam hardening correction (18), the kernels FC3/CTA and FC5/stent, an imaging matrix of 512 × 512 pixels, and 0.5-mm slice thickness on an 18-cm field-of-view using automated best-phase reconstructions and additional 5% intervals. A 0.25-mm slice increment improved rendering. Adaptive

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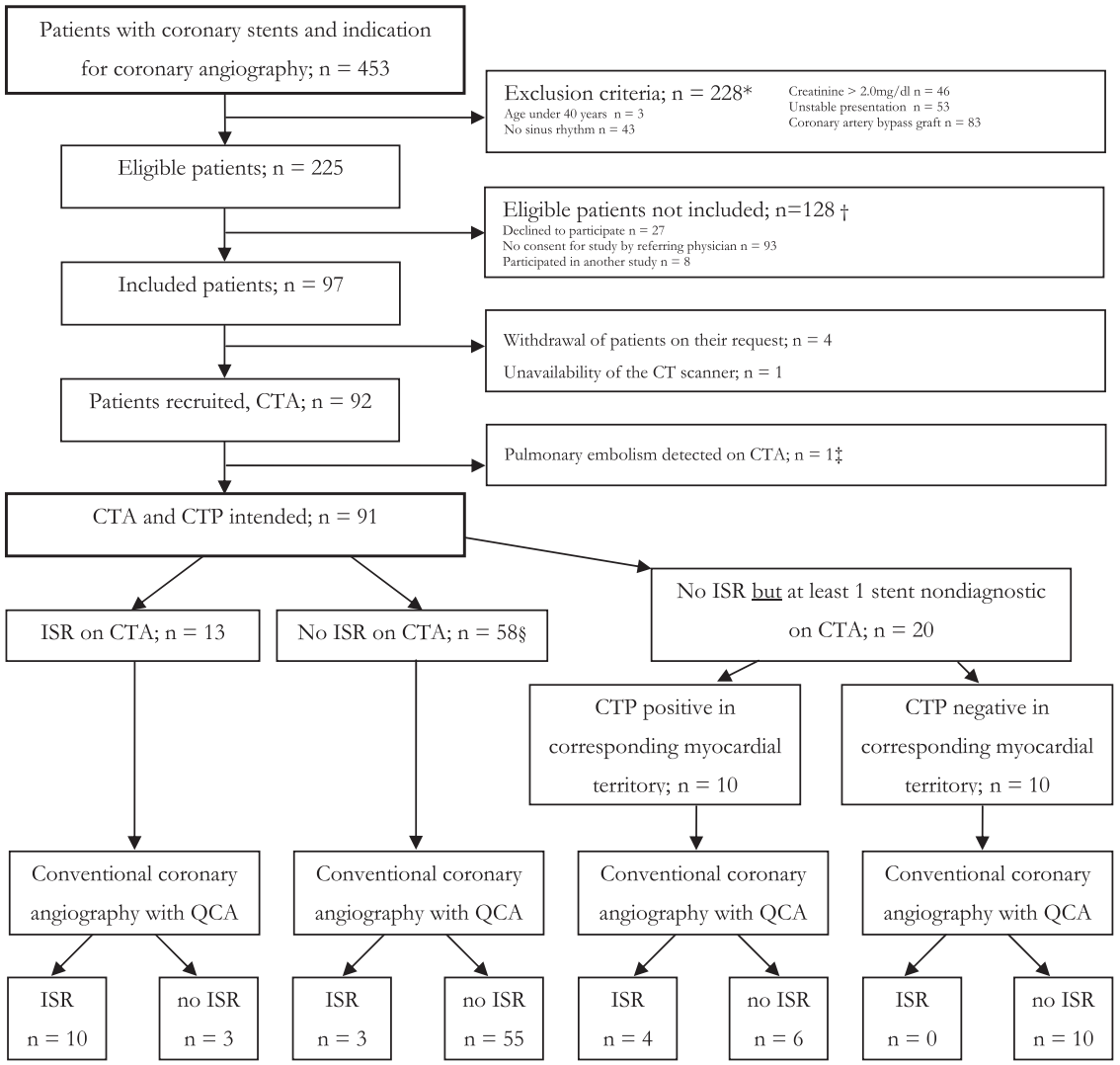

Figure 1 **Flow Diagram of Patient Recruitment and Examination According to the Standards for Reporting of Diagnostic Accuracy Statement**

*No patient had to be excluded for the following exclusion criteria: inability to hold breath for 10 s; body weight >300 kg; pregnancy; therapy with dipyridamole; second- or third-degree atrioventricular block; systolic hypotension; and guardianship at the time of the study. §Reasons given by those who declined to participate (n = 27): 20 gave no reason; given, 4 were afraid of adenosine application; 1 was not available on the ward for informed consent; 1 had orthopnea; 1 did not speak German or English. The 128 eligible patients who could not be included in comparison to the 91 patients included were more often women (34 vs. 20%; p = 0.02) and slightly older (66.3 ± 9.7 years; p = 0.08) but had the same prevalence of in-stent restenosis (ISR) (18 vs. 19%; p = 0.85). †Anticoagulation was initiated, but computed tomography perfusion (CTP) was not performed. Computed coronary angiography (CCA) in this patient showed ISR type IV (occlusion) in the mid–left anterior descending artery that was also seen on computed tomography angiography (CTA). ‡This includes 1 patient in whom CTP could not be performed because of severe angina pectoris during adenosine infusion but before CTP. In this patient, 3-vessel disease without ISR was seen on both CTA and CCA. CT = computed tomography; QCA = quantitative coronary angiography.

multisegment reconstruction was used in patients with heart rates above 65 beats/min (CTA: 4 patients; CTP: 60 patients) and half-scan reconstruction in patients with lower heart rates.

Stenosis assessment was performed with the workstation's (Vitrea fX, Vital Images, Plymouth, Minnesota) coronary artery CT protocol using automated vessel probing. ISR and stenoses in native vessels were detected visually on original slices, orthogonal planes, cross sections of the stent, and curved multiplanar reformations. At least 20% of visual diameter reductions were quantified on images orthogonal to the vessel (9). CTP was analyzed visually based on determination of the arterial input function (19) on a dedicated myocardial perfusion workstation (version 4.71GR001 W.I.P, Toshiba Medical Systems, Nasu, Japan) (16). Contiguous short- and long-axis analysis was performed visually in 3-mm intervals using 8-mm slice thickness to identify perfusion defects during rest and stress. In addition, 2

Table 1 Characteristics of the 91 Patients With Suspected ISR Who Completed the Study

Age, yrs	64 ± 10
Male	73 (80)
Hyperlipidemia	76 (84)
Arterial hypertension	76 (84)
Diabetes mellitus	25 (27)
Height, m	1.72 ± 0.08
Weight, kg	82.1 ± 12.0
Body mass index*	27.7 ± 3.8
Waist circumference, m	1.01 ± 0.10
Creatinine, mg/dl	0.94 ± 0.17
eGFR, ml/min/1.73 m^2	92.4 ± 25.2
Clinical presentation (27)	
Typical angina	15 (16)
Atypical angina	37 (41)
Nonspecific chest pain	31 (34)
No chest pain†	8 (9)
Stent information	
On the patient level (n = 91)	
No. of stents per patient	2.5 ± 1.8
Minimum and maximum no. of stents per patient	1 and 10
Time since first stent, months	41 ± 47 (min: 0.7; max: 190)
Time since last stent, months	31 ± 42 (min: 0.6; max: 190)
On the stent level (n = 221)	
Diameter, mm	3.0 ± 0.5
Stent diameter categories	
<3.0 mm	85 (38)
= 3.0 mm	100 (45)
>3.0 mm	39 (17)
Length, mm	17.1 ± 6.0
Location of stents in the main vessels	
Left anterior descending coronary artery	92 (41)
Left circumflex coronary artery	49 (22)
Left main coronary artery	2 (1)
Intermediate branch	2 (1)
Right coronary artery	79 (35)
Prior myocardial infarction	43 (47)
Current cigarette smoking	19 (21)
Medication	
Beta blockers	76 (84)
ACE inhibitors	55 (60)
Statins	81 (89)
ASA	84 (92)
At least 1 stress test prior to coronary angiography	41 (45)
Stress echocardiography	9 (10)
Positive	4 (4)
Negative	5 (6)
Exercise ECG	16 (18)
Positive	9 (10)
Negative	7 (8)
Duke score (28)	−0.28 ± 7.7
SPECT	23 (26)
Positive	18 (20)
Negative	5 (6)
Stress MRI	10 (11)
Positive	6 (7)
Negative	4 (4)
FFR	8 (9)
Positive (<0.80) (29)	3 (3)
Negative	5 (6)
Heart rate during CTA, beats/min	53.3 ± 7.1 (median: 52.4, range 39–80)
Heart rate during CTP, beats/min	68.1 ± 10.6 (median: 66.3, range 42–96)
Findings on coronary angiography‡	
On the patient level, n = 91	
No ISR	74 (81)
ISR	17 (19)
1-vessel	16 (18)
2-vessel	1 (1)
3-vessel	0 (0)
On the stent level, n = 224	
No ISR	206 (92)
ISR	18 (8)
<3.0-mm diameter stent	7 (39)
= 3.0-mm diameter stent	8 (44)
>3.0-mm diameter stent	3 (17)
Percentage of diameter stenosis§	66 ± 16

Continued in the next column

Values are mean ± SD or n (%) unless otherwise indicated. *Calculated as the weight in kilograms divided by the square of the height in meters. †Among the 8 patients (9%) without chest pain indicated for coronary angiography, 4 were scheduled for 6- or 12-month follow-up examination after intervention, 1 had positive ischemia testing, and 3 had remaining coronary stenosis of at least 50% in a nonstented vessel. ‡Based on assessment of all 17 coronary segments according to the American Heart Association classification (22) (regardless of the size of reference vessel diameters). §Among the 18 ISR, 2 stents were completely occluded.

ACE = angiotensin-converting enzyme; ASA = acetylsalicylic acid; CTA = computed tomography angiography; CTP = computed tomography perfusion; ECG = electrocardiography; eGFR = estimated glomerular filtration rate; FFR = fractional flow reserve; ISR = in-stent restenosis; MRI = magnetic resonance imaging; SPECT = single-photon emission computed tomography.

semiquantitative parameters, transmural perfusion ratio (<0.99) (20) and myocardial attenuation, were analyzed (16).

Conventional coronary angiography. CCA was performed using the transfemoral Judkins approach and standard techniques after right and left intracoronary administration of 100 to 150 μg isosorbide dinitrate. Radiation exposure was estimated using a conversion factor of 0.22 cGy × cm^2 (21). The decision to perform interventions was based on clinical judgment alone because interventionalists were blinded to CT.

Analysis of imaging tests. All 16 coronary artery segments of the American Heart Association classification (22) including the intermediate branch (segment 17, if present) were analyzed for detection of ≥50% (obstructive) diameter stenosis, independent of reference vessel size, in CTA and QCA. All 17 myocardial segments of the American Heart Association nomenclature (23) were evaluated by CTP (16). If a coronary stent was nondiagnostic on CTA, fixed perfusion defects and reversible ischemia on CTP in the corresponding myocardial territory were considered positive for combined CTA/CTP. CTA and CTP were processed

and evaluated separately by 2 independent readers (E.Z. and A.K. for CTA; M.R. and F.S. for CTP) blinded to the results of the other CT method, CCA, and clinical information. To ensure correct intermodality evaluation of coronary segments and assignment of myocardial territories to coronary arteries, a fifth reader not involved in reading CT and QCA (M.D.) adjudicated all coronary lesions and myocardial perfusion defects for comparison with CCA. The adjudication was done separately for detection of ISR and "any CAD" (including ISR and stenoses in native vessels). The independent adjudicator was unblinded to the QCA results, which were used in combination with CTA/CTP for intermodality adjudication. Unblinding was necessary to ensure comparison of identical coronary lesions. The adjudicator also ensured, by a parallel assessment of CTA and CTP, that the segmental perfusion assessment (23) documented by the CTP readers corresponded to coronary ISR or stenoses in native vessels, that is, using a conservative adjudication by including any coherent perfusion deficit seen on CTP as an indicator for an ISR if a nondiagnostic stent was present in the coronary artery supplying this myocardial territory. In case of stents with diagnostic image quality on CTA, the CTP reading was not used to influence the combined CTA/CTP assessment. For any CAD, the CTP was used only when a vessel was nondiagnostic on CTA.

QCA (Axiom Artis BC, Siemens, Erlangen, Germany) was performed and interpreted independently by another reader (M.L.), who was unaware of CT results and clinical information. At least 2 orthogonal projections were evaluated; percentage of diameter stenosis was measured in the projection showing the highest degree of narrowing.

Statistical analysis. We estimated that 90 patients were required to confirm that the diagnostic accuracy of CTA/CTP for coronary ISR was >75% in an exact 2-sided binomial test with significance at 0.05, assuming a true per-patient accuracy of 87% with a power of 80% (nQuery Advisor 7.0, Statistical Solutions, Cork, Ireland). The secondary objective was to analyze the diagnostic accuracy of CTA/CTP for coronary stenosis in any vessel (any CAD).

McNemar test and Student paired *t* test were used as appropriate for categorical and continuous variables. Generalized estimating equations were used to adjust for clustering of stents within patients (24). All data are reported as mean ± SD (normally distributed data), medians (data not normally distributed), or proportions with 95% confidence intervals (CI). For unclustered data (per-patient analysis), CI for proportions were obtained using the exact binomial distribution (25). Correlated receiver-operating characteristic (ROC) curves were compared using the approach described by DeLong et al. (26). The ROC curves quantify the readers' confidence: definitely no stenosis; most likely no stenosis; possibly no stenosis; probably no stenosis; unclear; probably stenotic; possibly stenotic; most likely stenotic; and definitely stenotic. In both ROC analyses, nondiagnostic results were censored as definitely stenotic. Statistical analyses were conducted using SPSS (version 18.0, SPSS Inc., Chicago, Illinois) and SAS (version 8.0, SAS Institute Inc., Cary, North Carolina). CI and p values for clustered data were calculated using proc genmod in SAS.

Results

The flow of patients is shown in Figure 1. No adverse events occurred after CTA or CCA. Two patients did not undergo CTP: 1 because of pulmonary embolism seen on CTA; another because of severe angina pectoris during adenosine infusion. The second patient was considered nondiagnostic by CTP (11). Our final cohort included 91 patients (Fig. 1).

Patient characteristics. Patient characteristics are given in Table 1 (27–29). The average number of stents per patient was 2.5 ± 1.8 with a median of 2 and a maximum of 10 (Table 1). Most stents were located in the proximal (30, 13%), mid–left anterior descending (37, 17%), or mid–right coronary (36, 16%) arteries. Nineteen percent (17) had obstructive coronary ISR by QCA. In addition, QCA showed obstructive stenosis of nonstented segments in 65% (n = 59), with 12% (11) also having ISR. About one-half (48) were over 65 years of age, and 79% (72) had a body mass index ≥25. Within 1 month, 10 patients underwent percutaneous ISR revascularization, and 1 patient with an ISR was surgically revascularized.

Study flow and further characteristics. The median interval between CT and CCA was 3 h 35 min (mean: 17 h 7 min; range 77 min to 12 days 23 h 42 min). Seventy patients (77%) had CT and CCA on the same day. The median CTA/CTP acquisition time was 0.41/0.86 s, using a median contrast-medium volume of 120 ml (range 100 to 140 ml; CCA [diagnostic part]: median: 56 ml; range 20 to 130 ml; $p < 0.001$).

Creatinine and radiation exposure. On creatinine follow-up 24 to 48 h after CCA, 3 patients showed an increase of >25% but below 0.5 mg/dl; 2 of them had same-day CT and CCA, and in 1, the elapsed time was 2 days. Creatinine normalized on further follow-up in all 3. There was no significant correlation of time between CT and CCA with the change in creatinine. The effective radiation dose of CTA/CTP was significantly lower than that of CCA (Fig. 2).

Diagnostic performance. Table 2 summarizes the diagnostic performance of CTA and CTA/CTP for ISR. The primary null hypothesis was rejected, with an observed per-patient diagnostic accuracy of CTA/CTP for ISR of 87% ($p = 0.01$; exact binomial test). This diagnostic accuracy was significantly higher than that of CTA alone (71%; $p < 0.001$), whereas the rate of nondiagnostic examinations was significantly reduced ($p < 0.001$) (Table 2). In the per-stent analysis, diagnostic accuracy and nondiagnostic rate were also significantly improved by the addition of CTP ($p < 0.001$) (Table 2). The per-patient sensitivity and specificity for ISR for combined CTA/CTP were 82% and 88%, respectively, versus 59% ($p = 0.13$) and 74%

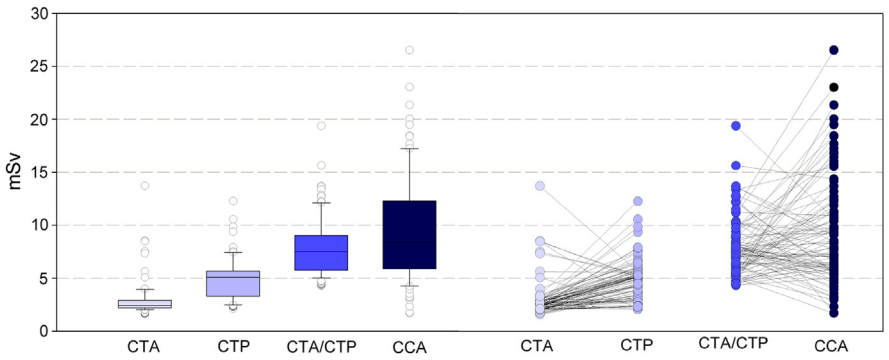

Figure 2 Comparison of Radiation Exposure for CTA, CTP, CTA/CTP, and CCA

The effective radiation dose for CTA (3.0 ± 1.8 mSv) was significantly lower than for CCA (9.5 ± 5.1 mSv; excluding revascularization; $p < 0.05$). CTA also had a significantly lower effective radiation dose than CTP did (4.9 ± 1.9 mSv; $p < 0.05$). CTA/CTP resulted in a significantly lower radiation dose (7.9 ± 2.8 mSv) than CCA did ($p = 0.005$). Abbreviations as in Figure 1.

Table 2 Performance of CTA, CTP, and Combined CTA/CTP for the Detection of Coronary ISR

	CTA	CTP	Combined CTA/CTP
QCA as the Reference Standard			
Per-patient analysis			
Diagnostic accuracy	65/91 (71 [61–80])	62/91 (68 [58–78])	79/91 (87 [78–93])*
Nondiagnostic rate	20/91 (22 [14–32])	1/91 (1 [0–6])	0/91 (0 [0–4])*
Sensitivity	10/17 (59 [33–82])	11/17 (65 [38–86])	14/17 (82 [57–96])
Specificity	55/74 (74 [63–84])	51/74 (69 [57–79])	65/74 (88 [78–94])*
Negative predictive value	55/58 (95 [86–99])	51/57 (90 [79–96])	65/68 (96 [88–99])
Positive predictive value	10/13 (77 [46–95])	11/33 (33 [18–52])	14/23 (61 [39–80])
Per-stent analysis			
Diagnostic accuracy	171/224 (76 [70–82])	151/224 (67 [61–74])	199/224 (89 [84–93])*
Nondiagnostic rate	45/224 (20 [15–26])	3/224 (1 [0–4])	0/224 (0 [0–2])*
Sensitivity	10/18 (56 [31–78])	12/18 (67 [41–87])	14/18 (78 [52–94])
Specificity	161/206 (78 [72–84])	139/206 (68 [61–74])	185/206 (90 [85–94])*
Negative predictive value	161/165 (98 [94–99])	139/145 (96 [91–99])	185/189 (98 [95–99])
Positive predictive value	10/14 (71 [42–92])	12/76 (16 [8–26])	14/35 (40 [24–58])
Coronary Revascularization as the Reference Standard			
Per-patient analysis			
Diagnostic accuracy	60/91 (66 [55–76])	60/91 (66 [55–76])	72/91 (79 [69–87])*
Nondiagnostic rate	20/91 (22 [14–32])	1/91 (1 [0–6])	0/91 (0 [0–4])*
Sensitivity	6/11 (55 [23–83])	7/11 (64 [31–89])	8/11 (73 [39–94])
Specificity	55/80 (69 [57–79])	53/80 (66 [55–76])	65/80 (81 [71–89])*
Negative predictive value	55/58 (95 [86–99])	53/57 (93 [83–98])	65/68 (96 [88–99])
Positive predictive value	6/13 (46 [19–75])	7/33 (21 [9–39])	8/23 (35 [16–57])
Per-stent analysis			
Diagnostic accuracy	168/224 (75 [69–81])	148/224 (66 [60–72])	200/224 (89 [85–93])*
Nondiagnostic rate	45/224 (20 [15–26])	3/224 (1 [0–4])	0/224 (0 [0–2])*
Sensitivity	6/11 (55 [23–83])	7/11 (64 [31–89])	8/11 (73 [39–94])
Specificity	162/213 (76 [70–82])	141/213 (66 [59–73])	192/213 (90 [85–94])*
Negative predictive value	162/165 (98 [95–100])	141/145 (97 [93–99])	192/195 (99 [96–100])
Positive predictive value	6/14 (43 [18–71])	7/76 (9 [4–18])	8/29 (28 [13–47])

Values are n/N (% [95% CI]). Results are provided on the per-patient and -stent level using the following reference standards: 1) QCA for detection of ≥50% diameter ISR; and 2) subsequent coronary revascularization of ISR (within 1 month). Using QCA as the reference, diagnostic accuracy ($p < 0.001$), specificity ($p = 0.004$), and nondiagnostic rate ($p < 0.001$) were significantly improved with CTA/CTP on the per-patient level of analysis. Diagnostic accuracy ($p < 0.001$), specificity ($p < 0.001$), and nondiagnostic rate ($p < 0.001$) were also significantly improved with the combination of CTA and CTP on the per-stent level of analysis. Similar results were found for coronary revascularization. 95% CI were estimated as described for unclustered data on the per-patient level (25) and clustered data (stent level) as described (24). *Significant difference ($p < 0.05$) in the comparison of CTA with combined CTA/CTP. The p values were obtained using the sign test.

CI = confidence interval(s); QCA = quantitative coronary angiography; other abbreviations as in Table 1.

Table 3 Performance of CTA and Combined CTA/CTP for the Detection of Any Coronary Artery Stenosis

	CTA	Combined CTA/CTP
QCA as the Reference Standard		
Per-patient analysis		
Diagnostic accuracy	74/91 (81 [72–89])	78/91 (86 [77–92])
Nondiagnostic rate	6/91 (7 [3–14])	0/91 (0 [0–4])*
Sensitivity	59/65 (91 [81–97])	61/65 (94 [85–98])
Specificity	15/26 (58 [37–77])	17/26 (65 [44–83])
Negative predictive value	15/18 (83 [59–96])	17/21 (81 [58–95])
Positive predictive value	59/67 (88 [78–95])	61/70 (87 [77–94])
Per-vessel analysis		
Diagnostic accuracy	335/396 (85 [81–88])	351/396 (89 [85–92])*
Nondiagnostic rate	24/396 (6 [4–9])	0/396 (0 [0–1])*
Sensitivity	89/106 (84 [76–90])	92/106 (87 [79–93])
Specificity	247/290 (85 [81–89])	259/290 (89 [85–93])*
Negative predictive value	247/257 (96 [93–98])	259/272 (95 [92–97])
Positive predictive value	89/115 (77 [69–85])	92/124 (74 [66–82])
Coronary Revascularization as the Reference Standard		
Per-patient analysis		
Diagnostic accuracy	54/91 (59 [49–70])	58/91 (64 [53–74])
Nondiagnostic rate	6/91 (7 [3–14])	0/91 (0 [0–4])*
Sensitivity	39/43 (91 [78–97])	40/43 (93 [81–99])
Specificity	15/48 (31 [19–46])	18/48 (38 [24–53])
Negative predictive value	15/18 (83 [59–96])	18/21 (86 [64–97])
Positive predictive value	39/67 (58 [46–70])	40/70 (57 [45–69])
Per-vessel analysis		
Diagnostic accuracy	289/396 (73 [68–77])	303/396 (77 [72–81])*
Nondiagnostic rate	24/396 (6 [4–9])	0/396 (0 [0–1])*
Sensitivity	38/47 (81 [67–91])	39/47 (83 [69–92])
Specificity	251/349 (72 [67–77])	264/349 (76 [71–80])*
Negative predictive value	251/257 (98 [95–99])	264/272 (97 [94–99])
Positive predictive value	38/115 (33 [25–42])	39/124 (32 [23–40])

Values are n/N (% [95% CI]). Results are provided on the per-patient and -vessel level using the following as the reference standard: 1) QCA for detection of ≥50% stenosis; and 2) subsequent coronary revascularization of coronary stenosis (within 1 month). Note that both stenosis in native vessel and ISR are considered in this table. The second reference standard was subsequent coronary revascularization of any stenosis within 1 month after coronary angiography. Nondiagnostic rate ($p < 0.001$) was significantly improved with the combination of CTA and CTP on the per-patient level of analysis. Also on the per-vessel level of analysis, diagnostic accuracy ($p < 0.001$) and nondiagnostic rate ($p < 0.001$) were significantly improved with CTA/CTP versus CTA alone. In 32 patients, an intermediate branch (segment 17) was present. Therefore, 396 vessels are available for the per-vessel analysis including the 4 standard vessels (left main, left anterior descending, left circumflex, and right coronary artery) in each of the 91 patients. Similar results were found for coronary revascularization. The p values were obtained using the sign test. 95% CI were estimated as described for unclustered data on the per-patient level (25) and clustered data (stent level) as described (24). *Significant difference ($p < 0.05$) in the comparison of CTA with combined CTA/CTP.

Abbreviations as in Tables 1 and 2.

($p = 0.004$) for CTA alone. CTP alone was insignificantly inferior to CTA in ruling out ISR, with negative predictive values of 90% and 95%, respectively (Table 2). In the per-stent analysis, the sensitivity and specificity of CTA/CTP were 78% and 90%, respectively, versus 56% ($p = 0.13$) and 78% ($p < 0.001$) for CTA alone (Table 2). Online Tables 1 to 4 provide detailed diagnostic performance results on all levels of analysis.

Table 3 summarizes the data for detection of any CAD by CTA and CTA/CTP. Diagnostic accuracy of combined CTA/CTP (86%) in the per-patient analysis was higher than that of CTA alone (81%; $p = 0.13$), whereas the rate of nondiagnostic examinations was significantly reduced ($p < 0.001$) (Table 3). In the per-vessel analysis, diagnostic accuracy and nondiagnostic rate were also significantly improved by the addition of CTP ($p < 0.001$) (Table 3). The per-patient sensitivity and specificity for combined CTA/CTP were 94% and 65%, respectively, versus 91% ($p = 0.48$) and 58% ($p = 0.48$) for CTA alone. In the per-vessel analysis, the sensitivity and specificity of CTA/CTP were 87% and 89%, respectively, versus 84% ($p = 0.13$) and 85% ($p < 0.001$) for CTA.

The correlation of stress imaging tests with CTA/CTP for detection of any CAD and ISR is summarized in Online Tables 5 and 6 and Online Tables 7 and 8, respectively, indicating superiority of CTA/CTP. Figure 3 compares CTA and CTP with CCA in a representative patient with ISR. Stents nondiagnostic on CTA due to metal artifacts (34 of 221, 15% of all stents) or motion (11 of 221, 5% of all stents) mainly accounted for the limited diagnostic accuracy of CTA. Coronary stent diameter significantly influenced interpretability on CTA but not on CTA/CTP, with more nondiagnostic stents on CTA being located in stents with diameters <3.0 mm (24 of 45, $p < 0.05$; after adjusting for clustering effects: $p = 0.14$) (Online Table 9).

The area under the ROC curve of CTA/CTP was superior to that for CTA in identifying patients with ISR (Fig. 4A). When subsequent revascularization was the reference standard, the area under the ROC curve of CTA/CTP was also superior (Fig. 4B). The ROC analysis results on the per-stent and per-patient level did not differ.

Discussion

Our results indicate that combined coronary CTA and myocardial CTP compares favorably with the diagnostic performance of CTA alone in detecting coronary ISR and CAD. Combined CTA/CTP had 87% accuracy for detection of ISR and 86% accuracy for CAD on the patient level, which is the most relevant level and indicates robust diagnostic performance. The per-patient diagnostic accuracy of CTA alone was only 71% for ISR and 81% for CAD with nondiagnostic rates of 22% and 7%. An intention-to-diagnose design using 3-×-2 tables was chosen because this provides a realistic picture of the clinical potential of diagnostic tests (11). If all nondiagnostic CTA were considered positive, sensitivity for ISR detection on the per-patient level would increase to 82% but the positive predictive value would decrease to 42%. Importantly, the use of CTP also improved the identification of the need for subsequent revascularization for ISR. However, our data also confirm the high negative predictive value of CTA, if

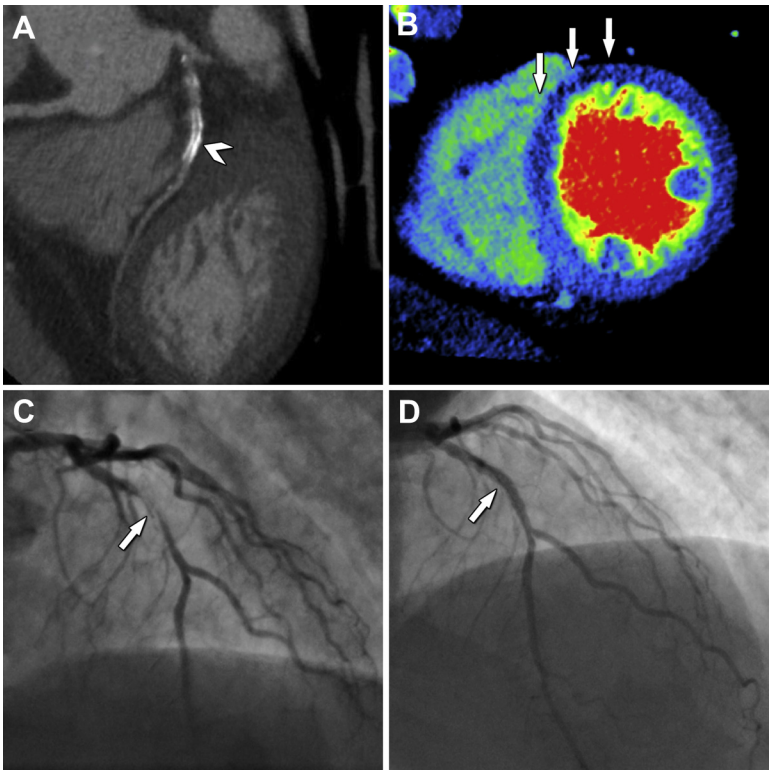

Figure 3 Coronary ISR in a 75-Year-Old Man With a 3-mm Stent in LAD

(A) Nondiagnostic CTA was performed because of artifacts related to metallic stent material **(arrowhead),** which were pronounced because of the small stent diameter and precluded identification of ISR. **(B)** CTP in the cardiac short axis identifies stress-induced anteroseptal myocardial ischemia **(arrows)** resulting from 80% coronary ISR confirmed on CCA **(arrow in C)**. **(D)** During the same invasive angiography, percutaneous coronary intervention with drug-eluting balloon was performed **(arrow)**. LAD = left anterior descending coronary artery; other abbreviations as in Figure 1.

evaluable, for coronary stent assessment (Table 2) and detection of CAD (Table 3), which cannot be improved by additional CTP. CTA/CTP detected 4 more of the 17 ISR cases (sensitivity increase from 59% to 82%), but positive predictive value decreased nonsignificantly from 77% to 61% (Table 2). About one-half of patients had prior myocardial infarctions and considering fixed perfusion defects as positive might have decreased specificity. Of 91 patients scanned by CT in our study, 43 underwent any coronary revascularization, for which CTA/CTP had 93% sensitivity (Table 3).

The need for 2 contrast agent injections of about 60 ml and an effective radiation dose of about 7.9 mSv for CTA/CTP argue against its routine clinical use. Nevertheless, the radiation dose of CTA/CTP was significantly smaller than that for CCA. The rather high dose for the diagnostic portion of CCA may be explained by the high prevalence and QCA-induced additional projections. As shown in our study, the analysis of myocardial perfusion by CT makes it possible to assess nondiagnostic stents on CTA, an important point because metal- and motion-related artifacts often limit coronary stent analysis by CTA alone (4).

CTP primarily uses visual analysis supplemented by assessment of absolute densities as well as transmural density differences (16,20). In other studies, this approach has provided incremental diagnostic power over CTA alone in suspected or known CAD (30). Our intraindividual comparison specifically addresses patients with coronary stents using 320-row CT and demonstrates that additional CTP facilitates the otherwise difficult evaluation of coronary stents but also of any CAD.

These findings must be interpreted in light of the performance of other common noninvasive imaging modalities such as myocardial single-photon emission CT, cardiac magnetic resonance imaging, and stress echocardiography, and CTP alone may not be accurate enough to reliably rule out ISR, whereas CTA/CTP was significantly more accurate than stress tests were. Our results confirm the increased nondiagnostic rate of CTA in stents with small (<3 mm) inner diameters (4). Importantly, CTP was not affected by such challenging stent characteristics.

Study limitations. Our CT protocol included a coronary artery calcium scan, which reduces the overall effective radiation dose by limiting the anatomical coverage of the subsequent CT scans (15). Calcium scans have shown to be important predictors for coronary events in population-based studies (31) but were not helpful for predicting ISR

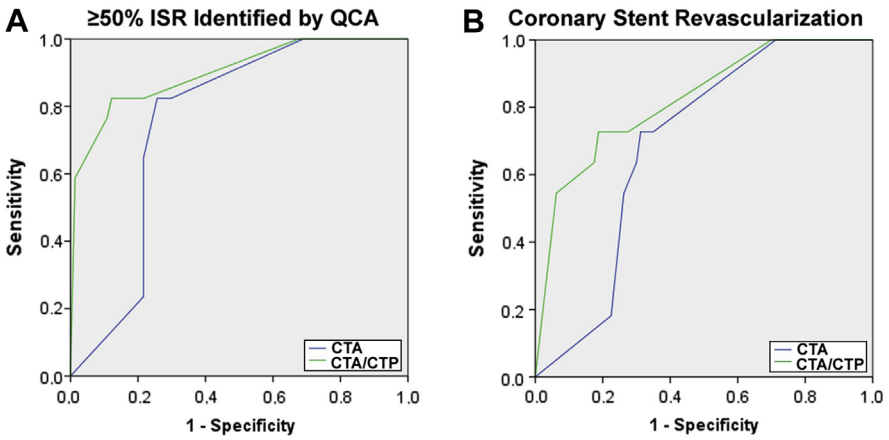

Figure 4 Diagnostic Performance of CTA and Combined CTA/CTP

Receiver-operating characteristic (ROC) curve analysis of the diagnostic performance of CTA and CTA/CTP on the patient level. **(A)** The area under the ROC curve of CTA alone for ≥50% ISR identified by quantitative coronary angiography (QCA) (0.76, 95% confidence interval [CI]: 0.65 to 0.86) was significantly smaller than that for CTA/CTP (0.90, 95% CI: 0.81 to 0.99; $p < 0.001$). **(B)** The area under the ROC curve of CTA alone for predicting coronary stent revascularization (0.69, 95% CI: 0.57 to 0.82) was also significantly smaller than that for CTA/CTP (0.82, 95% CI: 0.69 to 0.95; $p < 0.001$). Abbreviations as in Figure 1.

or any CAD in our study (data not shown). As it would be done in clinical practice, CTP was always performed after CTA. This may, however, have masked perfusion defects on CTP. Also, beta-blockade treatment that is necessary to reduce the heart rate for CTA (32) may have masked ischemia. We did not perform other stress imaging tests in all patients. Therefore, comparison of these tests with CT is limited by partial verification bias. Almost one-half of patients screened had to be excluded, and of those eligible, a considerable portion could not be included. Nevertheless, the meticulous recording of this information is unique for cardiac CT studies (32). Fractional flow reserve measurements, the functional reference standard for coronary lesions (33), were only done at the discretion of the interventionalists. Instead, we analyzed the ability of CTA/CTP to predict the need for subsequent coronary revascularization. Whereas the importance of the prognostic information provided by CTA has been established for coronary plaques as well as obstructive lesions (34), it is not clear whether CTP can add prognostic information.

Whether incorporating CT increases effectiveness, by reducing multiple diagnostic testing in patients with coronary stents, should be investigated in future studies. The expenditure on diagnostic imaging testing is increasing (35), and every effort should be made to decrease its economic burden. Whether CT can optimize cost-effectiveness compared with traditional tests in patients with stents is an important additional question (36).

Conclusions

The noninvasive detection of coronary stenosis in patients with stents by CTA alone is limited, and the combination of CTA and CTP has the potential to improve diagnostic performance by adding functional information that may also be relevant to the decision whether or not to perform revascularization in symptomatic patients. Thus, further studies are warranted to precisely define the role of CTA and CTP as a means of positively altering outcomes in patients with angina pectoris after coronary stent placement.

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Key Words: computed tomography ■ coronary angiography ■ coronary vessels ■ diagnostic accuracy ■ stents.

APPENDIX

For additional tables and a figure, please see the online version of this article.