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Coronary computed tomography angiography with model-based iterative reconstruction using a radiation exposure similar to chest X-ray examination

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Aims To evaluate the feasibility and image quality of coronary computed tomography angiography (CCTA) acquisition with a submillisievert fraction of effective radiation dose using model-based iterative reconstruction (MBIR) for noise reduction.

Methods and results In 42 patients undergoing standard low-dose (100–120 kV; 450–700 mA) and additional ultra-low-dose CCTA (80–100 kV; 150–210 mA) reconstructed with MBIR, segmental image quality was graded on a four-point scale [(i): non-evaluative, (ii): good, (iii): adequate, and (iv): excellent]. Signal-to-noise ratio (SNR) was calculated dividing left main artery (LMA) and right coronary artery (RCA) attenuation by the aortic root noise. Over a wide range of body mass index (18–40 kg/m^2), the estimated median radiation dose exposure was 1.19 mSv [interquartile range (IQR): 1.07–1.30 mSv] for standard and 0.21 mSv (IQR: 0.18–0.23 mSv) for ultra-low-dose CCTA ($P < 0.001$). The median image quality score per segment was 3.5 (IQR: 3.0–4.0) in standard CCTA vs. 3.5 (IQR: 2.5–4.0) in ultra-low dose with MBIR ($P = 0.29$). Diagnostic image quality (scores 2–4) was found in 98.7 vs. 97.8% coronary segments ($P = 0.36$). Introduction of MBIR for ultra-low-dose CCTA resulted in a significant increase in SNR ($P < 0.001$) for LMA (from 15 ± 5 to 29 ± 7) and RCA (from 14 ± 4 to 27 ± 6) despite 82% dose reduction.

Conclusion Coronary computed tomography angiography acquisition with diagnostic image quality is feasible at an ultra-low radiation dose of 0.21 mSv, e.g. in the range reported for a postero-anterior and lateral chest X-ray.

Keywords Ultra-low-dose coronary computed tomography angiography • Model-based iterative reconstruction • Feasibility

Introduction

Technical refinements in coronary computed tomography angiography (CCTA) have led to a rapid implementation of CCTA for non-invasive assessment of coronary artery disease (CAD) in daily clinical routine yielding high accuracy compared with invasive coronary angiography.[1,2] Recently, CCTA has been found to be most useful in patients with a low-to-intermediate pre-test probability for CAD as the strength of CCTA is based on a high negative predictive value.[3]

The radiation exposure from CCTA has obtained a growing attention due to its potential risk of cancer induction[4] and has stimulated the development of technical refinements for dose reduction. Although the initially reported high radiation dose exposure for CCTA has been substantially reduced from ~20 to ~2 mSv or less without loss of image quality or accuracy by introduction of prospective ECG triggering[5] including high-pitch spiral,[6] any further dose reduction is welcome. Further radiation dose reduction

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would require lowering tube voltage and current, which was so far hampered by image quality degradation from progressively increasing noise.

Recently, iterative reconstruction algorithms for image noise reduction[7] such as model-based iterative reconstruction (MBIR; GE Healthcare, Milwaukee, USA) have paved the way for lowering tube voltage and current with acceptable image quality in abdominal[8] and chest CT[9] but has not yet been implemented for CCTA.

We tested the hypothesis that ultra-low-dose CCTA achieving image quality comparable with standard CCTA with a submillisievert fraction of effective radiation dose is feasible by introducing the novel reconstruction algorithm MBIR.

Methods

Patients

We prospectively enrolled 42 consecutive patients who were referred for the assessment of known or suspected CAD with contrast-enhanced CCTA to undergo additional ultra-low-dose contrast-enhanced CCTA if none of the following exclusion criteria were present: hypersensitivity to iodinated contrast agent, renal insufficiency, non-sinus rhythm, and haemodynamic instability.

Patients were referred based on at least one of the following symptoms: dyspnoea ($n = 9$), typical angina pectoris ($n = 10$), atypical chest pain ($n = 22$), pathological exercise test or ECG ($n = 17$), for follow-up after coronary stenting ($n = 1$), and due to suspected CAD based on high-risk profile ($n = 1$). The study was approved by the local ethics committee and written informed consent was obtained from all patients.

Computed tomography data acquisition and post-processing

Prior to examination all patients received 2.5 mg isosorbiddinitrate sublingually (Isoket, Schwarz Pharma, Monheim, Germany) and metoprolol (up to 25 mg Beloc, AtraZeneca, London, UK) was administered intravenously if heart beats per minute were >65 b.p.m. in order to obtain optimal image quality for CCTA. Iodixanol (Visipaque 320, 320 mg/mL, GE Healthcare) was injected into an antecubital vein followed by 50 mL saline solution via an 18-cauge catheter. Volume and flow rate were adapted to body surface area (BSA) (50 mL via 4 mL/s: BSA <1.7 m^2; 55 mL via 4 mL/s: BSA 1.7–1.79 m^2; 60 mL via 4 mL/s: BSA 1.8–1.94 m^2; 80 mL via 4.5 mL/s: BSA 1.95–2.04 m^2; 80 mL via 5 mL/s: BSA 2.05–2.14 m^2; 85 mL via 5 mL/s: BSA 2.15–2.24 m^2; 95 mL via 5 mL/s: BSA 2.25–2.49 m^2; 105 mL via 5 mL/s: BSA ≥2.5 m^2), modified from Pazhenkottil *et al.*[10]

All CCTA examinations were performed on a 64 slice CT scanner (Discovery HD 750, GE Healthcare) using prospective ECG triggering during inspiration breath hold as previously reported.[5] The scanning parameters were as follows: slice acquisition 64 × 0.625 mm, z-coverage 40 mm with an increment of 35 mm, smallest X-ray window (75% of the RR-cycle), gantry rotation time 350 ms, and body mass index (BMI) adapted tube voltage and tube current for ultra-low-dose and standard CCTA (*Table 1*).

Standard CCTA was reconstructed using a blending factor of 30% of adaptive statistical iterative reconstruction (ASIR; GE Healthcare) according to clinical standards established in our institution.[11] In brief, ASIR reconstructs pictures by comparing measured projection with a synthesised projection using both statistical fluctuation calculations and system optics.[12] Ultra-low-dose CT was reconstructed using MBIR (GE Healthcare), an iterative reconstruction algorithm on the basis of multiple statistical models incorporating optical system geometry and system statistics (e.g. image noise).[13] As MBIR is not yet commercially available for CCTA reconstructions, datasets were transferred outside our department on an external workstation and reconstructed by the vendor (GE Healthcare). The effective radiation dose from CCTA was calculated as the product of dose-length product (DLP) times a conversion coefficient for chest [$k = 0.014$ mSv/(mGy × cm)].[2,14]

Table 1 Body mass index adapted tube current and voltage

BMI (kg/m^2)	Ultra-low-dose CCTA		Standard CCTA	
	Tube current (mA)	Tube voltage (kV)	Tube current (mA)	Tube voltage (kV)
<22.5	150	80	450	100
22.5–24.9	165	80	500	100
25–27.4	180	80	550	100
27.5–29.9	195	80	600	100
30–39.9	210	100	650	120
≥40	210	100	700	120

BMI, body mass index; CCTA, coronary computed tomography angiography.

Computed tomography image analysis

Coronary arteries were segmented as suggested by the American Heart Association.[15] All segments with a diameter of at least 1.5 mm at their origin were included. Two readers semi-quantitatively assessed independently the overall image quality on a four-point Likert scale [(i): non-evaluative, severe artefacts; (ii): adequate, moderate artefacts; (iii): good, minor artefacts; and (iv): excellent, no artefacts] adapted as previously reported.[1] To measure attenuation in the left main artery (LMA) and in the proximal right coronary artery (RCA), regions of interest (ROIs) were drawn as large as possible, carefully avoiding calcifications, plaques, and stenoses. Noise was defined as the standard deviation of the attenuation in a circular ROI placed into the aortic root. Signal-to-noise ratio (SNR) was calculated for LMA and RCA by dividing the attenuation in the respective coronary vessel by the noise.

Statistical analysis

SPSS 20.0 (SPSS, Chicago, IL, USA) was used for all statistical analysis. Quantitative data were expressed as mean ± SD or median and interquartile range (IQR), when appropriate. The Kolmogorov–Smirnov test was applied to evaluate the distribution of the data. Comparison of continuous variables with non-normal distributions between groups was performed with the Wilcoxon signed-rank test and with normal distribution with Student's paired *t*-test. Contingency analysis was performed using Fisher's exact test. We took into account the repeated structure of the measures and the hierarchical data structure (i.e. the fact that the segments and vessels were clusters of observations in the patients). To this aim, a multilevel analysis was performed on three levels (patient as the first level, vessels being the second level, and segments the third). Therefore generalised linear mixed modelling was used. Because of the skewness of the target variable gamma distribution was applied with identity link function.[16,17] *P*-values of <0.05 (two tailed) were considered statistically significant.

Results

Ultra-low-dose and standard CCTA was successfully performed in all 42 patients (14 women, 28 men; mean age 55 ± 10 years; age range 34–71 years) presenting with the following cardiovascular risk factors: 21 were smokers (50%), 1 had diabetes (2%), 13 had arterial hypertension (31%), 16 had dyslipidaemia (38%), and 13 had a positive family history of CAD (31%) (*Table 2*).

Coronary computed tomography angiography revealed unknown CAD in six patients. In one patient with known CAD, CCTA revealed an open bioabsorbable stent. The mean BMI of the study population was 25.2 ± 3.8 kg/m^2 (range: 18.4–40.2 kg/m^2) with a mean weight of 74.6 ± 13.1 kg (range: 46.5–112.0 kg). After i.v. beta-blocker administration for heart rate control prior to CCTA in 33 patients (79%) (14.5 ± 8.2 mg, range: 3–25 mg), the mean heart rate was 56.7 ± 5.7 b.p.m. during ultra-low-dose CCTA and 56.9 ± 5.7 b.p.m. during standard CCTA ($P = 0.95$).

The median DLP from ultra-low-dose vs. standard CCTA was 14.9 mGy cm (IQR: 13.2–16.2 mGy cm) vs. 84.7 mGy cm (IQR: 76.2–93.2 mGy cm) ($P < 0.0001$) resulting in an estimated median radiation dose of 0.21 mSv (IQR: 0.18–0.23 mSv) vs. 1.19 mSv (IQR: 1.07–1.30 mSv) ($P < 0.0001$; *Figure 1*). This represents an 82% dose reduction ($P < 0.0001$).

The calcium score in the study population ranged from 0 to 2189 (median 141). In the 20 patients with coronary calcifications (calcium score above 0), the calcium score averaged 335 ± 499.

In 42 patients, a total of 168 vessels and 551 coronary artery segments with a diameter of ≥1.5 mm were evaluated (of theoretically 672 segments in 42 patients with 16 coronary segments, 121 were missing because of anatomical variants or diameter <1.5 mm at their origin). Inter-observer agreement of image quality rating was good ($\kappa = 0.68$; *Figure 2*).

Both CCTA protocols yielded good to excellent image quality per segment, per coronary, and per patient (*Table 3*). The multilevel analysis showed no significant differences in the image quality between ultra-low-dose and standard CCTA ($n = 1104$ (third level), $P = 0.525$).

In ultra-low-dose and standard CCTA 97.8% and 98.7% of coronary segments were of diagnostic image quality (score >1) (*Figure 3*).

Mean image noise decreased significantly from 32 ± 8 Hounsfield units (HU) in standard CCTA to 20 ± 3 HU in ultra-low-dose CCTA ($P < 0.001$). Interestingly, this was accompanied by an increase in mean attenuation in LMA from 456 ± 82 to 558 ± 121 HU and in RCA from 444 ± 72 to 511 ± 100 HU ($P < 0.001$). Thus, the introduction of ultra-low-dose CCTA with MBIR resulted in a significant increase in SNR ($P < 0.001$) for LMA (from 15 ± 5 to 29 ± 7) and RCA (from 14 ± 4 to 27 ± 6, *Table 4*).

Table 2 Patient baseline characteristics

Number of patients (*n*)	42
Age (years)	55 ± 10 (34–71)
Male/female	28/14
BMI (kg/m^2)	25.2 ± 3.8 (18.4–40.2)
Drug administration, *n* (%)	
Beta-blocker	33 (79)
Nytroglycerin	42 (100)
Heart rate (b.p.m)	
Standard CCTA	56.9 ± 5.7 (49–70)
Ultra-low-dose CCTA	56.7 ± 5.7 (49–75)
Clinical symptoms, *n* (%)	
Dyspnoea	9 (21)
Typical AP	10 (24)
Atypical chest pain	22 (52)
None	10 (24)
Cardiovascular risk factors, *n* (%)	
Smoking	21 (50)
Diabetes	1 (2)
Arterial hypertension	13 (31)
Dyslipidaemia	16 (38)
Positive family history	13 (31)

Values are given as mean ± SD and ranges (in brackets) or absolute numbers and percentages (in brackets).
BMI, body mass index; CCTA, coronary computed tomography angiography; AP, angina pectoris.

Discussion

This study is the first to demonstrate the feasibility of ultra-low-dose CCTA using MBIR for noise reduction in a broad spectrum of patients as seen in daily clinical routine over a wide range of BMI. Despite a substantial radiation dose reduction, median image quality was not significantly different to standard CCTA and 97.8% of coronary segments were interpretable yielding comparable or even higher image quality scores than reported in other CCTA studies.[5]

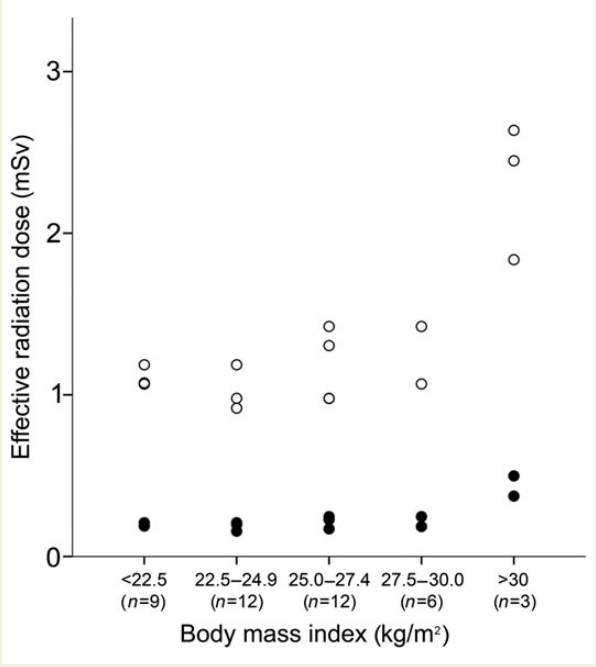

Figure 1 Effective estimated radiation dose for each patient from ultra-low-dose (•) and standard coronary computed tomography angiography (○).

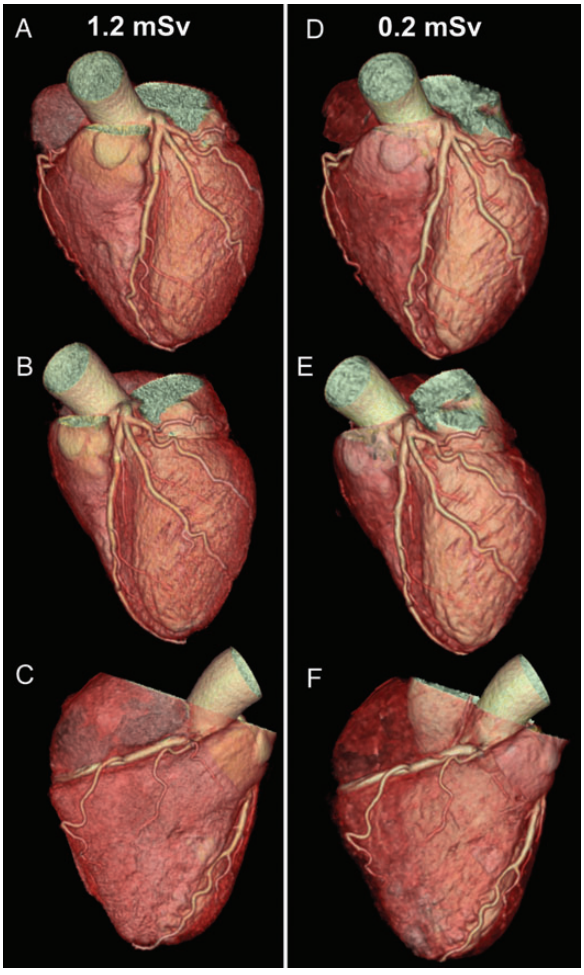

Figure 2 Three-dimensional volume rendered images from standard (*A*–*C*) and ultra-low-dose (*D*–*F*) coronary computed tomography angiography of the same patient acquired with 1.2 and 0.2 mSv.

Table 3 Image quality

	Ultra-low-dose CCTA	Standard CCTA	*P*-value
Per segment ($n = 551$)	3.5 (2.5–4.0)	3.5 (3.0–4.0)	0.29
Per artery ($n = 168$)	3.5 (3.1–4.0)	3.5 (3.0–4.0)	0.84
Per patient ($n = 42$)	3.4 (2.9–3.6)	3.3 (3.1–3.6)	0.60

Values of image quality are given as median and IQR (in brackets).
P-values are reported from Wilcoxon signed-rank test.
CCTA, coronary computed tomography angiography.

The comparable image quality of ultra-low-dose vs. standard CCTA was enabled by an effective noise reduction by MBIR resulting in an even lower image noise in ultra-low-dose compared with standard CCTA. In combination with the shift towards higher beam attenuation by iodine in low tube voltage scanning, this resulted in an SNR substantially higher than in standard CCTA. Despite increasing noise due to less photon emission at such low tube current and peak voltage, this containment of radiation dose was enabled by one of the latest iterative reconstructions algorithms such as MBIR, which incorporates modelling of the photon and noise statistics, but also involves modelling of system optics.[18] Recently, CCTA with reasonable image quality and a radiation dose as low as 0.06 mSv has been achieved in a study population with <100 kg using a similar modern iterative reconstruction algorithm from another vendor (SAFIRE, Siemens Healthcare, Forcheim, Germany).[19] However, their reported SNR for the coronary arteries averaged 5, whereas in our study this value averaged 27–29.

It is relevant to point out that the median effective radiation dose of 0.21 mSv achieved with the present protocol is even substantially lower than, for example, the effective radiation dose for standard coronary calcium score scanning.[20] Coronary computed tomography angiography at such low exposure opens new doors for non-invasive assessment. This is particularly remarkable as our protocol resulted in a median exposure of 0.21 mSv, close to the dose of a postero-anterior and lateral chest X-ray, which is reported to range from 0.05 to 0.24 mSv in the literature.[21–23]

It is generally accepted that the strength of CCTA lies in its high negative predictive value for CAD. Consequently, the consensus is to consider the use of CCTA mainly in low-to-intermediate probability populations[24] due to its excellent ability to rule out CAD. As such populations, however, are inherently characterised by a low risk for cardiac events it is unlikely that any diagnostic or therapeutic procedure will further improve the outcome.[25] This put the bars very high for any technique to keep a positive balance of harms and benefits for any diagnostic tool, evoking a vivid discussion on the potential carcinogenic risk of CCTA and its justification for a purely diagnostic test. As a consequence, this has fuelled an intense search for strategies to minimise radiation exposure while maintaining image quality. In the past years radiation dose reduction has been successfully achieved by introducing scanning protocols with prospective ECG triggering, limiting the beam to a narrow diastolic phase.[5] The new protocol represents yet another milestone for further substantial dose reduction from CCTA as new reconstruction algorithms for noise reduction allow decreasing tube current and voltage. This further shifts the tip of the benefit-to-harm balance favourably towards clinical benefits, where potentially even screening and monitoring of CAD therapy effects may no longer appear prohibitive for radiation safety concerns. It appears foreseeable that the presented development of latest iterative reconstruction algorithms will soon enter the clinical arena for CCTA and its implementation on different scanners from multiple vendors will allow a widespread use offering substantial decrease in radiation from CCTA to a large patient population in the near future.

It may be perceived as a potential limitation of this study that diagnostic accuracy and stenosis measurement was not compared with invasive coronary angiography. However, the high accuracy of standard CCTA has been previously established and, therefore, it seems reasonable to use it as a ground of truth reference standard. Another limitation is that the MBIR algorithm is currently not yet approved for clinical use in CCTA, whereas it is commercially

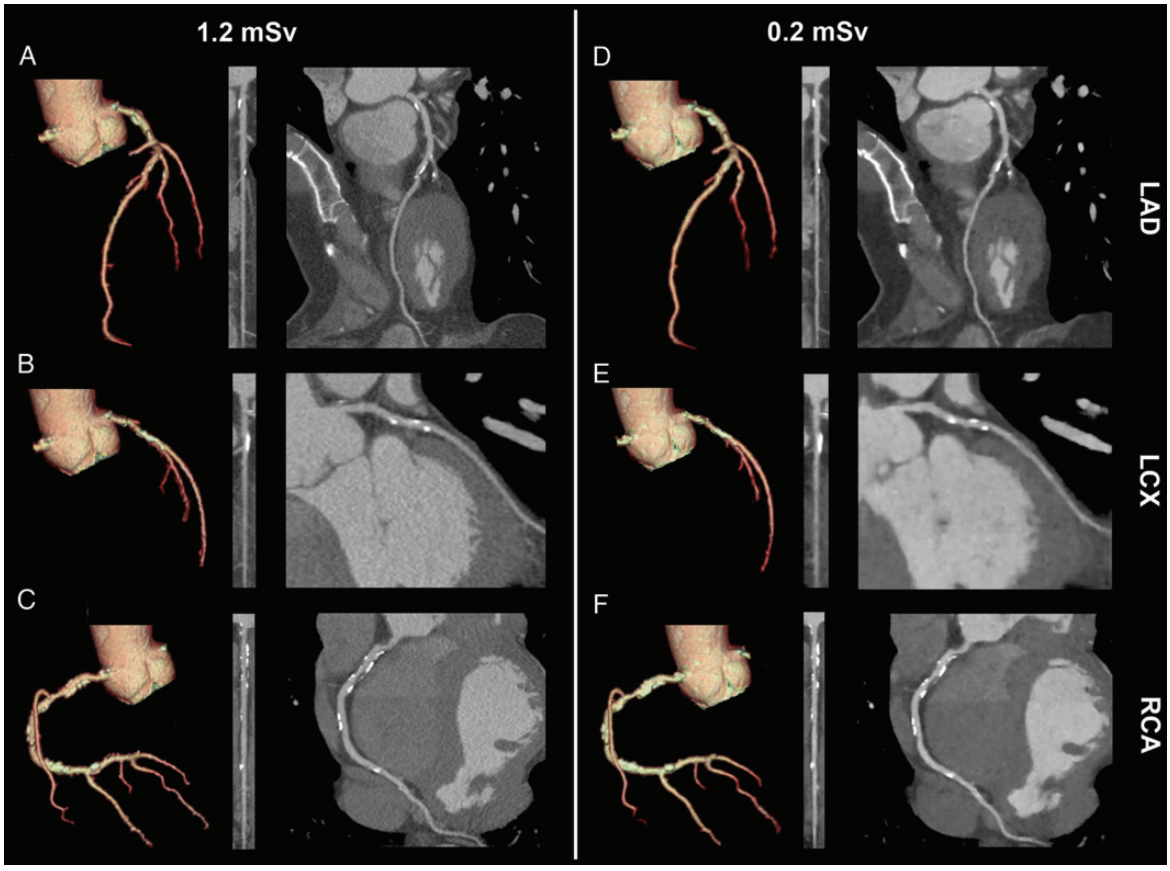

Figure 3 Three-dimensional volume rendered images and corresponding multiplanar and curved multiplanar images of a patient with calcifications in the left anterior descending (LAD), the left circumflex (LCX), and the right coronary artery (RCA) from standard (*A*–*C*) and ultra-low-dose (*D*–*F*) coronary computed tomography angiography of the same patient acquired with 1.2 and 0.2 mSv. Both ultra-low-dose and standard coronary computed tomography angiography revealed a 50% luminal narrowing in the RCA, which was confirmed by invasive coronary angiography.

Table 4 Image quality parameters

	Ultra-low-dose CCTA	Standard CCTA	*P*-value
Noise	20 ± 3	32 ± 8	<0.001
Attenuation LMA	558 ± 121	456 ± 82	<0.001
Attenuation RCA	511 ± 100	444 ± 72	<0.001
SNR LMA	29 ± 7	15 ± 5	<0.001
SNR RCA	27 ± 6	14 ± 4	<0.001

Noise and attenuation are given in HU as mean ± SD.
CCTA, coronary computed tomography angiography; SNR, signal-to-noise ratio; LMA, left main artery; RCA, right coronary artery.

available for non-cardiac use since several years. Furthermore, prevalence of coronary calcifications in the present study population was moderate. It cannot be excluded that in patients with higher prevalence of massive coronary calcifications image quality may be impaired, particularly in ultra-low-dose CCTA. However, we are in line with the general recommendations[3] to use CCTA preferentially in patients with low CAD risk profile and, thus, lower prevalence of coronary calcifications. Finally, larger studies may be helpful to establish how the promising results of the present study can be implemented into daily routine.

In conclusion, CCTA acquisition with diagnostic image quality is feasible at an ultra-low radiation dose of 0.21 mSv, e.g. in the range reported for a postero-anterior and lateral chest X-ray.

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