Published in final edited form as:

Eur Radiol. 2018 October ; 28(10): 4077–4085. doi:10.1007/s00330-018-5418-y.

Subtraction CT angiography improves evaluation of significant coronary artery disease in patients with severe calcifications or stents—the C-Sub 320 multicenter trial

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Abstract

Objectives—Diagnostic accuracy of conventional coronary CT angiography (CCTA_{conv}) may be compromised by blooming artifacts from calcifications or stents. Blooming artifacts may be reduced by subtraction coronary CT angiography (CCTA_{sub}) in which non-contrast and contrast CT data sets are subtracted digitally. We tested whether CCTA_{sub} in patients with severe coronary calcification or stents reduces the number of false-positive stenosis evaluations compared with CCTA_{conv}.

Methods—In this study, 180 symptomatic patients scheduled for invasive coronary angiography (ICA) were prospectively enrolled and CT scanned (2013–2016) at three international centers. CCTA_{conv} and CCTA_{sub} data sets were reconstructed. Target segments were defined as motion-free coronary segments with a suspected stenosis (> 50% of lumen) potentially due to blooming of either calcium or stents. Target segments were evaluated with respect to misregistration artifacts from the CCTA_{sub} reconstruction process, in which case evaluation was omitted. CCTA_{sub} and

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Guarantor The scientific guarantor of this publication is tenured senior author: Klaus Fuglsang Kofoed.

Conflict of interest

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry Lene Theil Skovgaard, Associate Professor at the Department of Biostatistics, University of Copenhagen, kindly provided statistical advice for this manuscript.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology

- prospective
- diagnostic or prognostic
- multicentre study

CCTA_{conv} were compared with ICA. Primary outcome measure was the frequency of false positives by CCTA_{conv} versus CCTA_{sub} to identify > 50% coronary stenosis by ICA on a per-segment level.

Results—After exclusion of 76 patients, 104 (14% females) with mean age 67 years and median Agatston score 852 were included. There were 136 target segments with misregistration and 121 target segments without. Accuracy calculations in target segments without misregistration showed a reduction of the false positives from 72% [95% confidence interval (CI): 63–80%] in CCTA_{conv} to 33% (CI:25–42%) in CCTA_{sub}, at the expense of 7% (CI:3–14%) false negatives in CCTA_{sub}.

Conclusions—In severely calcified coronary arteries or stents, CCTA_{sub} reduces the false-positive rate in well-aligned, calcified or stent segments suspected of significant stenosis on CCTA_{conv}. Nevertheless, misregistration artifacts are frequent in CCTA_{sub}.

Keywords

Subtraction technique; Artifact reduction; Computed tomography angiography; Coronary artery disease; Stents

Introduction

Coronary computed tomography angiography (CCTA) is widely used as a non-invasive test in patients suspected of stable coronary artery disease (CAD) [1]. Due to its high negative predictive value, CCTA is used to exclude obstructive disease. However, the positive predictive value of CCTA is only moderate, mainly because of overestimation of stenosis in the presence of calcified plaques or stents, where blooming artifacts may lead to over-diagnosis and excessive downstream testing [2, 3].

A coronary subtraction technology has become available that removes calcium and stents from CCTA images using a dedicated subtraction algorithm on the scan console. Corresponding non-contrast and contrast data sets are aligned and co-registered before obtaining subtracted images. These are essentially lumenograms, in which only the contrast-filled lumens are displayed and blooming artifacts are removed [4]. The initial results on the accuracy of this method for the assessment of significant luminal stenosis of > 50% on CCTA compared with ICA have been encouraging [4–12].

We conducted a prospective, international, multicenter trial to test whether subtracted CCTA in patients with severe coronary calcification or stents reduces the number of false-positive stenosis evaluations compared with conventional CCTA.

Methods

The Danish Committee System on Health Research Ethics approved the study. The institutional review board at the National Institutes of Health and Clínica Creu Blanca approved the study as well ([Clinicaltrials.gov](https://clinicaltrials.gov):). Informed written consent was obtained from all patients.

Between October 2013 and July 2016, patients suspected of stable CAD scheduled for invasive coronary angiography (ICA) were prospectively enrolled for CCTA at three centers: Rigshospitalet, Copenhagen, Denmark; the National Institutes of Health, Maryland, USA; and the Clínica Creu Blanca, Barcelona, Spain. Inclusion criteria for the study were referral for ICA, age > 55 years, normal kidney function (eGFR > 60) and absence of an implanted cardiac device. Secondary exclusion criteria were heart rate > 75 bpm or atrial fibrillation during the scan.

The diagnostic accuracy of CCTA to identify a > 50% coronary artery stenosis using conventional (CCTA_{conv}) and subtracted (CCTA_{sub}) CT images was assessed in coronary artery target segments using ICA as a reference. A target segment (Fig. 1) was defined on CCTA_{conv} as a motion-free coronary segment, which was non-diagnostic because of blooming of either coronary calcification or a stent, i.e., blooming > 50% of the lumen. Coronary target segments were thus all deemed stenotic. Misregistration (Fig. 2) was defined as an artifact in a target segment due to misalignment between non-contrast and contrast data sets during co-registration in the image subtraction process, causing evaluation to be uninterpretable. CT images with insufficient image quality or absence of any target segment in the CCTA_{conv} were excluded from further analysis.

CT Image Acquisition

CCTA was performed using a 320-detector row CT scanner (Aquilion ONE Vision Edition, Canon Medical Systems) with 0.5-mm detector elements and a rotation time of 275 ms using Adaptive Iterative Dose Reduction 3D (AIDR3D). The protocol consisted of a non-contrast scan followed by a contrast scan, thus using a two-breathhold acquisition technique [11]. A cardioselective beta-blocker (metoprolol 25–150 mg) was administered orally 1 h before scanning in individuals with a heart rate > 60 bpm and no contraindications. Nitroglycerin was given orally 2 min before the scan. Intravenous contrast media (Visipaque, GE Healthcare, Denmark)—dose (50, 70, 90 ml) depending on weight (< 80, 80–100, > 100 kg)—was infused with a flow rate of 5 ml/s. Image acquisition triggering was set at an aortic attenuation density of 180 Hounsfield units.

Tube voltage and tube current were determined by automated exposure control function (SURE^{EX}posure) with a target image noise level of SD 33 for both non-contrast and contrast scans. Depending on the BMI, 100, 120 or 135 kV was used for both scans. The prospectively acquired scans were reconstructed with 0.5/0.25 mm slice thickness/interval with an FC03 algorithm and AIDR3D. The non-contrast scan was additionally reconstructed with 3.0/3.0-mm slice thickness/interval with an FC03 algorithm for evaluation of the Agatston score.

CT Image Post Processing: Alignment and Subtraction

Alignment and subtraction of coronary images was performed using a dedicated algorithm, volumetric CT digital subtraction angiography (CTDSA) on the scanner console [13]. For CTDSA, two data sets were required: with and without coronary contrast enhancement. The subtraction was performed by first registering the non-contrast acquisition to the contrast acquisition and then subtracting the registered non-contrast data set from the contrast data

set [4]. The registration was a two-step process in which both non-rigid and rigid transformation was computed and applied: First, a dense-field non-rigid registration method was used to align the entire non-contrast volume to the contrast volume [14]. Second, calcified lesions and stents were identified in both data sets and a rigid registration was performed close to each calcification and stent as identified in the non-contrast data set [13]. The result of the subtraction was a 3D image volume in which coronary calcifications and stents had been removed leaving the contrast-enhanced blood in the lumen as the only high intensity material.

CT Image Evaluation

Image analysis was performed in three steps: (1) Initial clinical evaluation: CCTA_{conv} images were evaluated according SCCT guidelines [15] with respect to the presence of calcium/stents, obstructive CAD (defined as > 50% luminal stenosis), motion artifacts and image noise (SD of mean attenuation density in aorta ROI). Target segments were detected according to the above definition. CCTA_{conv} with severe motion artifacts or no target segments were excluded. (2) Evaluation of co-registration: Expert consensus reading comparing lesions in target segments in CCTA_{sub} to CCTA_{conv} to evaluate co-registration. Target segments in CCTA_{sub} where the calcium/stent lesion was out of place or enlarged compared with the corresponding lesion in CCTA_{conv} were deemed as misregistration. (3) C-Sub320 evaluation: Expert consensus reading in CCTA_{sub} assessing obstructive CAD in target segments without misregistration, blinded to results of initial clinical evaluation and ICA findings. All readings were carried out by two readers with more than 6 years of cardiac CT experience (AF, JTK) with commercial software (Vitrea 6.6, Vital Images Inc., MN, USA).

Invasive Coronary Angiography

Clinically indicated ICA was obtained according to clinical routine and international guidelines. Evaluation of the presence of obstructive CAD was performed visually according to clinical practice in target by an expert interventional cardiologist with more than 20 years of clinical ICA experience unaware of the CT findings (S.H.).

Statistical Analyses

For data analysis SAS 9.4 (SAS Institute, NC, USA) was used. Data are presented as mean (95% confidence interval), median (interquartile range) or amounts (percentage). Relations between categorical and continuous variables were made with logistic regression. Diagnostic accuracy was calculated for target segments without misregistration for CCTA_{conv} and CCTA_{sub}, including 95% confidence intervals (CI) assuming binomial distribution. Due to the nature of the setup with no negative test results for CCTA_{conv}, it was not possible to calculate *p* values for diagnostic accuracy. Subgroup analyses were made for implanted stents, calcium segments, according to the level of calcification (Agatston score > 600) [11], proximal segments and according to heart rate. Proximal segments were defined as previously described [4]. The diagnostic accuracy for target segments including misregistration deemed as positives was also calculated. Primary outcome measures were frequencies of true and false positives by CCTA_{conv} versus CCTA_{sub} to detect > 50% coronary stenosis identified by ICA on a per-segment level. True and false negatives for

CCTA_{sub} were also recorded. p values for comparison between diagnostic tests in subgroups were calculated by chi-square and Student's t-test.

Results

We included 180 patients. Seven patients were excluded because of scan-related issues and three because of high heart rate (Fig. 3). A further 64 patients were excluded because of no target segments and 2 because of severe motion artifacts in CCTA_{conv}, comprising a study group of 104 patients with CCTA and ICA recordings and target segments. Demographics, radiation dose, image noise and Agatston score for the study group are shown in Table 1.

Study group

The study group was divided into patients who had at least one target segment without misregistration (group A = 63 patients) and patients with misregistration in all target segments (group B = 41 patients). Patients in group B had higher heart rates during CT acquisition, a higher frequency of women and a lower frequency of previous stents compared with group A. ICA was performed within a median of 6 days of the CT scan (interquartile range: 2–31 days).

Out of 257 target segments in the study group, 136 (53%) had misregistration. Distribution of misregistration in subgroups is shown in Table 2. The correlations of misregistration with heart rate and Agatston score were both statistically insignificant.

In group A, there were 121 (79 calcified, 42 stented) target segments without misregistration for evaluation. Stents had a mean diameter of 3.0 ± 0.5 mm and mean length of 19.1 ± 6.9 mm. ICA identified a significant coronary stenosis in 34 (28%) target segments, including 28 (23%) in calcified segments and 6 (5%) in stent segments.

Accuracy calculations in target segments without misregistration

Accuracy calculations in the 121 target segments without misregistration (Fig. 4) showed a reduction of the false positives from 87 (72%) in CCTA_{conv} to 40 (33%) in CCTA_{sub}, at the expense of 9 (7%) false negatives in CCTA_{sub}. Of the nine false negatives (including 4 stent segments), one was treated with balloon angioplasty (in stent), one was treated with a stent, and two were referred for bypass operation.

Subanalyses

Subanalysis in CCTA_{sub} (Fig. 5) showed that the true negative rate in stent segments without misregistration was high (67% vs. 24%), and the false-positive rate was correspondingly low (19% vs. 41%) compared with calcified segments without misregistration. Further subanalyses in CCTA_{sub} for target segments with heart rate ≤ 55 , Agatston score ≤ 600 and Proximal segments are shown in Table 3; for these groups, there were large overlaps in CI.

Accuracy calculations in target segments including segments with misregistration

Taking into account the target segments with misregistration and deeming these as positive with respect to stenosis in CCTA_{sub}, the accuracy calculations in all 257 target segments

including misregistration were as follows for CCTA_{conv}: 68 (26%, CI: 21–32%) true positives and 189 (74%, CI: 68–79%) false positives and for CCTA_{sub}: 9 (3%, CI: 2–7%) false negatives, 59 (23%, CI: 18–29%) true positives, 47 (19%, CI: 14–24%) true negatives and 142 (55%, CI: 49–61%) false positives. Correspondingly, in 56 stent segments including segments with misregistration, we found for CCTA_{conv}: 7 (12%, CI: 5–24%) true positives and 49 (88%, CI: 76–95%) false positives and for CCTA_{sub}: 4 (7%, CI: 2–17%) false negatives, 3 (5%, CI: 1–15%) true positives, 28 (50%, CI: 36–64%) true negatives and 21 (38%, CI: 25–51%) false positives. In 201 calcified segments including misregistration, we found for CCTA_{conv}: 61 (30%, CI: 24–37%) true positives and 140 (70%, CI: 63–76%) false positives and for CCTA_{sub}: 5 (2%, CI: 0–6%) false negatives, 56 (28%, CI: 22–35%) true positives, 19 (10%, CI: 6–14%) true negatives and 121 (60%, CI: 53–67%) false positives.

Discussion

The current study is the first to test a new coronary subtraction software in a prospective, international, multicenter study. We found (1) that included patients had a very high degree of coronary calcification with a corresponding high rate of false-positive studies and (2) that false-positive stenoses in these lesions may be significantly reduced using coronary subtraction software. Nevertheless, (3) a high frequency of misregistration was seen in segments, which had to be excluded. (4) Due to the high diagnostic accuracy and low number of misregistrations, stent segments may be especially well suited for subtraction.

Patients in the study group were characterized by a high calcium score, high cardiovascular risk profile and known CAD. In these patients who would normally all need an invasive angiogram for diagnosis, the subtraction procedure lowered the false-positive rate in target segments without misregistration from 72% to 33%. Even when taking into account the misregistration segments, the reduction in false positives was significant according to confidence intervals. This is in accordance with previous retrospectively designed studies [4, 6, 9, 10]. In the present study, the reduced false-positive rate in CCTA_{sub} came at the expense of nine (7%) false-negative segments, of which four segments had an intervention. In the CCTA_{sub} subgroup analysis of stent segments, we found the greatest increase in true negatives and reduction in false positives. The stent patients seemed easier to register, and since the stents are uniform, better subtraction was obtained. The average stent diameter was ~3.0 mm, fairly large.

Misregistration artifacts are specific to the subtraction method and may appear if co-registration of calcium lesions and stents is not well aligned between the non-contrast and contrast data sets. Registering images as different in appearance as coronary non-contrast and contrast data sets is difficult, and the most accurate registration method requires a certain level of similarity of appearance between data sets to register and align. Slight motion artifacts have been identified as the main reason for the different appearance, but the dose, blooming, position of the rotation gantry and contrast injection regime may all cause differences in appearance between two scans [13].

In this study misregistration was found in approximately half of all target segments (136, i.e., 53%), and in 41 (39%) patients misregistration was found in all target segments.

Subanalyses found misregistration to be more frequent in distal target segments and less frequent in stents. In addition, patients with misregistration in all target segments (group B) had a higher heart rate more often and were female more often. This may suggest that subtraction is less successful in smaller arteries (i.e., distal segments and in females [16]) and requires stringent heart rate control, whereas subtraction is more successful in lesions with a distinct, uniform structure (i.e., stents).

In subtraction, one- and two-breathhold acquisition techniques have been demonstrated. Whereas the one-breathhold approach requires a relatively longer breathhold as well as adaptation of the scanning protocol (including the need for additional radiation if a separate non-contrast image is needed for Agatston calcium scoring), the two-breathhold approach allows for short breathhold (< 5 s) and uses a normal clinical scan protocol [11, 12]. As many patients with a high coronary artery calcium score have advanced age and obstructive lung disease [17], these may not be able to hold their breath for a prolonged time, and thus the two-breathhold approach was applied in this study. Nevertheless, misregistration artifacts have been shown to be more pronounced in the two-breathhold approach due to different heart rate [18] or breathhold variability between the non-contrast and the contrast data sets obtained approximately 60 s apart [11, 12].

Improvements for the method are sought. Manual correction can be considered in case of significant lesions but is very time consuming. Most likely, a single breathhold protocol, ideally one where the contrast data set is acquired first and the non-contrast data set acquired later, during contrast wash out may improve the quality of the first non-rigid registration. In addition, use of motion compensation could improve image quality in both the non-contrast and contrast data sets. Finally, more sophisticated similarity metrics are being implemented in the rigid refinement stage, to limit the number of total failures.

Exclusion of segments due to reduced image quality is also seen within other new CT technological advancements, such as FFR-CT [19].

In highly selected patients who are challenging for CCTA_{conv} because of a high calcium load, with successful registration, CCTA_{sub} reduces the rate of false-positive coronary segments. However, misregistration artifacts occur frequently and are an important limitation of the current technique.

Acknowledgements

The authors thank project nurses Christina Møller and Bente Andersen for excellent assistance.

Funding The authors state that this work has not received any funding.

Abbreviations

AIDR3D	Adaptive iterative dose reduction 3D
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography

CI	Confidence interval
CTDSA	Computed tomography digital subtraction angiography
ICA	Invasive coronary angiography

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Key Points

- A high calcium-score reduces the diagnostic accuracy in patients scanned with cardiac CT.
- These patients would normally need an invasive angiogram for diagnosis.
- In this prospective, multicenter study, subtraction CT, when evaluable, reduces false-positive stenosis evaluations.
- Subtraction coronary CT angiography may, when evaluable, reduce excessive downstream testing.

Fig. 1.

Subtraction in target segment. Panel **a** shows a severely calcified right coronary artery. After performing subtraction (using the contrast and non-contrast data sets in panel **a** and **b**), a diagnostic image is obtained (panel **c**), which closely resembles the invasive coronary angiogram (panel **d**). Panels **e-h** illustrate the corresponding subtraction process for a stented left anterior descending coronary artery. Similar to panel **a-d**, the non-diagnostic stent became interpretable after subtraction

Fig. 2. Misregistration. Shows example of misregistration artifact. Calcium in contrast (**a**) and non-contrast (**b**) images is not identical. Therefore, misregistration artifacts occur in the resulting subtraction image (**c**)

Fig. 3.

Flowchart of inclusion, exclusion and image analysis; 180 stable CAD patients met the inclusion criteria (referral for ICA, age > 55 years, eGFR > 60, absence of implanted cardiac device). Seven patients were excluded because of CTscan and reconstruction related issues (scan field, contrast time, failure during reconstruction), and 3 patients were excluded because of heart rate > 75 bpm. Image analysis was made in three steps: (1) Initial clinical evaluation: Coronary segments in $CCTA_{conv}$ images were evaluated according SCCT guidelines in 170 patients. Motion-free segments that were non-diagnostic because of calcium or stents were deemed target segments. Sixty-four patients did not have target segments, and two patients had insufficient image quality in the form of severe motion artifacts preventing further analysis. (2) Evaluation of co-registration: Misregistration segments in $CCTA_{sub}$ were detected in all target segments in 41 patients (group B). (3) C-Sub320 evaluation: Coronary segments in $CCTA_{sub}$ images were evaluated in 63 patients with at least one target segment without misregistration (group A). Group A had 121 target segments without and 58 with misregistration, whereas group B had 78 target segments with misregistration. Abbreviations: CAD: coronary artery disease, CCTA: cardiac computed tomography angiography. $CCTA_{conv}$: conventional cardiac computed tomography angiography. $CCTA_{sub}$: subtraction cardiac computed tomography angiography. ICA: invasive coronary angiography

Diagnostic accuracy in all target segments by CCTA_{conv} and CCTA_{sub}

Fig. 4.

Diagnostic accuracy (with 95% confidence intervals) in all target segments by CCTA_{conv} and CCTA_{sub} in high calcification patients. Median Agatston score = 836 (25–75%: 380–2277). $N = 121$ calcified and stented target segments. The false-positive rate of 72% by CCTA_{conv} is reduced to 33%, and a corresponding true negative rate of 39% by the use of CCTA_{sub}, at the expense of a reduction in true positives from 28% to 21% and a corresponding false-negative rate of 7%. Abbreviations: CCTA_{conv}: conventional cardiac computed tomography angiography. CCTA_{sub}: subtraction cardiac computed tomography angiography. FN: false negative. FP: false positive. TN: true negative. TP: true positive

Diagnostic accuracy in calcified and stent segments by CCTA_{conv} and CCTA_{sub}

Fig. 5.

Diagnostic accuracy (with 95% confidence intervals) in calcified and stent target segments by CCTA_{conv} and CCTA_{sub}. Calcified segments, $n = 79$. Stent segments, $n = 42$. In stent segments by CCTA_{sub}, the true-negative rate is higher and false-positive rate lower compared with calcified segments. The true-positive rate is lower in stent segments, which may be due to a lower frequency of significant disease in stents (5%) compared with calcified segments (23%). Abbreviations: CCTA_{sub}: subtraction cardiac computed tomography angiography. FN: false negative. FP: false positive. TN: true negative. TP: true positive

Table 1

Study group characteristics. Group A consists of patients with at least one target segment without misregistration. Group B consists of patients with misregistration in all target segments

Characteristics	Study group	Group A	Group B	p value
<i>n</i>	104	63	41	-
Female, <i>n</i> (%)	15 (14)	4 (6)	11 (27)	0.007
Age, years, mean (5–95%)	67 (54–77)	67 (54–78)	67 (55–77)	0.85
BMI, mean (5–95%)	27 (22–34)	27 (22–32)	28 (25–31)	0.15
Active smoker, <i>n</i> (%)	18 (17)	10 (16)	8 (19)	0.26
Former smoker, <i>n</i> (%)	52 (50)	29 (46)	23 (58)	
Never smoker, <i>n</i> (%)	33 (32)	24 (38)	9 (23)	
Diabetes, <i>n</i> (%)	24 (23)	14 (22)	10 (25)	0.75
Hypertension, <i>n</i> (%)	66 (63)	40 (63)	26 (67)	0.74
Family history of CAD, <i>n</i> (%)	46 (44)	31 (49)	15 (38)	0.24
Hypercholesterolemia, <i>n</i> (%)	73 (70)	47 (76)	26 (65)	0.24
History of myocardial infarction, <i>n</i> (%)	40 (38)	26 (41)	14 (36)	0.59
Previous stent, <i>n</i> (%)	46 (45)	33 (53)	13 (33)	0.04
History of heart failure, <i>n</i> (%)	25 (24)	13 (21)	12 (30)	0.28
Heart rate, mean (5–95%)	56 (44–68)	55 (44–67)	58 (47–69)	0.02
Radiation dose, mSv, mean (5–95%)	5.8 (2.0–9.3)	5.4 (2.6–9.0)	6.5 (1.8–9.8)	0.06
Image noise (CCTA _{conv}), HU, mean ± SD	26 ± 4	26 ± 5	26 ± 4	0.47
Image noise (CCTA _{sub}), HU, mean ± SD	31 ± 5	31 ± 5	30 ± 4	0.68
Agatston score, median (25–75%)	852 (424–1768)	836 (380–2277)	867 (505–1456)	-

Abbreviations: BMI: body mass index. CAD: coronary artery disease. CCTA_{conv}: conventional cardiac computed tomography angiography. CCTA_{sub}: subtraction computed tomography angiography. HU: Hounsfield units. mSv: milli-Sievert. N: number. SD: standard deviation

Table 2

Distribution of misregistration in subgroup analyses. There was no difference in the distribution of target segments with misregistration among coronary arteries, with respect to heart rate or with respect to Agatston score. Misregistration was less common in the proximal and stent segments

	<i>n</i> (%)	<i>p</i> value
RCA	33 (52%)	0.13
LAD	85 (57%)	
LCx	18 (40%)	
Heart rate ≤ 55	52 (49%)	0.30
Heart rate > 55	84 (56%)	
Agatston score < 600	38 (51%)	0.64
Agatston score ≥ 600	98 (54%)	
Proximal segments	76 (48%)	0.03
Distal segments	60 (62%)	
Stent segments	14 (25%)	< 0.0001
Calcified segments	122 (61%)	

Abbreviations: LAD: left anterior descending artery, LCx: left circumflex artery, RCA: right coronary artery

Table 3

Diagnostic accuracy (with 95% confidence intervals) in subgroups by CCTA_{sub}

CCTA _{sub}	<i>n</i>	False negative	True positive	True negative	False positive
Heart rate	55	54	15% (5–24%)	43% (29–56%)	35% (22–48%)
Agatston score	600	83	23% (14–32%)	30% (20–40%)	40% (29–50%)
Proximal segments	84	6%	20% (12–30%)	42% (31–53%)	32% (22–43%)

Abbreviations: CCTA_{sub}: subtraction cardiac computed tomography angiography, *n*: number of segments