

False-Negative Low Tube Voltage Coronary CT Angiography: High Intravascular Attenuation at Coronary CT Angiography Can Mask Calcified Plaques

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Conflicts of interest are listed at the end of this article.

See also the commentary by Truong in this issue.

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Purpose: To determine the impact of low tube voltage coronary CT angiography on detection of subclinical atherosclerosis.

Materials and Methods: Retrospective sampling of an emergency department coronary CT angiography registry was performed. All patients in the registry underwent a noncontrast coronary artery calcium (CAC) scoring scan at 120 kV before coronary CT angiography. The study sample ($n = 264$) constituted patients with subclinical atherosclerosis (Coronary Artery Disease Reporting and Data System™ [CAD-RADS] 1 or 2) randomly mixed one-to-one with patients without atherosclerosis (CAD-RADS 0). The patients with coronary CT angiography performed at 70–90 kV were considered the low tube voltage group ($n = 159$) and patients with coronary CT angiography performed at 100–120 kV were considered the standard tube voltage group ($n = 105$). The number of coronary plaques and overall CAD-RADS classification (per patient) were evaluated twice: initially, by reading coronary CT angiography alone, and then, by coronary CT angiography in combination with a CAC scan. Considering the combined reading (CT angiography plus CAC scan) as the reference standard, the performance of coronary CT angiography alone was assessed for plaque detection and appropriate CAD-RADS (per patient) classification. The comparisons were made between the low tube voltage and standard tube voltage groups by using a Fisher exact test and χ^2 test for proportions and a Mann-Whitney test and Kruskal-Wallis test for means.

Results: In total, 455 plaques were identified in 118 patients (70 of 159 patients in the low tube voltage group; 48 of 105 in the standard tube voltage group). When reading coronary CT angiographic images alone, 97 of 455 (21%) plaques were missed that led to an incorrect CAD-RADS classification in 16 of 264 (6%) studies (interpreted as CAD-RADS 0 instead of CAD-RADS 1 or 2). Missed plaques were significantly more frequent in the low tube voltage group versus the standard tube voltage group (41% [85 of 206] vs 5% [12 of 249], respectively; $P < .001$). Incorrect CAD-RADS classification was also seen more commonly in the low tube voltage group (8.8% [14 of 159] vs 2% [two of 105]; $P = .01$), typically at low plaque burden (median CAC score, 1; range, 1–4). Calcified plaques that appeared isodense to luminal contrast material attenuation were seen more frequently in the low tube voltage group compared with the standard tube voltage group (20% [32 of 159] vs 7.6% [eight of 105], respectively; $P = .005$).

Conclusion: Coronary artery plaques may be missed at low tube voltage coronary CT angiographic examination performed without a concomitant CAC scan.

Supplemental material is available for this article.

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The low tube potential (kilovoltage) technique effectively reduces radiation exposure at coronary CT angiography (1). Depending on patient body habitus and the necessary tube current (milliamperere), most modern scanners allow the use of 80 kV, and some CT systems can perform diagnostic coronary CT angiography at as low as 70 kV (2). In addition to reducing the radiation exposure, the low tube voltage technique also results in increased vascular attenuation at coronary CT angiography as the effective energy of the x-ray beam moves closer to the k-edge of iodine at 33 keV. Increased attenuation has beneficial effects on image quality as it compensates for increased image noise at low tube voltage. Coronary atherosclerotic plaques have a wide attenuation range depending on their structure, degree of calcification, and lipid content (3). At standard 100–120 kV coronary CT angiography, calcified

plaques usually have higher attenuation than the contrast material-opacified coronary artery lumen. However, lower tube voltage increases iodine attenuation in the coronary lumen, which results in a decreased attenuation difference between plaques and lumen attenuation, referred to as isodense plaques in this article. This phenomenon may result in obscuration of small calcified plaques in subclinical atherosclerosis, which constitutes most of the coronary CT angiographic results, as coronary CT angiography is performed in low-to-intermediate-risk patients (4,5). It could also potentially lead to technical challenges in determining the degree of luminal stenosis in clinically significant lesions. The Society of Cardiovascular Computed Tomography guidelines recommend an unenhanced low-dose coronary artery calcium (CAC) scoring scan after scout views are obtained during coronary CT angiography

Abbreviations

CAC = coronary artery calcium, CAD-RADS = Coronary Artery Disease Reporting and Data System™, CI = confidence interval, CNR = contrast-to-noise ratio, SD = standard deviation

Summary

Low tube voltage coronary CT angiography acquired without a concomitant coronary calcium scoring scan may give false-negative results in patients with low plaque burden.

Key Points

- Calcified plaques may appear isodense to intraluminal contrast attenuation more frequently at low tube voltage coronary CT angiography.
- High-lumen attenuation at low tube voltage coronary CT angiography may obscure subclinical atherosclerosis.
- A noncontrast coronary calcium scoring scan is an important adjunct to contrast-enhanced CT angiography in these patients and can help avoid underdiagnoses and undertreatment in a significant minority of these patients.

protocol (6). Calcium scoring allows for the quantification of the calcium burden of coronary arteries, which can be used to improve cardiovascular risk stratification. However, the acquisition of a concomitant CAC scan is not a universal practice, and it is omitted by some of the sites from their coronary CT angiography protocols in the interest of limiting radiation exposure (7). The potential effect of this omission on low tube voltage coronary CT angiography results is not known.

This study was conducted to detect the impact of low tube voltage technique and the resultant high coronary lumen attenuation on detection of subclinical atherosclerosis and to determine the incremental value of a concomitant CAC scan in plaque detection at low tube voltage imaging.

Materials and Methods

Our local ethics committee approved the retrospective single-center study (Fig 1) and waived the need for consent.

Patient Selection

This study included patients from an emergency department coronary CT angiography registry for acute chest pain between January 2015 and June 2016, which had a fixed protocol in all patients. A random one-to-one mix of all studies read clinically as Coronary Artery Disease Reporting and Data System™ (CAD-RADS) 1 or 2 and those read as CAD-RADS 0 acquired at 70–90 kV (low tube voltage) were considered as the low tube voltage group. CAD-RADS 1 or 2 patients who were scanned with 100, 110, or 120 kV were also identified and randomly mixed one-to-one with CAD-RADS 0 patients at the same tube voltage. As there were many patients who were scanned with 100 and 120 kV, using this entire cohort as the standard tube voltage group was impractical. Hence, out of this pool of patients, we randomly sampled 50 patients scanned at 100 kV and 120 kV, and all patients scanned with 110 kV were selected as part of the standard tube voltage group. Studies with disease processes other than atherosclerosis, such as spontaneous coronary artery dissection, anomalous aortic origin of the coronary

artery, or patients scanned using nonstandard protocols (ie, high pitch helical prospective triggering), were excluded.

Image Acquisition

All patients were scanned with 128-section or 192-section dual-source CT scanners (SOMATOM Definition Flash or SOMATOM Definition Force; Siemens Healthineers, Forchheim, Germany), as published previously (8). Noncontrast CT (prospective electrocardiographically triggered at 350-msec absolute delay after the R wave of the cardiac cycle, 120 kV, reference 80 mAs [CareDose4D; Siemens Healthineers], 192×0.6 [Force]/ 32×1.2 [Flash] collimation) was performed in all patients. Coronary CT angiography was performed with prospective electrocardiographic triggering or retrospective electrocardiographic gating depending on patient factors as determined by the protocol and judgment of the supervising physician (8). Coronary CT angiography phase tube current and tube potential were selected via an automatic algorithm (CARE kV; Siemens Healthineers) (9), reference 280 mAs, 128 (Flash)/192 (Force) $\times 0.6$ mm collimation. Images were reconstructed using an iterative reconstruction algorithm (strength level 3 out of 5, I31F SAFIRE/Bv40 ADMIRE; Siemens Healthineers), with 3-mm section thickness and 1.5-mm increment at 350 msec for non-contrast images and 0.6-mm thickness and 0.4-mm increment at 220–440 msec (20-msec interval) for coronary CT angiographic images. Images were saved to the hospital's picture archiving and communication system.

Intravenous Contrast Material

Intravenous contrast material (iopamidol, Isovue 370; Bracco Diagnostics, Monroe Township, NJ) volume and rate were determined by using the patient's weight, and scan time was determined by using the Certegra P3T algorithm (Bayer; Warrendale, Pa) (8,10,11). A timing bolus with 20 mL of contrast material was performed in all patients to ascertain the appropriate scan delay and duration using the P3T algorithm.

Image Analysis

Coronary CT angiographic images were reviewed by a cardiovascular imaging fellow (V.B., with 5 years of experience in imaging) on a diagnostic picture archiving and communication system workstation (AGFA Impax; AGFA Technical Imaging Systems, Ridgefield Park, NJ), with the reviewer blinded to the clinical interpretation. First, coronary CT angiographic images alone were reviewed. A circular region of interest was drawn at the aortic root to measure attenuation (mean attenuation in Hounsfield units) and noise (standard deviation [SD]). Another region of interest was drawn in the epicardial fat, and mean attenuation and SD were recorded. These values were used to calculate the contrast-to-noise ratio (CNR, calculated as mean attenuation in aorta – mean attenuation in fat)/SD in aorta). Dose-length products of the CAC scan and coronary CT angiography were recorded for radiation dose. A conversion factor of 0.014 was used for calculation of the effective dose in millisieverts. In the first image reading session, coronary plaques were counted and the overall CAD-RADS score (per patient)

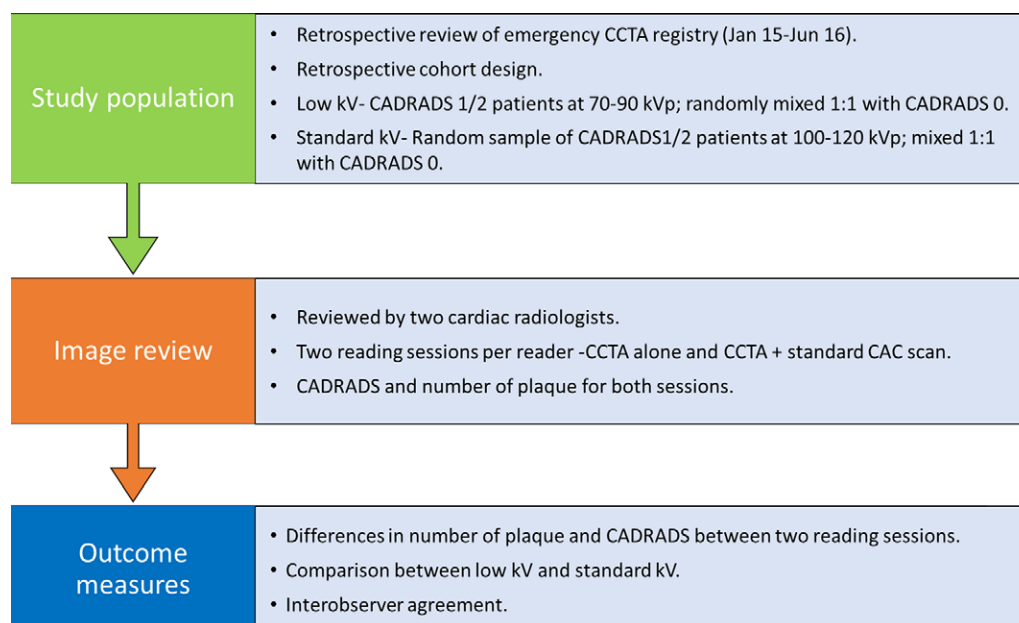


Figure 1: Pictorial representation of the study design. CAC = coronary calcium scoring, CAD-RADS = Coronary Artery Disease Reporting and Data System™, CCTA = coronary CT angiography.

Table 1: Demographic and Background Risk Characteristics of Low and Standard Tube Voltage Groups

Demographic Parameter	Low Tube Voltage	Standard Tube Voltage	P Value
Median age (y)*	52.0 (50.7, 54.3)	51.0 (50.0, 54.0)	.57
Male-to-female ratio	76:83	58:47	.25
Median BMI (kg/m ²)*	25.5 (24.9, 26.0)	31.0 (29.9, 33.2)	<.001
CAD risk	TIMI score < 4 in all patients	TIMI score < 4 in all patients	NA
Prior history of CAD	No known CAD in any patient	No known CAD in any patient	NA

Note.—BMI = body mass index, CAD = coronary artery disease, NA = not applicable, TIMI = Thrombolysis in Myocardial Infarction.

* Data in parentheses are 95% confidence intervals.

was assigned based only on the coronary CT angiographic images. Plaques were classified as calcified, partially calcified, and noncalcified. The readers were free to change window settings during review and frequently did so as this is a standard way of reading coronary CT angiography (6). In the second reading session, CAC scan images were reviewed to analyze the number of calcified plaques. Finally, CAC scan images combined with coronary CT angiographic images were used to designate a separate overall CAD-RADS score (per patient). A threshold of 130 HU was used for the definition of a calcified plaque on a CAC scan (7). If there were any additional plaques identified in a combined read (missed at coronary CT angiography alone), a note was made of those plaques being isodense in nature in comparison with the iodine-enhanced intraluminal attenuation on a per-patient basis. The results were compared to detect the number of missed plaques and change in CAD-RADS between the two reading sessions. To assess the reproducibility of these results, 20 randomly selected patients (from either the low tube voltage or standard tube voltage group) were reviewed by another cardiac radiologist (S.H.) with 5 years of experience in cardiac imaging, and interindividual comparisons were performed.

Statistical Analysis

Software (Excel 2007; Microsoft, Redmond, Wash) (Med-Calc, version 18.2.1; Ostend, Belgium) was used for statistical analysis. The results of quantitative parameters were described as mean $\pm$ SD, and categorical data were presented as proportions. A Fisher test and χ^2 test were used for the comparison of proportions. A Kruskal-Wallis test and Mann-Whitney test were used for comparison of means. A *P* value less than .05 was considered significant. κ statistics were used for interobserver agreement. Results of κ statistics were represented in the form of κ values (κ < 0.20 = poor; 0.21–0.40 = fair; 0.41–0.60 = moderate; 0.61–0.80 = good; and 0.81–1.00 = excellent) with 95% confidence intervals (CIs).

Results

The study included 264 patients with an average age of 52.4 years $\pm$ 10.4 (SD) and 130 women (49%) (Table 1). A total of 159 patients were considered the low tube voltage group (70–90 kV) and 105 were considered the standard tube voltage group (100–120 kV) based on the tube voltage parameters of

Table 2: Coronary Attenuation, Image Quality, Radiation Dose of Coronary Calcium Scoring Scan, and Total Radiation Dose for Respective Tube Voltage

Parameter	Tube Voltage						Tube Voltage Group	
	70 kV (n = 44)	80 kV (n = 87)	90 kV (n = 28)	100 kV (n = 49)	110 kV (n = 9)	120 kV (n = 47)	Low Tube Voltage (n = 159)	Standard Tube Voltage (n = 105)
Mean attenuation (HU)	820 ± 157	632 ± 128	534 ± 101	456 ± 82	439 ± 56	377 ± 83	667.2 ± 166.2	419.4 ± 88.7
Image noise (HU)	57 ± 12	45 ± 10	49 ± 11	33 ± 8	38 ± 7	28 ± 9	49.2 ± 12.0	31.1 ± 8.8
Mean CNR	16.8 ± 4.7	16.6 ± 4.1	13.4 ± 3.6	18.3 ± 7.8	14.3 ± 3.5	17.6 ± 4.3	16.1 ± 4.4	17.7 ± 6.1
DLP total (CT angiography+CAC; mGy · cm)	135 ± 42	183 ± 64	292 ± 145	312 ± 96	501 ± 192	655 ± 210	188.9 ± 95.2	478.6 ± 231.4
Effective dose total (CT angiography+CAC; mSv)	1.9 ± 0.6	2.6 ± 0.9	4.1 ± 2.0	4.4 ± 1.3	7.0 ± 2.9	9.2 ± 2.9	2.6 ± 1.3	6.7 ± 3.2
DLP CAC scan (mGy · cm)	26 ± 8	29 ± 8	35 ± 9	37 ± 10	44 ± 10	56 ± 20	30.9 ± 9.7	45.6 ± 17.5
CAC scan effective dose (mSv)	0.36 ± 0.11	0.40 ± 0.11	0.49 ± 0.12	0.51 ± 0.14	0.61 ± 0.14	0.78 ± 0.28	0.43 ± 0.13	0.63 ± 0.24

Note.—Values are mean ± standard deviation. CAC = coronary artery calcium, CNR = contrast-to-noise ratio, DLP = dose-length product.

Table 3: Body Size and Coronary CT Angiography Injection Parameters at Different Tube Voltages

Parameter	70 kV (n = 44)	80 kV (n = 87)	90 kV (n = 28)	100 kV (n = 49)	110 kV (n = 9)	120 kV (n = 47)
Weight (kg)	70.6 ± 11.9	72.1 ± 12.6	89.9 ± 15.8	83.8 ± 14.8	103.4 ± 22	104.8 ± 24.7
BMI (kg/m ²)	24.6 ± 3.3	26.2 ± 6.8	30.4 ± 4.6	28.9 ± 4.1	34.5 ± 7.3	35.7 ± 6.4
Total contrast material (mL)	95.2 ± 10.4	97.1 ± 10.3	100.9 ± 12.8	101 ± 9.9	112.3 ± 8.2	109.1 ± 10.9
Injection rate (mL/sec)	5.3 ± 0.5	5.0 ± 0.6	5.7 ± 0.5	5.4 ± 0.5	5.9 ± 0.5	6.0 ± 0.7
Contrast material for coronary CT angiography (mL)	75.2 ± 10.4	77.1 ± 10.3	80.9 ± 12.8	81.5 ± 10.0	92.3 ± 8.2	89.1 ± 10.9

Note.—Values are mean ± standard deviation. BMI = body mass index.

their coronary CT angiography. The average body mass index was 28.8 kg/m² ± 6.8. The average calcium score for the entire cohort was 28 ± 83 (range, 0–605).

Coronary Attenuation, Injection Parameters, Image Quality, and Radiation Dose

The mean attenuation at the aortic root for the entire cohort (n = 264) was 568.7 HU ± 185.6. The mean attenuation for the low tube voltage group was 667.2 HU ± 166.2 (median, 654.0 HU; 95% CI: 634.7, 689.0) and was 419.4 HU ± 88.7 (median, 417.0 HU; 95% CI: 394.9, 442.0; *P* < .001) for the standard tube voltage group. The mean attenuation values for 70, 80, 90, 100, 110, and 120 kV were 820 HU ± 157 (median, 818.5 HU; 95% CI: 738.5, 872.0), 632 HU ± 128 (median, 646.0 HU; 95% CI: 607.7, 684.4), 534 HU ± 101 (median, 560.5 HU; 95% CI: 484.8, 602.5), 456 HU ± 82 (median, 453.0 HU; 95% CI: 434.0, 486.1), 439 HU ± 56 (median, 442.0 HU; 95% CI: 374.9, 493.9), and 377 HU ± 83 (median, 359.0 HU; 95% CI: 326.9, 396.1), respectively (*P* < .001) (Table 2). The mean of the total (including the test bolus) intravenous contrast material volume used was 100.6

mL ± 11.7 per patient including 20 mL for the test bolus and 80.6 mL ± 11.7 per patient for coronary CT angiography at a mean injection rate of 5.4 mL/sec ± 0.7 (Table 3). All studies were of diagnostic quality with the mean CNR ranging from 13.4 ± 4.6 to 18.3 ± 7.8 for different tube voltages (Table 2). The total dose-length product (coronary CT angiography plus CAC) and dose-length product of the CAC score alone were 302.8 mGy · cm ± 215.7 and 35.6 mGy · cm ± 15.2, respectively (mean effective dose 4.2 mSv ± 3.0 and 0.49 mSv ± 0.21, respectively; Table 2). The mean radiation dose at coronary CT angiography plus CAC scan and that of the CAC scan were 2.6 mSv ± 1.3 and 0.43 mSv ± 0.13 in the low tube voltage group, respectively, and 6.7 mSv ± 3.2 and 0.63 mSv ± 0.24 in the standard tube voltage group, respectively (Table 2).

Plaque Detection and Grading of Luminal Narrowing (CAD-RADS Classification)

At coronary CT angiography alone, 358 plaques were identified, and on a per-patient basis, 161, 42, 60, and one patient(s) were classified as CAD-RADS 0, 1, 2, and N (nondiagnostic), respectively. However, based on a combined CAC plus

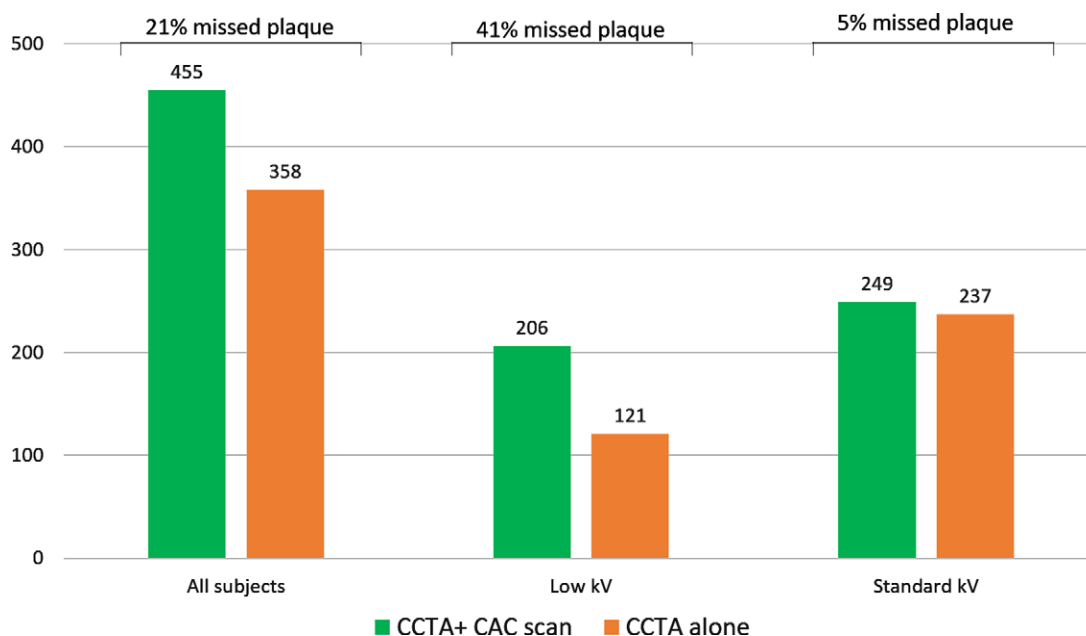


Figure 2: Graphs show plaque detected at combined read (coronary CT angiography [CCTA] plus coronary calcium scoring [CAC] scan; green) and at coronary CT angiography alone (orange) in all patients, low tube voltage and standard tube voltage groups. Percent-age values show the proportion of plaque missed at coronary CT angiography alone in a given category.

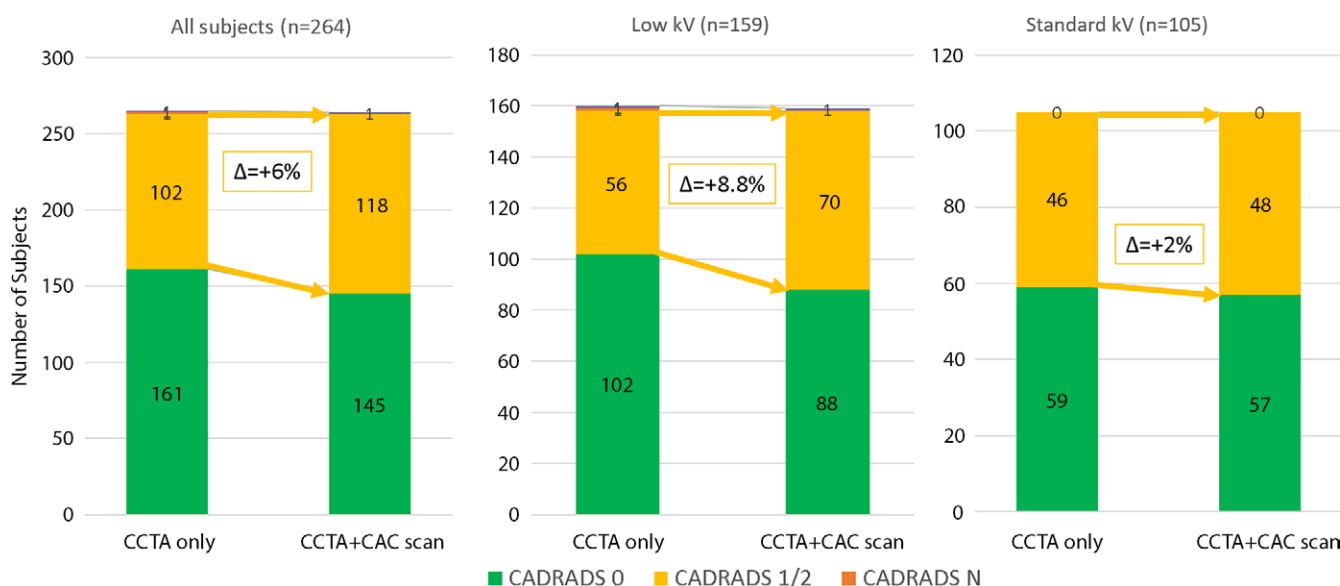


Figure 3: Graphs show change in Coronary Artery Disease Reporting and Data System™ (CAD-RADS) classification between coronary CT angiography (CCTA) alone and combined read (coronary CT angiography plus coronary calcium scoring [CAC] scan) in all patients, low tube voltage and standard tube voltage groups. The delta (Δ) represents the reclassification of patients with CAD-RADS 0 at coronary CT angiography alone to CAD-RADS 1 or 2 on combined reading (CAC plus coronary CT angiography).

coronary CT angiography reading, a total of 455 plaques were identified in 118 patients (70 in the low tube voltage and 48 in the standard tube voltage groups; 3.85 plaques per patient $\pm$ 4.0; 95% CI: 3.1, 4.6) and on a per-patient basis, 145, 54, 64, and one patient(s) were classified as CAD-RADS 0, 1, 2, and N, respectively. Thus, 97 of 455 (21%) plaques were missed at coronary CT angiography alone, which resulted in an incorrect CAD-RADS classification for 16 of 264 (6%) patients (Figs 2, 3; Figs E1, E2; Table E1 [supplement]). All of these patients were reclassified from CAD-RADS 0 to CAD-RADS 1 or 2 at

a combined reading (Fig 3). The average age of patients with an incorrect CAD-RADS category (at coronary CT angiography alone) was 54.8 years $\pm$ 9 (age range, 39–72 years; 11 of these were $\leq$ 60 years of age). The body mass index of patients with an incorrect CAD-RADS classification ($24.9 \text{ kg/m}^2 \pm 3.3$; median, 24.8 kg/m^2 ; 95% CI: 22.6, 26.0) was lower than that of patients with a correct CAD-RADS classification ($29.02 \text{ kg/m}^2 \pm 6.8$; median, 27.6 kg/m^2 ; 95% CI: 26.6, 29.2; $P = .008$). Among the patients who had atherosclerosis (CAC > 0), the mean CAC score of the incorrectly classified patients was 1.5

Table 4: CAD-RADS Reclassification and Missed Plaque at CT Angiography Alone: Low versus Standard Tube Voltage Groups

Group	Missed Calcified Lesions at Coronary CT Angiography Alone	Patients Incorrectly Classified at Coronary CT Angiography Alone	Patients With Isodense Plaques
Low tube voltage (<i>n</i> = 159)	41 (85/206)	8.8 (14/159)	20 (32/159)
Standard tube voltage (<i>n</i> = 105)	5 (12/249)	2 (2/105)	7.6 (8/105)
<i>P</i> value	<.0001*	.01*	.005*

Note.—Unless otherwise indicated, data are percentages, with raw data in parentheses.

* Fisher test.

± 0.23 (median CAC score, 1; 95% CI: 1, 1.7; range, 1–4), which was lower than the CAC score of patients with a correct CAD-RADS classification at coronary CT angiography alone (79.7 ± 123.8 ; median CAC score, 26; 95% CI: 15, 45; range, 1–605; $P < .0001$). The number of plaques per patient was also significantly lower in patients with an incorrect CAD-RADS classification (median, 1; 95% CI: 1, 2 vs median, 2; 95% CI: 2, 4; $P = .008$).

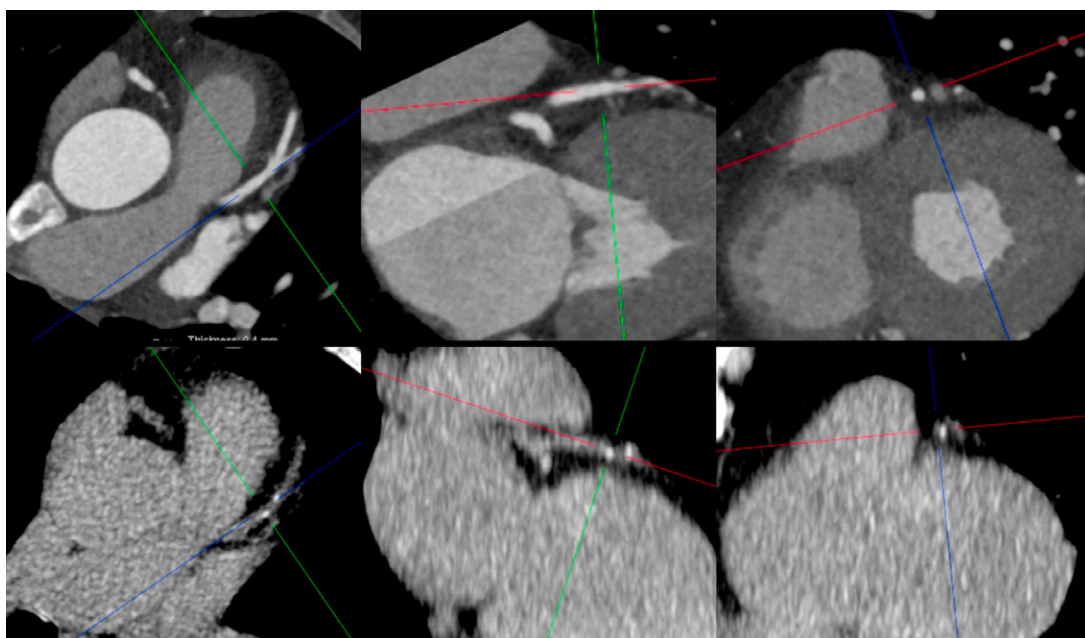


Figure 4: A 54-year-old woman underwent 70-kV coronary CT angiography to rule out significant coronary stenosis. Top row: On the CT angiographic images, no calcified plaques were identified by the observer. As no stenosis was detected, the coronary CT angiography study was read as CAD-RADS 0. Bottom row: On coronary calcium scoring scans, calcified plaques in the proximal left anterior descending coronary artery were detected, which only minimally narrowed the coronary artery at coronary CT angiography. Thus, final diagnosis was changed to CAD-RADS 1. The attenuation in the coronary lumen was $1134 \text{ HU} \pm 52$, and plaques were isodense to the lumen.

Low Versus Standard Tube Voltage Groups

The mean CAC score of the standard tube voltage versus low tube voltage groups (46.9 ± 119.2 [range, 0–605; median, 0; 95% CI: 0, 0] vs 16.8 ± 42.7 [range, 0–233; median, 0; 95% CI: 0, 0.1]) was not statistically different ($P = .59$). Missed plaques were significantly more frequent in the low tube voltage group compared with the standard tube voltage group (number of total missed plaques, 41% [85 of 206] vs 5% [12 of 249]; $P < .001$). In addition, within the low tube voltage group, studies were more often incorrectly classified as CAD-RADS 0 compared with studies in the control cohort (8.8% [14 of 159] vs 2% [two of 105]; $P = .01$; Table 4). Two clinical examples are depicted in Figures 4 and 5. There was a significant increasing trend toward missed plaques when interpreting coronary CT angiographic images alone with decreasing tube voltage values (70 kV [45%; 31 of 69 plaques], 80 kV [48%; 43 of 89], 90 kV [23%; 11 of 48],

100 kV [11%; eight of 69], 110 kV [5%; one of 21], 120 kV [2%; three of 158]; $P < .001$). Calcified plaques that were isodense to lumen attenuation at coronary CT angiography were observed more frequently in the low tube voltage group compared with the standard tube voltage group (20% [32 of 159] vs 7.6% [eight of 105]; $P = .005$).

Interobserver Agreement

Among the 20 patients who were co-reviewed, both reviewers had excellent agreement on the incorrect CAD-RADS category at coronary CT angiography alone (four patients for both; $\kappa = 1$; 95% CI: 1, 1) and missed plaques at coronary CT angiography alone (15 patients for both; $\kappa = 0.8$; 95% CI: 0.58, 1; Table 5). There was also good agreement on the incidence of isodense plaques on a per-patient basis, reported as seven of 20 by observer 1 versus nine of 20 by observer 2 ($\kappa = 0.8$; 95% CI: 0.52, 0.9). The total number of plaques was slightly differ-

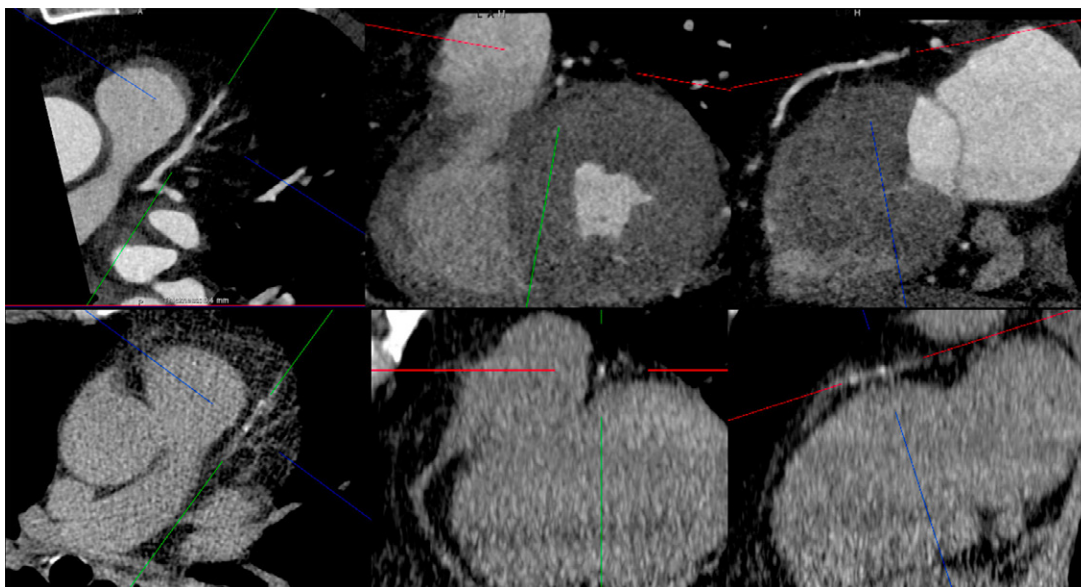


Figure 5: A 58-year-old man underwent 120-kV coronary CT angiography to rule out significant coronary stenosis. Top row: On the coronary CT angiographic images, calcified plaques were identified in the proximal left anterior descending coronary artery by the observer with mild coronary stenosis. The coronary CT angiographic study was read as CAD-RADS 2. All calcified plaques were confirmed by a noncontrast coronary calcium scoring (CAC) scan. Thus, the plaques were accurately identified on coronary CT angiographic images, and the final diagnosis did not change after a review of the CAC scan (bottom row). The attenuation in the coronary lumen was $434 \text{ HU} \pm 312$.

Table 5: CAD-RADS Reclassification and Missed Plaques at Different Tube Voltages

Parameter	70 kV (n = 44)	80 kV (n = 87)	90 kV (n = 28)	100 kV (n = 49)	110 kV (n = 9)	120 kV (n = 47)	P Value
Missed lesions at coronary CT angiography alone out of total plaques on combined reading	45 (31/69)	48 (43/89)	23 (11/48)	11 (8/69)	5 (1/21)	2 (3/158)	<.0001*
Incorrect CAD-RADS classification at coronary CT angiography alone	11 (5/44)	11 (9/44)	0 (0/28)	4 (2/44)	0 (0/9)	0 (0/47)	.06*
Incidence of patients with isodense plaques	30 (13/44)	18 (16/87)	11 (3/28)	10 (5/49)	0 (0/9)	6 (3/47)	.01*

Note.—Unless otherwise indicated, data are percentages, with raw data in parentheses.

* χ^2 test.

ent but still had a good interobserver agreement (34 plaques by observer 1 and 27 by observer 2; $\kappa = 0.8$; 95% CI: 0.65, 0.9). Discrepancies tended to be most commonly due to one observer defining several plaques as a single confluent plaque versus the second reader discretely counting plaques.

Discussion

This retrospective cohort study showed that the interpretation of coronary CT angiography in isolation without a CAC image set resulted in a lower number of detected plaques, which led to an incorrect CAD-RADS classification, as compared with a combined interpretation of a CAC scan and coronary CT angiography in patients with an overall low plaque burden. The missed plaques and CAD-RADS “underclassification” were more frequently observed in the low tube voltage group (70–90 kV) compared with the standard tube voltage group (100–120 kV). These findings paralleled increasing cor-

onary lumen attenuation and increasing incidence of isodense plaques on lower tube voltage acquisitions. Interestingly, the body mass index of patients with an incorrect CAD-RADS classification was lower, which may initially seem counterintuitive. As it is usually higher, body mass index results in increased image noise and can have a detrimental effect on plaque detection (12,13). The incidences of missing plaque in patients with relatively lower body mass index can be explained by the fact that a tube voltage selection in automatic kilovoltage selection method is based on patient size, meaning that a lower kilovoltage will be selected more frequently in relatively smaller patients, which is likely a confounding factor that is responsible for this observation (Tables 1, 3). Through the use of automatic kilovoltage selection, the increasing image noise is well compensated by an appropriate selection of tube voltage and tube current–time product (and thus good CNR in all groups), so the direct impact of increasing body mass index is not apparent

in this study.

The observation of an incorrect CAD-RADS classification was also limited to an overall low calcific burden. This is a small but significant observation considering the increased use of low tube voltage coronary CT angiography with modern scanners in an era of heightened awareness of diagnostic radiation exposure.

Small calcium burden may not have an incremental value in guiding therapy for low- or high-risk patients, but based on current guidelines, it can modify the therapy in intermediate-risk patients (atherosclerotic cardiovascular disease score, 5%–20%) (14). Within this subset of patients, statin therapy is not recommended in the absence of coronary artery disease on a CAC scan (CAC = 0). However, preventive statin therapy is recommended for a CAC score > 0 with an atherosclerotic cardiovascular disease score of 5%–20% (14). It implies that some intermediate-risk patients may be undertreated because of an erroneous diagnosis of CAD-RADS 0. In addition, the atherosclerotic cardiovascular disease risk scores may be unknown at the time of presentation to an emergency department for chest pain, and in this setting, an accurate detection of coronary artery disease at coronary CT angiography (CAD-RADS > 0; CAC > 0) may invoke further assessment and risk stratification that can potentially result in appropriate therapy. Additionally, small plaque burden and sub-clinical atherosclerosis may be hemodynamically insignificant and may not affect the short-term outcome (7) but may tend to risk-stratify patients well over longer follow-up horizons (5,15–18). In total, 69% (11 of 16) of the patients with an incorrect CAD-RADS classification at coronary CT angiography alone were ≤ 60 years of age and could potentially derive significant benefits from primary prevention. Carr et al evaluated coronary artery calcification burden in adults aged < 60 years and its impact on clinical coronary heart disease, cardiovascular disease, and all-cause mortality during 12.5 years of follow-up (17). They concluded that any coronary artery calcification in early adulthood, even at very low scores of 0–20, indicates a significant risk of having a myocardial infarction during the next decade (17). This risk was incremental to traditional coronary artery disease risk factors, and the authors suggested that the calcium score identifies individuals at a particularly elevated risk for coronary heart disease for whom aggressive prevention is likely warranted (17). In a recent randomized trial on patients with low atherosclerotic cardiovascular disease risk, Mitchell et al demonstrated that patients with a CAC score > 0 benefit from statin therapy with a lower incidence of major adverse cardiac events (19). Although the benefits were mostly observed in patients with a CAC score > 100 but in the 10-year number-needed-to-treat analysis, even patients with a CAC score of 1 to 100 demonstrated a trend toward benefit (number needed to treat = 100; $P = .095$). In addition, in the central illustration of Mitchell et al (19), the graphs between statin versus nonstatin have already been split in the CAC 1–100 group, although it is not statistically significant. It is possible that a longer time horizon will further split these curves to a level of statistical significance (the SCOT-HEART trial is a recent example) (5). This is furthered by the concept of the “Power of Zero” campaign that highlights the simplicity of a zero-calcium score to exclude most (but not all) atherosclerotic coronary disease (20,21). Owing to these considerations, it is

imperative to detect even small burdens of coronary artery disease to facilitate coronary risk assessment and appropriate interventions including risk factor modification and potential statin initiation. In contrast to the prior findings of Kwon et al (7), it makes a strong case in favor of performing a concomitant CAC score CT acquisition before a contrast-enhanced coronary CT angiography acquisition in all patients who are being imaged, especially when considering a low tube voltage CT angiography, to avoid isodense plaques and mitigate an incorrect CAD-RADS classification. This acquisition of a concomitant CAC score CT scan has been long advocated by some sites but is not a universal practice (7).

This problem can also be solved by disregarding automated selection of tube voltage based on CARE kV and scanning at a higher tube voltage. However, increasing the tube voltage from that selected for the patient by the software algorithm is an unlikely option, given the fact that radiation dose penalty with a higher kilovolt peak value (double radiation dose with 15% kilovolt peak increment) will be much higher than performing a CAC scan (22). Another potential solution to this problem could be the reduction in contrast material bolus rate and volume (2) at a low tube voltage. The strategy of lowering contrast material rate and volume can possibly address the underlying problem of isodense plaques by avoiding excessively high coronary luminal attenuation. It would also be potentially helpful in addressing difficult cases with isodense plaques in a setting of hemodynamically significant disease. But this question was not investigated by this study and would mandate further research. In a prior study by Meyer et al, the authors could successfully reduce the contrast material volume at low tube voltage coronary CT angiography (2). However, there is a potential caveat to this strategy. There is higher image noise at low tube voltage imaging which would mandate a relatively higher intravascular attenuation to maintain adequate CNR. So, the strategy of lowering the contrast rate and volume would need careful optimization to ensure adequate iodine flux. Dual-energy coronary CT angiography is also another attractive alternative to performing a CAC scan as it can generate virtual noncontrast images that are potentially analogous to a CAC scan. However, at present, the use of dual-energy coronary CT angiography has been limited to research, and clinical application of this technology has been limited (23), in part because the radiation dose benefits of low tube voltage scanning are obviated by the simultaneous low- and high-tube voltage acquisitions of dual energy. Delayed-phase acquisitions are sometimes acquired for incidentally detected filling defects at coronary CT angiography that can also be helpful in detecting the calcified plaque, which were missed owing to high attenuation of coronary artery lumen. However, the performance of delayed scan is uncommon and, at most sites, is used selectively. Owing to all these considerations, at present, performing a concomitant CAC scan appears to be the most reasonable approach to mitigate the challenge of isodense plaques at low tube voltage coronary CT angiography.

This study bears the limitations of a single-center retrospective study design and lack of clinical follow-up. Owing to these limitations, we could not address the question of clinical impact of missed plaques or an incorrect CAD-RADS classification; this

would likely require a very large sample and extremely thorough follow-up, likely requiring the setting and expense of a randomized trial. Additionally, not all patients scanned at 100–120 kV from the duration of this study were included, which has a potential to introduce a selection bias. Therefore, we performed random sampling to mitigate this limitation. In addition, the per-plaque analysis is prone to overestimation as a result of correlated observations (more than one measurement per patient). To mitigate such effects, a second-order (per-patient) CAD-RADS analysis was performed. In addition, it should be borne in mind that specific reconstruction methods were used in this study that include strength level 3 of 5 (I31F SAFIRE or Bv40 ADMIRE). Plaque imaging literature suggests that changing kernel or the strength of iteration can influence plaque detection independently (24,25), and hence, changing tube voltage with different reconstruction techniques may affect plaque detection differently.

In conclusion, calcified plaques appear isodense more frequently on low tube voltage coronary CT angiography that can lead to disease underclassification and undertreatment. A concomitant CAC score CT acquisition prevents disease underdetection and incorrect CAD-RADS classification that can be performed at under 1 mSv in nearly all patients.

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