Predictive Value of Zero Calcium Score and Low-End Percentiles for the Presence of Significant Coronary Artery Stenosis in Stable Patients with Suspected Coronary Artery Disease

Prädiktiver Wert eines negativen Kalzium-Scores und niedriger Perzentilen für die Präsenz signifikanter koronararterieller Stenosen bei stabilen Patienten mit Verdacht auf koronare Herzkrankheit

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Key words
- coronary calcium score
- coronary artery disease
- invasive coronary angiography
- coronary CT angiography

Zusammenfassung

Ziel: Prospektive Ermittlung des prädiktiven Wertes eines negativen Kalzium-Scores (CS) sowie niedriger geschlechts- und altersspezifischer Perzentilen hinsichtlich der Präsenz signifikanter koronararterieller Stenosen bei stabilen Patienten mit Verdacht auf koronare Herzkrankheit (CAD).

Material und Methoden: Insgesamt wurden 87 stabile Patienten mit Verdacht auf CAD (33 Frauen, 66 ± 10 Jahre) in diese prospektive Studie eingeschlossen. Alle Patienten erhielten eine native CT zur Messung des Kalk-Scores (CSCT), eine Koronar-CT-Angiografie (cCTA) sowie als Referenzstandard eine invasive Koronarangiografie (ICA). Die diagnostische Genauigkeit des CS hinsichtlich der Präsenz signifikanter Stenosen (≥ 50 % Durchmesser) wurde separat im Vergleich zur cCTA und ICA ermittelt.

Ergebnisse: Die ICA zeigte bei 56/87 Patienten (64 %) eine signifikante Stenose. Der mittlere CS betrug 571 ± 599. Auf Patientenbasis ergaben sich für Patienten mit einem negativen CS Sensitivität, Spezifität, positiver prädiktiver Wert (PPV) und negativer prädiktiver Wert (NPV) von 98,5 %, 18,2 %, 78,0 % und 80,0 % im Vergleich zur cCTA und 100 %, 16,1 %, 68,3 % und 100 % im Vergleich zur ICA. Niedrige, von asymptomatischen Kaukasiern abgeleitete, geschlechts- und altersspezifischen Perzentilen zeigten vergleichbare Ergebnisse.

Schlussfolgerung: Bei stabilen Patienten mit Verdacht auf CAD sind signifikante Stenosen sowohl bei einem negativen CS als auch bei einem Wert unterhalb bestimmter geschlechts- und altersspezifischer Perzentilen selten. Daher sollte der CS bei diesen Patienten als Filter vor Durchführung weiterer diagnostischer Maßnahmen dienen. Ein CS-Wert unterhalb bestimmter geschlechts- und altersspezifischer Perzentilen scheint bei stabilen Patienten eine dem negativen CS gleichwertige Aussagekraft zu besitzen.

Abstract

Purpose: To prospectively investigate the predictive value of a zero calcium score (CS) value as well as age- and sex-adjusted low-end CS percentiles for the presence of significant coronary artery stenosis in stable patients with suspected coronary artery disease (CAD).

Materials and Methods: In total, 87 consecutive stable patients with suspected CAD were prospectively enrolled in this study (33 women; 66 ± 10 years). All patients underwent non-enhanced CT for calcium scoring (CSCT) and contrast-enhanced coronary CT angiography (cCTA). Invasive coronary angiography (ICA) served as the reference standard in all patients. Diagnostic performance for the presence of significant stenosis (≥ 50 % diameter) was calculated separately for CS in comparison to cCTA and ICA.

Results: ICA identified significant stenosis in 56/87 patients (64 %). The mean CS was 571 ± 599. On a per patient based analysis, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for patients with a zero CS were 98.5 %, 18.2 %, 78.0 % and 80.0 %, respectively, compared to cCTA and 100 %, 16.1 %, 68.3 % and 100 %, respectively, compared to ICA. Low-end age- and sex-adjusted percentiles derived from asymptomatic Caucasian populations showed results comparable to a CS of zero.

Conclusion: The prevalence of significant coronary artery stenosis is low in stable patients with suspected CAD and a CS of zero but also in patients below certain low-end age- and sex-adjusted percentile ranks. Thus, CS should be used as a gatekeeper prior to further diagnostic procedures in these patients. A CS value below certain age- and sex-adjusted percentile ranks seems to be of identical diagnostic value to a CS of zero in stable patients.

eingereicht 20.1.2013
akzeptiert 29.5.2013

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DOI http://dx.doi.org/10.1055/s-0033-1335964
Published online: 2013
Fortschr Röntgenstr 2013; 185: 726–732 © Georg Thieme Verlag KG Stuttgart · New York · ISSN 1438-9029

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Introduction

Coronary artery disease (CAD) is known to be the leading cause of death in industrialized countries. In addition, it is a major expense factor in the healthcare systems of industrialized countries. Although there is a necessity to provide decisive diagnostic examinations, performing an invasive coronary angiography (ICA) to detect coronary artery stenosis in all patients with suspected CAD is not appropriate. It has been unequivocally shown that coronary CT angiography (cCTA) is a safe and cost-efficient alternative to rule out coronary artery stenosis in symptomatic patients [1, 2]. Nonetheless, two disadvantages of cCTA are its extensive radiation exposure and its susceptibility to extensive calcification. Although advancement in scanner technology made it possible to substantially reduce the impact of these drawbacks, this is still an issue because 64-row MDCT scanners are currently the most common type of scanner used in cardiac imaging [1, 3, 4]. Nowadays the radiation exposure of cCTA in general clinical practice is typically in the range of 5 – 30 mSv with a median radiation exposure of 12 mSv as reported by Hausleiter et al. [5, 6]. There are numerous approaches to reduce overall radiation exposure. For example, Zimmerman et al. suggested using CSCT instead of a conventional scanogram in order to shorten the scan range of cCTA on the z-axis [7]. Another approach would be to restrict the use of cCTA to patients who are more likely to suffer from CAD. This lead to the idea to use non-enhanced CT for calcium scoring (CSCT) as a gatekeeper prior to further diagnostic measures since CSCT in general is associated with a much lower radiation burden than cCTA [8]. Various studies reported that a calcium score (CS) of zero makes the presence of significant coronary artery stenosis very unlikely in asymptomatic stable populations and therefore might be used to rule out significant stenosis [9 – 15]. On the other hand, there are studies that report a non-extraneous prevalence of significant stenosis in symptomatic acute patients with a CS of zero, thus detaining the use of CSCT in this approach [16 – 19].

The purpose of this study was to evaluate whether a negative CS or low-end percentile ranks adjusted for age and sex lead to a definite conclusion whether CS obtained by dual-source CT is a safe means for ruling out the presence of significant coronary artery stenosis in stable non-acute patients with an intermediate risk for CAD.

Materials and Methods

Study population

Between October 2009 and August 2011, we prospectively performed CSCT, cCTA and ICA in 90 consecutive patients who presented in our institutional ambulance in stable clinical condition with symptoms suspicious for CAD. Three patients were excluded due to the presence of coronary stents that precluded the possibility to perform CSCT and because CAD was already known. Hence, the final study population comprised 87 patients. All patients were classified as being at intermediate risk for suffering from CAD according to the TIMI risk score [20]. Our institutional review board approved this study. Written informed consent was obtained for all patients and the information gathered was treated according to the Health Insurance Portability and Accountability Act (HIPAA).

CT scanning protocol

All CT examinations were performed on a 1st generation dual-source CT scanner (SOMATOM Definition, Siemens Healthcare Sector, Forchheim, Germany). Prior to contrast-enhanced cCTA, non-enhanced CSCT was performed in all patients using the following scan parameters: prospective ECG triggering, slice thickness 3 mm with 50 % overlap, detector collimation 3 × 64 × 0.6 mm, gantry rotation time 330 ms, tube current time product 320 mAs per rotation. In patients with a body mass index (BMI) ≥ 25 kg/m^2, a 120 kV tube potential was used, whereas in patients with a BMI < 25, the tube potential was reduced to 100 kV. For cCTA the scanning technique was chosen individually for each patient depending on heart rate, heart rhythm and BMI to achieve decent image quality while maintaining minimal radiation exposure. The scan techniques included retrospective ECG gating with ECG-dependent tube current modulation and prospective ECG triggering. The acquisition parameters were: 2 × 32 × 0.6 mm detector collimation, gantry rotation time 330 ms, tube current time product 320 mAs per rotation. As in the CSCT protocol, the default tube potential was 120 kV, which was reduced to 100 kV in patients with BMI < 25 kg/m^2. Contrast medium enhancement was achieved by injecting 80 ml of iodinated contrast agent (Imeron 400, Iomeprol 400 mg I/ml, Bracco Imaging S.p.A., Milano, Italy) at 5 ml/s through an 18G intravenous antecubital catheter followed by a 50 ml bolus of saline solution using a dual-syringe injector (Stellant D, Medrad, Indianola, PA). Acquisition was cranio-caudal from above the origin of the coronary arteries to below the dome of the diaphragm.

Image analysis

The CS derived from the CSCT data sets were calculated by one experienced radiologist using a dedicated software application (Syngo CaScore, Siemens Healthcare Sector, Forchheim, Germany). Besides absolute CS values, we evaluated low-end age- and sex-adjusted percentile ranks derived from asymptomatic Caucasian populations [21, 22].

All cCTA examinations were evaluated by one experienced radiologist for the presence of significant stenosis (> 50 % lumen diameter) in the coronary artery vessels using the 15-segment model proposed by the American Heart Association [23]. ICA was performed as the reference standard in all patients within an interval not exceeding four months from the CSCT and cCTA examination. ICA was performed according to the conventional Judkins technique with at least two views of the right coronary artery and four views of the left coronary artery. Evaluation for the presence of significant stenosis was accomplished by one experienced cardiologist, using the same 15-segment model.

Statistical analysis

The statistical analysis was performed using JMP9 (SAS Institute, Cary, North Carolina, USA). Continuous variables were expressed as mean ± standard deviation (SD). ICA served as the reference standard in all patients. A p-value < 0.05 was considered significant. All comparisons of mean values were two-tailed. Comparisons between groups were analyzed using the two-tailed student's t-test if data were normally distributed and using the Mann-Whitney U-test if the data were not normally distributed. Dichotomous variables were analyzed using the chi-squared test. Binary classification statistics were used to evaluate the diagnostic performance of CSCT for significant CAD on cCTA and ICA including sensitivity, specificity, positive and negative predictive values for estimated cut-off points. One-on-one comparison of

CS with significant stenosis on cCTA or ICA, age and gender was performed either with an independent t-test or with a Mann-Whitney U-test. Receiver operating characteristics (ROC) analysis was performed for CS compared to both cCTA and ICA.

Results

Study population

Patient characteristics are summarized in ▶ **Table 1**. Altogether 87 patients were included in this study. Therefore, a total of 87 patients, 348 vessels and 1305 segments were available for evaluation. All 87 CSCT and ICA examinations were successfully completed. On cCTA diagnostic image quality was found in 97.8 % of all segments. However, in 29 segments (2.2 %) the image quality was considered non-diagnostic and thus the affected segments were considered as positive for the presence of significant stenosis. The participating women were significantly older than the men (p = 0.0231). 55 patients (63 %) had a BMI ≥ 25. In 29 patients (33 %) the average heart rate was ≥ 75 beats per minute (bpm).

Prevalence of coronary artery stenosis and calcifications

ICA revealed significant stenosis in 56 patients (64.4 %), 91 vessels (26.1 %) and 129 segments (9.9 %). Analysis of the diagnostic accuracy of cCTA resulted in a sensitivity, specificity, PPV and NPV of 98.2 %, 67.7 %, 84.6 %, and 95.5 %, respectively. All diagnostic accuracy parameters are shown in ▶ **Table 2**. The mean CS was 571 ± 599 (range 0 – 3.586) for all patients. It was significantly higher in patients with significant stenosis (690 ± 621 [range 2.9 – 3.586]) than in patients without significant stenosis (358 ± 499 [range 0 – 2.146]) (p = 0.0007). ▶ **Fig. 1** exemplarily shows calcification of varying degrees in two study participants. Five patients showed no coronary artery calcification (CS = 0) at all.

Diagnostic accuracy of CS

The diagnostic accuracy of CS in defining significant coronary artery stenosis depends on the chosen CS threshold. All parameters of CS's diagnostic accuracy compared to ICA (▶ **Table 3**) and cCTA (▶ **Table 4**) are shown for all investigated absolute and percentile-based thresholds.

Compared to ICA, a CS threshold of ≥ 2.9 provided a sensitivity of 100 %, while a CS threshold of ≥ 3586 provided a specificity of

Table 1 Patient characteristics.

Tab. 1 Patientencharakteristika.

men	54 (62 %)
women	33 (38 %)
mean age	66 ± 10 (47 – 86)
BMI	28 ± 5 (15 – 41)
mean heart rate (bpm)	74 ± 17 (64 – 94)
mean CS (total collective)	571 ± 599 (0 – 3,586)
mean CS (no significant stenosis on ICA)	358 ± 499 (0 – 2,146)
mean CS (significant stenosis on ICA)	690 ± 621 (2.9 – 3,586)
significant stenosis present on ICA	64.4 %
significant stenosis present on cCTA	74.7 %
hypertension	77 %
nicotine abuse	51 %
diabetes mellitus	24 %
dyslipidemia	43 %
family history of cardiovascular disease	45 %
known cardiac arrhythmia[1]	34 %

Note: BMI = body mass index; bpm = beats per minute; CS = calcium score; ICA = invasive coronary angiography; cCTA = coronary CT angiography.
Anmerkung: BMI = Body-Mass-Index; bpm = Schläge pro Minute; CS = Calcium Score; ICA = invasive Koronarangiografie; cCTA = Koronar-CT-Angiografie.
[1] Including atrial fibrillation.
Einschließlich Vorhofflimmern.

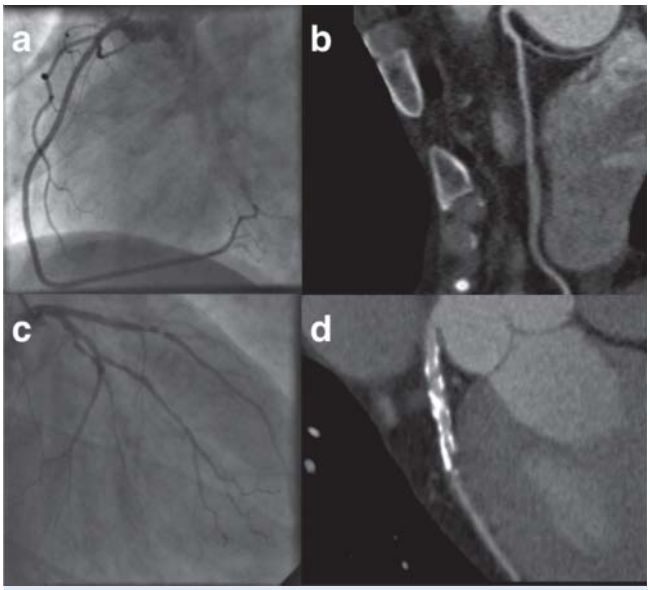

Fig. 1 Calcification to varying degrees in two study participants. Note: ICA **a** and cCTA **b** of a non-calcified RCA (CS = 0) in a 52-year-old female patient with no significant stenosis; ICA **c** and cCTA **d** of a distinctly calcified LCA (CS = 1.508) in a 71-year-old male patient with significant stenosis.

Abb. 1 Kalzifikationen unterschiedlichen Ausmaßes bei 2 Studienteilnehmern. Anmerkung: ICA **a** und cCTA **b** einer nicht kalzifizierten RCA (CS = 0) bei einer 52-jährigen weiblichen Patientin ohne signifikante Stenose; ICA **c** und cCTA **d** einer ausgeprägt kalzifizierten LCA (CS = 1,508) bei einem 71-jährigen männlichen Patienten mit signifikanter Stenose.

Table 2 Diagnostic performance of cCTA for the prediction of significant stenosis on ICA.

Tab. 2 Diagnostische Genauigkeit der cCTA für die Detektion signifikanter Stenosen in der ICA.

	n	TP	TN	FP	FN	accuracy %	sensitivity %	specificity %	PPV %	NPV %
patient	87	55	21	10	1	87.4 % (78.7 – 89.5)	98.2 % (91.5 – 99.9)	67.7 % (55.6 – 70.8)	84.6 % (78.8 – 86.1)	95.5 % (78.3 – 99.8)
vessel	348	80	227	36	5	88.2 % (84.9 – 90.0)	94.1 % (87.2 – 97.8)	86.3 % (84.1 – 97.8)	69.0 % (63.9 – 71.6)	97.8 % (95.3 – 99.2)
segment	1305	108	1091	94	12	91.9 % (90.7 – 92.7)	90.0 % (83.5 – 94.4)	92.1 % (91.4 – 92.5)	53.5 % (49.6 – 56.1)	98.9 % (98.2 – 99.4)

Note: Numbers in parentheses represent 95% confidence interval values; n = number; TP = true positive; TN = true negative; FP = false positive; FN = false negative; PPV = positive predictive value; NPV = negative predictive value.
Anmerkung: Die Zahlen in Klammern repräsentieren das 95%-Konfidenzintervall; n = Anzahl; TP = richtig positiv; TN = richtig negativ; FP = falsch positiv; FN = falsch negativ; PPV = positiver prädiktiver Wert; NPV = negativer prädiktiver Wert.

Table 3 Diagnostic performance of CS for the prediction of significant stenosis on ICA.

Tab. 3 Diagnostische Genauigkeit des CS für die Detektion signifikanter Stenosen in der ICA.

CS threshold	n	TP	TN	FP	FN	accuracy %	sensitivity %	specificity %	PPV %	NPV %
> 0	87	56	5	26	0	70.1 % (64.1 – 70.1)	100 % (95.3 – 100)	16.1 % (7.7 – 16.1)	68.3 % (65.1 – 68.3)	100 % (47.6 – 100)
≥ 10	87	54	8	23	2	71.3 % (63.5 – 75.0)	96.4 % (90.4 – 99.4)	25.8 % (14.9 – 31.1)	70.1 % (65.7 – 72.3)	80.0 % (46.1 – 96.4)
≥ 10th [1]	87	56	5	26	0	70.1 % (64.1 – 70.1)	100 % (95.3 – 100)	16.1 % (7.7 – 16.1)	68.3 % (65.1 – 68.3)	100 % (47.6 – 100)
≥ 25th [1]	87	55	6	25	1	70.1 % (63.3 – 72.3)	98.2 % (92.9 – 99.9)	19.4 % (9.8 – 22.4)	68.8 % (65.1 – 69.9)	85.7 % (43.5 – 99.2)
≥ 25th [2]	87	56	7	24	0	72.4 % (65.6 – 72.4)	100 % (94.7 – 100)	22.6 % (13.1 – 22.6)	70.0 % (66.3 – 70.0)	100 % (57.9 – 100)

Note: Numbers in parentheses represent 95% confidence interval values; n = number; TP = true positive; TN = true negative; FP = false positive; FN = false negative; PPV = positive predictive value; NPV = negative predictive value.
Anmerkung: Die Zahlen in Klammern repräsentieren das 95%-Konfidenzintervall; n = Anzahl; TP = richtig positiv; TN = richtig negativ; FP = falsch positiv; FN = falsch negativ; PPV = positiver prädiktiver Wert; NPV = negativer prädiktiver Wert.
[1] Percentile for patients with no regular intake of cardiovascular medication according to Schmermund et al. [29].
Perzentile für Patienten ohne regelmäßige Einnahme kardiovaskulär wirksamer Medikamente nach Schmermund et al. [29].
[2] Percentile for Caucasian patients according to MESA [30].
Perzentile für Kaukasier nach MESA [30].

Table 4 Diagnostic performance of CS for the prediction of significant stenosis on cCTA.

Tab. 4 Diagnostische Genauigkeit des CS für die Detektion signifikanter Stenosen in der cCTA.

CS threshold	n	TP	TN	FP	FN	accuracy %	sensitivity %	specificity %	PPV %	NPV %
> 0	87	64	4	18	1	78.2 % (72.5 – 80.3)	98.5 % (94.7 – 99.9)	18.2 % (7.0 – 22.5)	78.0 % (75.1 – 79.2)	80.0 % (30.9 – 98.9)
≥ 10	87	61	6	16	4	77.0 % (69.8 – 82.9)	93.8 % (89.0 – 97.8)	27.3 % (13.1 – 38.9)	79.2 % (75.2 – 82.5)	60.0 % (28.8 – 85.6)
≥ 10th [1]	87	64	4	18	1	78.2 % (72.5 – 80.3)	98.5 % (94.7 – 99.9)	18.2 % (7.0 – 22.5)	78.0 % (75.1 – 79.2)	80.0 % (30.9 – 98.9)
≥ 25th [1]	87	63	5	17	2	78.2 % (71.7 – 81.9)	96.9 % (92.6 – 99.4)	22.7 % (10.0 – 30.2)	78.8 % (75.3 – 80.8)	71.4 % (31.5 – 94.8)
≥ 25th [2]	87	64	5	17	1	79.3 % (73.0 – 81.5)	98.5 % (94.3 – 99.9)	22.7 % (10.3 – 27.0)	79.0 % (75.6 – 80.2)	83.3 % (37.9 – 99.1)

Note: Numbers in parentheses represent 95% confidence interval values; n = number; TP = true positive; TN = true negative; FP = false positive; FN = false negative; PPV = positive predictive value; NPV = negative predictive value.
Anmerkung: Die Zahlen in Klammern repräsentieren das 95%-Konfidenzintervall; n = Anzahl; TP = richtig positiv; TN = richtig negativ; FP = falsch positiv; FN = falsch negativ; PPV = positiver prädiktiver Wert; NPV = negativer prädiktiver Wert.
[1] Percentile for patients with no regular intake of cardiovascular medication according to Schmermund et al. [29].
Perzentile für Patienten ohne regelmäßige Einnahme kardiovaskulär wirksamer Medikamente nach Schmermund et al. [29].
[2] Percentile for Caucasian patients according to MESA [30].
Perzentile für Kaukasier nach MESA [30].

100 %. A CS threshold ≥ 6.6 provided a sensitivity (98.2 %) comparable to cCTA but was associated with a much lower specificity (19.35 % vs. 67.7 % on cCTA). ROC analysis resulted in an area under the curve (AUC) of 0.721 when compared to ICA (**Fig. 2**).
Compared to cCTA, a CS threshold of > 0 provided a sensitivity of 100 % while a CS threshold of ≥ 3586 provided a specificity of 100 %. In comparison to cCTA, ROC analysis (**Fig. 3**) showed similar results (AUC = 0.688) as when compared to ICA.
There were no significant differences in sensitivity, specificity and NPV when comparing the diagnostic accuracy of CS to ICA and cCTA (all p > 0.05).

Discussion

One of the main purposes of CS is the detection of subclinical stages of CAD, especially in asymptomatic patients at intermediate risk [12]. In this approach a CS of zero results in the exclusion of CAD and in the waiver of further diagnostic measures. In addition, it has been demonstrated that CS is superior to traditional risk factors and clinical risk scores in estimating the risk of experiencing a cardiac event [12, 24]. Moreover, results from recent studies suggest that CSCT is a valuable tool for therapy monitoring [25]. Repeated scans allow conclusions about disease progression and therapy response in the individual patient. High CS values or rapid CS progression provides an indication for intensified treatment of risk factors [11, 12]. Furthermore, the patient's knowledge of his CS seems to have beneficial effects on lifestyle changes and the use of preventive medical treatment [25].
Currently, in clinical practice the radiation exposure associated with CSCT is about fivefold to tenfold lower than that of cCTA [8]. Due to the ongoing technical development, the effective dose associated with cCTA will continue to drop. If the latest scanner technology is available and the patient fulfills certain requirements (e. g. low BMI and heart rate), low-dose cCTA with a radiation exposure similar to CSCT is feasible [3]. In those cases low-dose cCTA is the method of choice. This is especially true since CS with all potential benefits can be obtained from a cCTA data set [26].
Concerning our study, the relevant application for CS is its diagnostic value to exclude significant stenosis. Elevated CS values are associated with an increased risk for the prevalence of significant stenosis [13]. Depending on the chosen threshold, CS can detect significant stenosis with high sensitivity but only moderate specificity [10 – 12]. A copious meta-analysis from Sarwar et al. (n = 10 355) in symptomatic non-acute patients showed a pooled sensitivity, specificity and NPV of 90 %, 40 % and 93 %, respectively, for a CS threshold > 0. Unfortunately, the NPV values are widely scattered from 68 % up to 100 %, depending on the study they are based on [10]. Studies like this led to the conclusion that a negative CS (CS = 0) is very unlikely to be accompanied by significant coronary artery stenosis, even in symptomatic patients [9].

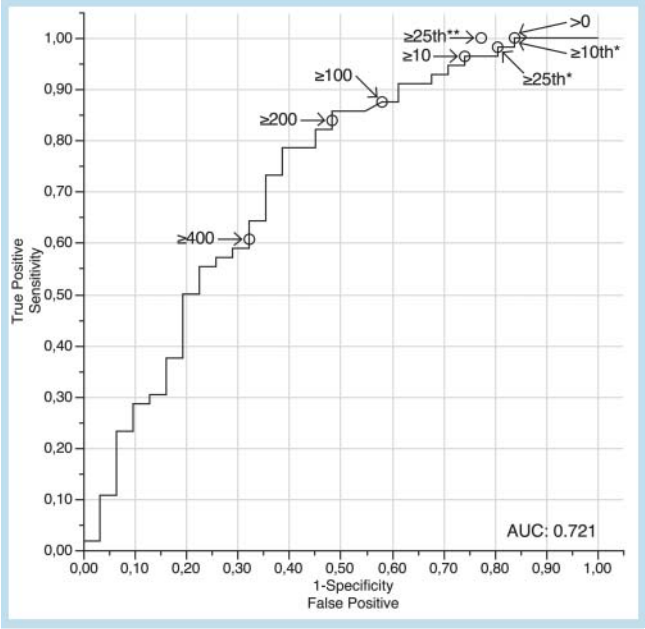

Fig. 2 ROC analysis of CS compared to ICA. Note: Curve represents absolute CS thresholds; AUC = Area under the curve; *percentile for patiens with no regular intake of cardiovascular medication according to Schmermund et al. [29]; **percentile for Caucasian patients according to MESA [30].

Abb. 2 ROC-Analyse des CS im Vergleich zur ICA. Anmerkung: Der Graph repräsentiert absolute CS-Schwellenwerte; AUC = Fläche unter der Kurve; *Perzentile für Patienten ohne regelmäßige Einnahme kardiovaskulär wirksamer Medikamente nach Schmermund et al. [29]; **Perzentile für Kaukasier nach MESA [30].

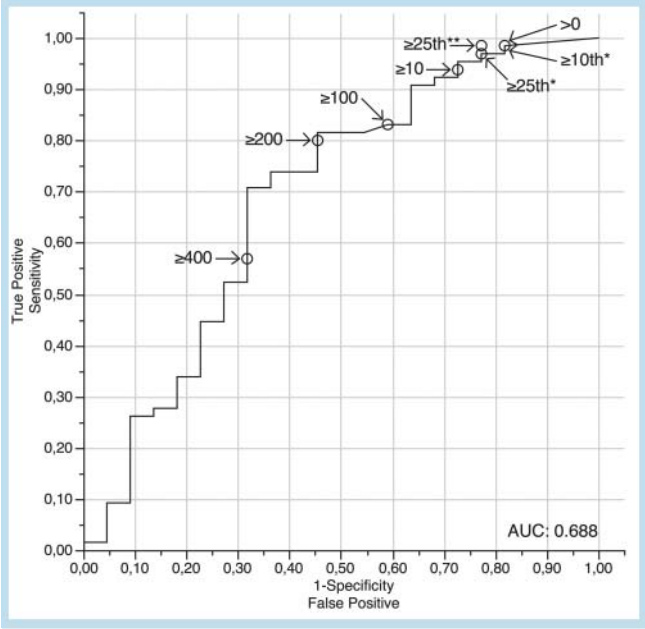

Fig. 3 ROC analysis of CS compared to cCTA. Note: Curve represents absolute CS thresholds; AUC = Area under the curve; *percentile for patients with no regular intake of cardiovascular medication according to Schmermund et al. [29]; **percentile for Caucasian patients according to MESA [30].

Abb. 3 ROC-Analyse des CS im Vergleich zur cCTA. Anmerkung: Der Graph repräsentiert absolute CS-Schwellenwerte; AUC = Fläche unter der Kurve; *Perzentile für Patienten ohne regelmäßige Einnahme kardiovaskulär wirksamer Medikamente nach Schmermund et al. [29]; **Perzentile für Kaukasier nach MESA [30].

However, it is still controversially discussed whether CSCT is an effective filter prior to further diagnostic measures in symptomatic patients. While some authors like Budoff et al. and Oudkerk et al. support this approach, other authors like Gottlieb et al. and Truong et al. decline the use of CSCT as a filter prior to further diagnostic measures [11, 12, 16, 17]. Others authors like Haberl et al. have published contradictory results [13, 18]. Van Werkhoven et al. suggest that CSCT may be used as a gatekeeper prior to cCTA depending on clinical presentation [19]. In contrast, Uretsky et al. demand further research to determine whether patients with a CS of zero but the presence of plaque represent a group at elevated risk before CSCT can be used as a safe means of exclusion [15]. Since the American College of Cardiology Foundation, the American Heart Association as well as the National Institute for Health and Clinical Excellence regard a negative CSCT as an effective filter prior to further diagnostic measures, we affiliate ourselves with that opinion [9, 27]. However, it is uncontroversial that even slightly elevated absolute CS thresholds are not reliable in this approach [12]. Furthermore, CSCT is not reliable as a means of exclusion in symptomatic patients at high risk, such as patients suffering from acute coronary syndrome [19].

To further investigate the limits of CS in the exclusion of significant coronary artery stenosis, we evaluated two different percentile systems derived from asymptomatic Caucasian populations, which allowed minor calcification in the elderly (men above 65 years and women above 75 years) without pushing them over the low-end percentile thresholds we chose for evaluation [21, 22]. We consider that a reasonable approach because a 75-year-old patient's coronary plaques are calcified to a greater extent than those of a 45-year-old patient [28]. This results in higher absolute CS values in elderly patients compared to younger patients with the same coronary plaque burden. Therefore, an elderly non-acute patient with only minor calcification (e.g. CS = 2) is presumably less likely to be affected by significant stenosis than a 45-year-old patient with identical absolute CS. To our knowledge, there is just one study by Akram et al. that ever evaluated low-end age- and sex-adjusted CS percentile ranks in the prediction of significant coronary artery stenosis [29].

Although the AUC values of our study indicate that CS is equally valid for ruling out significant stenosis compared to cCTA (AUC = 0.688) and ICA (AUC = 0.721), there are some considerable differences pertaining to other diagnostic accuracy parameters. The accuracy and PPV for a CS threshold of zero and certain percentile thresholds are significantly better when compared to cCTA than to ICA (all $p < 0.05$). This has no effect in clinical practice because these parameters are of no interest in the evaluated rule out approach. Under these premises, the NPV is of relevant importance for patient management. The NPV for a CS threshold of zero is just 80 % when compared to cCTA, whereas it is 100 % when compared to ICA. The reason for this is a single segment that was not evaluable on cCTA due to motion artifacts and was therefore considered positive. Because that segment did not show significant stenosis on ICA, it was considered false positive. Due to the small number of patients (n = 87), this diminished the NPV to 80 %. This NPV value is considerably worse than the NPV published by other authors like Meyer at al. (NPV = 100 %) and Akram et al. (NPV = 92 %) [30, 31]. In consequence, the low-end percentile ranks are affected by this coincidence, too. If this non-di-

agnostic segment, which was negative on ICA, had not been classified as positive, the NPV would have been 100 % as well which would confirm the results of the two studies cited above.

Another noticeable fact concerns the small number of non-diagnostic segments on cCTA. At a mean heart rate of 74 bpm, merely 2.2 % of the segments were considered non-diagnostic. This is lower than in some other publications and therefore might not be achievable in general clinical practice, especially at high mean heart rates [32]. This emphasizes the usefulness of ruling out obstructive CAD with CSCT, which is less susceptible to higher heart rates than cCTA.

Our study demonstrates that for a threshold of zero, CS is highly sensitive (100 % compared to ICA) but poorly specific (16.1 % compared to ICA), which is consistent with the results of other previous studies [12, 33]. For a CS threshold of zero, the NPV is 100 %. This supports the thesis that the absence of calcification is convenient to exclude significant stenosis in stable patients with suspected CAD. Interestingly, when using percentile-based thresholds that equal a CS of zero for most patients (≥ 10th percentile according to Schmermund [21] or ≥ 25th percentile according to data from MESA [22]), the NPV was 100 % as well.

Up to now, only minimal data on CS percentile thresholds is available. As a result of a retrospective study by Akram et al. in 210 consecutive asymptomatic and symptomatic patients, the authors stated that absolute CS was superior to MESA percentile rank in predicting obstructive CAD [29]. Though our data indicates the contrary, we do not want to challenge that conclusion in general since it is of no interest concerning the goal of our study. A closer look at the ROC curves by Akram et al. reveals that in their study a CS of zero (AUC = 0.80) is indeed superior to the MESA percentile rank (AUC = 0.72) in predicting significant stenosis. However, considering only cutoffs with a high sensitivity such as a CS of zero and low-end MESA percentile rank, these thresholds are of identical diagnostic value and thus equally valid for ruling out significant stenosis in asymptomatic as well as symptomatic patients. This is consistent with our results with respect to non-acute patients with suspected CAD.

Another study by Knez et al. in 2115 symptomatic patients using volumetric calcium scoring that evaluated percentile ranks derived from the collective under observance published a sensitivity of 95 % for a threshold > 25th percentile [14]. This rather high sensitivity value is surprising considering that the percentile ranks are derived from symptomatic patients who are likely to have higher CS values, which lead to higher thresholds for the corresponding percentile, thus increasing the risk to include patients suffering from significant coronary artery stenosis in the corresponding low-end percentile.

In knowledge of these results and although our study suggests that low-end percentile ranks may be an effective filter prior to further diagnostic measures and there is no contrary data published, considering the rather small database (data on 221 symptomatic patients published up to now), the exclusion of significant stenosis due to a CS below a low-end percentile rank does not seem appropriately evaluated yet to use it in general clinical practice. Further research on this topic is needed. In contrary, even slightly elevated absolute CS thresholds (e. g. CS = 10; NPV = 80.0 % compared to ICA) are not eligible to exclude significant coronary artery stenosis. This finding is equally valid for comparison to ICA and cCTA and is consistent with the results of other studies [13, 14, 33].

Limitations

We acknowledge the following limitations to our study. The prevalence of significant coronary artery stenosis in our study (64.4 %) was higher than in other studies investigating CS [13, 14, 33]. The reason might be that some patients objected to ICA after a negative cCTA and therefore had to be excluded from our study. That contingently led to overestimation of sensitivity and underestimation of NPV. Furthermore, we did not collect data on patient ethnicity. Since patient recruitment took place in an urban part of Germany. It is most likely that the vast majority of patients were Caucasian. Because coronary artery calcification is dependent on patient ethnicity, our results may only be applied to Caucasian patients [22].

Conclusion

Significant coronary artery stenosis is extremely unlikely in stable patients with an intermediate risk of suffering from CAD and a CS of zero. A CS of zero may be used as a gatekeeper prior to further diagnostic procedures in these patients. A CS value below low-end age- and sex-adjusted percentiles (< 25th percentile according to MESA; < 10th percentile for patients with no regular intake of cardiovascular medication according to Schmermund et al.) derived from asymptomatic Caucasian populations seems to have identical diagnostic value and thus might be used as a gatekeeper in the future. Since data is currently insufficient to make a reliable statement on diagnostic safety, further research on percentile thresholds is needed.

Acknowledgement

The authors thank the Federal Office for Radiation Protection (BfS) and its staff members for their advice and the financial support of this study.

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