

What is the optimal cut-off point for low coronary artery calcium score assessed by computed tomography? Multi-Detector Computed Tomography ANIN Registry

Jaki jest optymalny punkt odcięcia niskiego indeksu zwapnień tętnic wieńcowych?
Multi-Detector Computed Tomography ANIN Registry

Edyta Kaczmarska¹, Cezary Kęпка¹, Zofia Dzielińska¹, Radosław Pracownik¹, Karolina Kryczka¹, Joanna Petryka¹,
Jerzy Pręgoski², Mariusz Kruk¹, Marcin Demkow¹

¹Department of Coronary and Structural Heart Diseases, Institute of Cardiology, Warsaw, Poland

²Department of Interventional Cardiology and Angiology, Institute of Cardiology, Warsaw, Poland

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Abstract

Aim: This prospective study was conducted to evaluate the incidence and predictors of coronary artery disease (CAD) in relation to the low coronary artery calcium (CAC) score among patients with intermediate probability of CAD.

Material and methods: A total of 1132 consecutive patients were included in the analysis (58.7 ± 10.9 years, 46.7% males). Coronary computed tomography (CCT) angiography was performed in a multi-detector computed tomography scanner. Coronary artery calcium score was calculated by the Agatston method. Obstructive CAD was defined as the presence of coronary artery stenosis ≥ 50% on CCT angiography.

Results: Coronary artery disease was diagnosed in nearly one-fourth of patients ($n = 272$, 24%). In the receiver operating characteristics (ROC) curve analysis a CAC score of 10 was used as an optimal cut-off point for discriminating obstructive CAD (sensitivity: 0.79, specificity: 0.75, $p < 0.0001$) whereas for a CAC score of 100 the sensitivity and specificity were 0.48 and 0.92, respectively. On multivariate analysis after adjustment for age, gender, hypertension, hyperlipidemia, creatinine levels, only in patients with CAC score ≤ 10 age (OR = 1.05, 95% CI: 1.02-1.08, $p = 0.0005$, OR = 1.05, 95% CI: 1.03-1.08, $p < 0.0001$) and male gender (OR = 3.45, 95% CI: 1.92-6.22, $p < 0.0001$), likewise in group with CAC score ≤ 100 age (OR = 1.05, 95% CI: 1.03-1.08, $p < 0.0001$) and male gender (OR = 3.31, 95% CI: 1.88-5.81, $p < 0.0001$) were independent predictors of obstructive CAD.

Conclusions: The cut-off point of 10 for CAC score determined patients with CAD with the best sensitivity and specificity. Therefore, a total CAC score < 10 should be classified as “low”. In patients with a low CAC score obstructive high risk plaques prone to rupture are presented and are associated with increasing age and male gender.

Key words: coronary artery calcium score, coronary computed tomography, coronary artery disease.

Streszczenie

Cel: Zdefiniowanie punktu odcięcia dla niskiego indeksu zwapnień tętnic wieńcowych (*coronary artery calcium* – CAC) oraz ocena częstości występowania choroby wieńcowej (*coronary artery disease* – CAD) i jej predyktorów w grupie pacjentów z niskim indeksem CAC.

Materiał i metody: Analizie poddano 1132 kolejnych pacjentów (58,7 ± 10,9 roku, 46,7% mężczyzn), u których wykonano wielorzędowną tomografię komputerową tętnic wieńcowych. Indeks CAC obliczono półautomatycznie, stosując metodę Agatston. Chorobę wieńcową zdefiniowano jako obecność istotnego zwężenia (≥ 50%) w obrazie angiograficznym tomografii komputerowej.

Wyniki: Chorobę wieńcową rozpoznano u 24% pacjentów ($n = 272$). Na podstawie krzywej ROC punkt odcięcia 10 dla indeksu CAC charakteryzował się najwyższą czułością i specyficznością w przewidywaniu choroby wieńcowej (AUC = 0,84, czułość 0,79, specyficzność 0,75, $p < 0,0001$), natomiast w przypadku indeksu CAC 100 czułość i specyficzność wyniosły odpowiednio 0,48 i 0,92. W analizie wieloczynnikowej – uwzględniającej wiek, płeć, nadciśnienie, hiperlipidemię, stężenie kreatyniny – w grupie CAC ≤ 10 wiek (OR = 1,05, 95% CI: 1,02–1,08, $p = 0,0005$) i płeć męska (OR = 3,45, 95% CI: 1,92–6,22, $p < 0,0001$), a także w grupie pacjentów z CAC ≤ 100 wiek (OR = 1,05, 95% CI: 1,03–1,08, $p < 0,0001$) i płeć męska (OR = 3,31, 95% CI: 1,88–5,81, $p < 0,0001$) były niezależnymi predyktorami wystąpienia CAD.

Corresponding author/Adres do korespondencji:

Edyta Kaczmarska MD, Department of Coronary and Structural Heart Diseases, Institute of Cardiology, 42 Alpejska St, 04-628 Warsaw, Poland, tel.: +48 22 343 43 42, e-mail: edytaka@gmail.com

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Wnioski: Punkt odcięcia 10 indeksu CAC z najlepszą czułością i specyficznością określa wystąpienie CAD. Indeks CAC < 10 powinien być sklasyfikowany jako niski. W grupie z niskim indeksem CAC obecność istotnych, nieuwapnionych zwężeń wiąże się ze starszym wiekiem oraz płcią męską.

Słowa kluczowe: indeks zwapnień tętnic wieńcowych, tomografia komputerowa tętnic wieńcowych, choroba wieńcowa.

Introduction

Coronary computed tomography (CCT) has been approved for direct, noninvasive imaging of the coronary artery. Contrast-enhanced CCT angiography evaluates stages of atherosclerosis, demonstrates the percentage of luminal stenosis and provides an opportunity for identifying calcified and non-calcified components within coronary plaques. The coronary artery calcium (CAC) score, assessed on CCT at the first scan without contrast enhancement, is highly specific for atherosclerosis, and occurs only in the intima. The CAC score is a marker of the extent of coronary calcified atherosclerotic plaques. A high CAC score is predictive for obstructive coronary artery disease (CAD); therefore patients with low CAC scores are generally considered as those at very low risk of CAD and are referred to as low risk patients. Furthermore, as the absence of CAC is highly predictive of the absence of coronary artery stenosis, low CAC score has been proposed as an effective diagnostic tool for ruling out CAD [1-6].

The incidence and clinical relevance of CAD in patients with low CAC scores are unclear. Recent studies involving CCT angiography have reported that negative CAC does not exclude significant coronary artery stenosis. Among those study populations with low or negative CAC scores, CAD was reported in considerably different incidences [7-11]. The incidence of CAD depended mainly on the patient population and on cut-off points applied for a low CAC score. Some studies evaluate CAD incidence with the applied cut-off for a low CAC score as 100, whereas a few analyses assign the cut-off as 10. In fact, the current guidelines and expert consensus for CCT assessment do not provide a definition of low CAC score [1-3, 5, 12].

The leading issue is to distinguish patients with minor calcifications and CAD from patients with severe calcifications, since it has been established that non-calcified plaques or plaques with very low calcification are vulnerable and prone to rupture, whereas severe calcifications are generally interpreted as a kind of plaque stabilization [13, 14].

Aim

In this context, the present study investigated the incidence and predictors of obstructive CAD in CCT angiography in relation to low CAC score in intermediate risk persons.

Material and methods

Study population

There were 1132 consecutive patients identified from the prospective ANIN-CCT registry, referred for CCT angiography at the Department of Coronary and Structural Heart Dis-

eases between January 2009 and December 2010. Contrast-enhancement CCT scans were performed in patients with a history of (1) atypical angina and abnormal stress tests, (2) typical angina and negative stress tests. Each patient provided a written statement of informed consent for the diagnostic procedures performed.

Demographic and cardiovascular risk factors

Basic clinical data, including age, gender, hypertension, hyperlipidemia, diabetes, smoking history, and family history of CAD, were all prospectively determined at the time of the scan. Patients with a history of percutaneous angioplasty or surgical revascularization, valve surgery, history of myocardial infarction, or congestive heart failure were excluded from the analysis. Hypertension was defined as systolic blood pressure over 140 and/or diastolic blood pressure over 90 mm Hg and/or use of blood pressure-lowering medication. Hyperlipidemia was defined as elevated total cholesterol > 5.2 mmol/l, low-density lipoprotein (LDL) > 2.59 mmol/l, or triglycerides (TG) > 1.65 mmol/l and/or low high-density lipoprotein (HDL) < 1.15 mmol/l and/or use of lipid-lowering therapy. Diabetes was defined as present if the participant used insulin or oral hypoglycemics or if the glucose level exceeded 200 mg/dl (11.0 mmol/l) for a single blood sample. Cigarette smoking was reported as ever (past and/or current use). A patient was considered to have a positive family history if a first degree relative had a history of coronary heart disease or stroke at an age of < 65 years.

CAC scoring and CCT angiography

All CCT scans were performed at the Institute of Cardiology with a dual-source computed tomography scanner (Somatom Definition, Siemens, Forchheim, Germany) after single sublingual administration of nitrates. Non-contrast enhanced scans with 100- to 120-kV tube voltage were performed to calculate the CAC score prior to CCT angiography. Contrast-enhanced scans were then performed using a bolus of iodinated contrast medium (80 ml to 120 ml, Iomeron 400, Bracco Altana Pharma, Konstanz, Germany). The CAC score was manually marked by the operator and automatically calculated using the Agatston scoring method [15]. The measurements of CAC score involved the left main coronary artery (LMCA), the left anterior descending (LAD), the left circumflex (Cx) and the right coronary artery (RCA). The total CAC score was determined by summing CAC scores for all coronary arteries. The total CAC scores were categorized as ≤ 10 , 11-100 and > 100.

The finest quality images for all coronary segments were obtained from datasets reconstructed routinely in mid- to

end-systole and diastole with retrospective electrocardiogram gating. The percent stenosis was calculated as the narrowest diameter of the lumen divided by the normal lumen diameter of the nearest normal proximal portion of the same segment in CCT angiography. Obstructive CAD was defined as stenosis $\geq 50\%$ of the main coronary arteries.

Statistical analysis

All continuous data are expressed as mean \pm standard deviation (SD) and were compared using the Student *t* test or one-way analysis of variance (ANOVA) as appropriate. Categorical data are presented as frequencies and were compared using the χ^2 test. Independent predictors of CAD were identified using multiple logistic regression with the odds ratio (OR) and 95% confidence interval (CI). Receiver operating characteristics (ROC) curve analysis with area under the curve (AUC) was used to assess the relation of total CAC score to CAD prediction. Significance was assumed at the two-tailed *p* value of < 0.05 . The data analysis was performed using SPSS 9.0 (Chicago, IL, USA).

Results

The study group consisted of 1132 patients (46.7% men). The mean age was 58.7 ± 10.9 years. Baseline characteristics of the study population are presented in Table 1. Hypertension and hyperlipidemia were observed in half of the study population. Over one-fourth of the patients had ab-

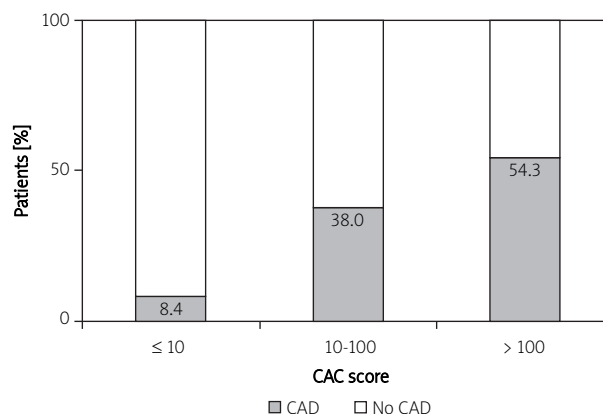


Fig. 1. The relation of increasing prevalence of obstructive CAD with increasing CAC score in the group studied ($n = 1132$)

Ryc. 1. Wzrost częstości występowania CAD w grupach z podwyższonym indeksem CAC w badanej grupie ($n = 1132$)

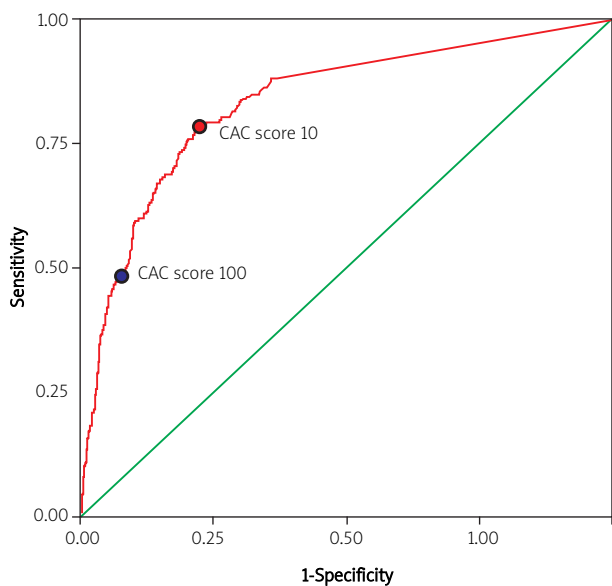
normal low HDL levels. Diabetes was observed in 7.3%. Smoking history was reported by one-fifth of the patients. Coronary artery disease was diagnosed in nearly one-fourth of the study group ($n = 272$, 24%).

A total CAC score ≤ 10 , 10-100, and > 100 was found in 668 (59.0%), 221 (19.5%), and 243 (21.5%) patients, respec-

Table 1. Baseline characteristics of 1132 patients and association of CAC score with cardiovascular risk factors
Tabela 1. Wyjściowa charakterystyka 1132 pacjentów oraz rozkład czynników ryzyka w zależności od wartości indeksu CAC

Parameter	Study group ($n = 1132$)	CAC score			Value of <i>p</i>
		≤ 10 ($n = 668$)	10 to 100 ($n = 221$)	> 100 ($n = 243$)	
Age [year]	58.7 ± 10.9	55.34 ± 10.7	61.97 ± 9.2	0.000	64.8 ± 9.2
Gender (male)	46.7	39.8	48.6	0.023	64.2
Hypertension	54.5	52.7	57.7	NS	56.8
Diabetes	7.3	5.8	8.6	NS	10.3
Smoking	21.8	19.3	25.9	NS	23.5
Family history of CAD	52.6	26.5	20.4	NS	21.0
Hyperlipidemia	24.1	51.5	53.2	NS	55.1
Creatinine [mmol/l]	77.9 ± 17.8	75.38 ± 16.5	79.47 ± 16.7	0.003	84.63 ± 19.9
Fasting glucose [mmol/l]	5.93 ± 1.41	5.8 ± 1.2	6.0 ± 1.7	NS	6.12 ± 1.5
Total cholesterol [mmol/l]	4.96 ± 1.15	5.00 ± 1.1	5.04 ± 1.2	NS	4.73 ± 1.2
HDL [mmol/l]	1.47 ± 1.02	1.55 ± 1.2	1.41 ± 0.4	NS	1.31 ± 0.4
HDL (< 1.15 mmol/l)	26.7	20.55	30.22	0.025	38.2
TG [mmol/l]	1.50 ± 0.95	1.40 ± 0.9	1.58 ± 0.9	0.055	1.63 ± 1.0
TG (> 2.3 mmol/l)	12.3	8.5	14.4	0.050	13.8
LDL [mmol/l]	3.17 ± 1.05	3.20 ± 1.0	3.25 ± 1.1	NS	3.02 ± 1.1
CAD	24.0	8.4	38.0	0.000	54.3

Values are reported as proportion with condition (%); continuous variables are reported as mean (\pm SD)



AUC = 0.84, cut-off point CAC score 10 with sensitivity: 0.79, specificity: 0.75; cut-off point CAC score 100 sensitivity: 0.48, specificity: 0.92; $p < 0.0001$

Fig. 2. The ROC curve in the entire group for CAC score to predict obstructive CAD

Ryc. 2. Wykres krzywej ROC dla indeksu CAC w przewidywaniu wystąpienia CAD w badanej grupie

tively. We observed a stepwise increase in the incidence of CAD with increasing CAC score (Figure 1). Interestingly, there was an ~5-fold difference in rates of CAD between those with CAC scores ≤ 10 , and 10-100 (8.4% vs. 38.0%, $p < 0.0001$). Patients' characteristics, depending on the cut-off points applied (< 10 vs. 10-100) for CAC score, are presented in Table 1. Patients with higher CAC scores (10-100), in comparison to patients with lower CAC scores (≤ 10), were older, more frequently male, with significantly higher serum creatinine levels. Patients with CAC scores of 10-100 significantly more frequently present with inappropriate low HDL and high triglycerides levels (Table 1).

For the entire group the ROC curve for total CAC score and obstructive ($\geq 50\%$) coronary artery stenosis showed an AUC of 0.84, $p < 0.0001$ (Figure 4). Based on the ROC curve, CAC score of 9.8 (≈ 10) presented as an optimal cut-off point for discriminating obstructive CAD (sensitivity: 0.79, specificity: 0.75). Yet, when the cut-off was upgraded to 100, the sensitivity and specificity were 0.48 and 0.92, respectively.

Table 2 presents characteristics of the patient populations with the CAC score ≤ 10 and ≤ 100 according to the presence of CAD. Similarly in both groups (CAC score ≤ 10 and ≤ 100) CAD was present among older males with hypertension, smoking history, hyperlipidemia, and higher creatinine levels. Univariate analysis was performed to determine predictors of CAD in CCT angiography in patients with CAC score ≤ 10 and those with CAC score ≤ 100 . Results are presented in

Table 2. Relation of clinical covariates to CAC score and presence of CAD

Tabela 2. Rozkład zmiennych klinicznych w zależności od wielkości indeksu CAC i obecności CAD

Parameter	CAC score					
	≤ 10 (n = 668)			≤ 100 (n = 889)		
	With CAD n = 56 (8.4%)	Without CAD n = 612 (91.6%)	Value of p	With CAD n = 140 (15.7%)	Without CAD n = 749 (84.2%)	Value of p
Age [year]	59.5 \pm 10.62	55.0 \pm 10.60	0.002	61.57 \pm 9.9	56.14 \pm 10.7	< 0.001
Gender (male)	60.7	37.6	0.001	56.4	39.1	< 0.001
Hypertension	69.6	50.9	0.008	63.6	51.8	0.01
Diabetes	8.9	5.6	NS	8.6	6.2	NS
Smoking	28.6	18.9	NS	29.3	19.4	0.012
Family history of CAD	30.4	26.1	NS	25.0	25.1	NS
Hyperlipidemia	64.3	50.2	0.050	60.0	50.1	0.034
Creatinine [mmol/l]	82.711 \pm 16.29	73.83 \pm 16.14	< 0.001	81.69 \pm 16.7	75.3 \pm 16.4	< 0.001
Fasting glucose [mmol/l]	6.21 \pm 1.44	5.72 \pm 1.04	0.012	5.92 \pm 1.2	5.83 \pm 1.3	NS
Total cholesterol [mmol/l]	4.99 \pm 1.01	5.03 \pm 1.07	NS	4.96 \pm 1.1	5.03 \pm 1.1	NS
HDL [mmol/l]	1.41 \pm 0.47	1.58 \pm 1.36	NS	1.35 \pm 0.4	1.55 \pm 1.2	NS
HDL (< 1.15 mmol/l)	32.4	19.2	0.077	31.9	21.3	0.039
TG [mmol/l]	1.46 \pm 0.66	1.41 \pm 0.95	NS	1.53 \pm 0.9	1.42 \pm 0.9	NS
TG (> 2.3 mmol/l)	8.8	8.2	NS	9.8	11.0	NS
LDL [mmol/l]	3.19 \pm 0.96	3.19 \pm 0.99	NS	3.21 \pm 0.9	3.21 \pm 1.0	NS

Values are reported as proportion with condition (%); continuous variables are reported as mean (\pm SD)

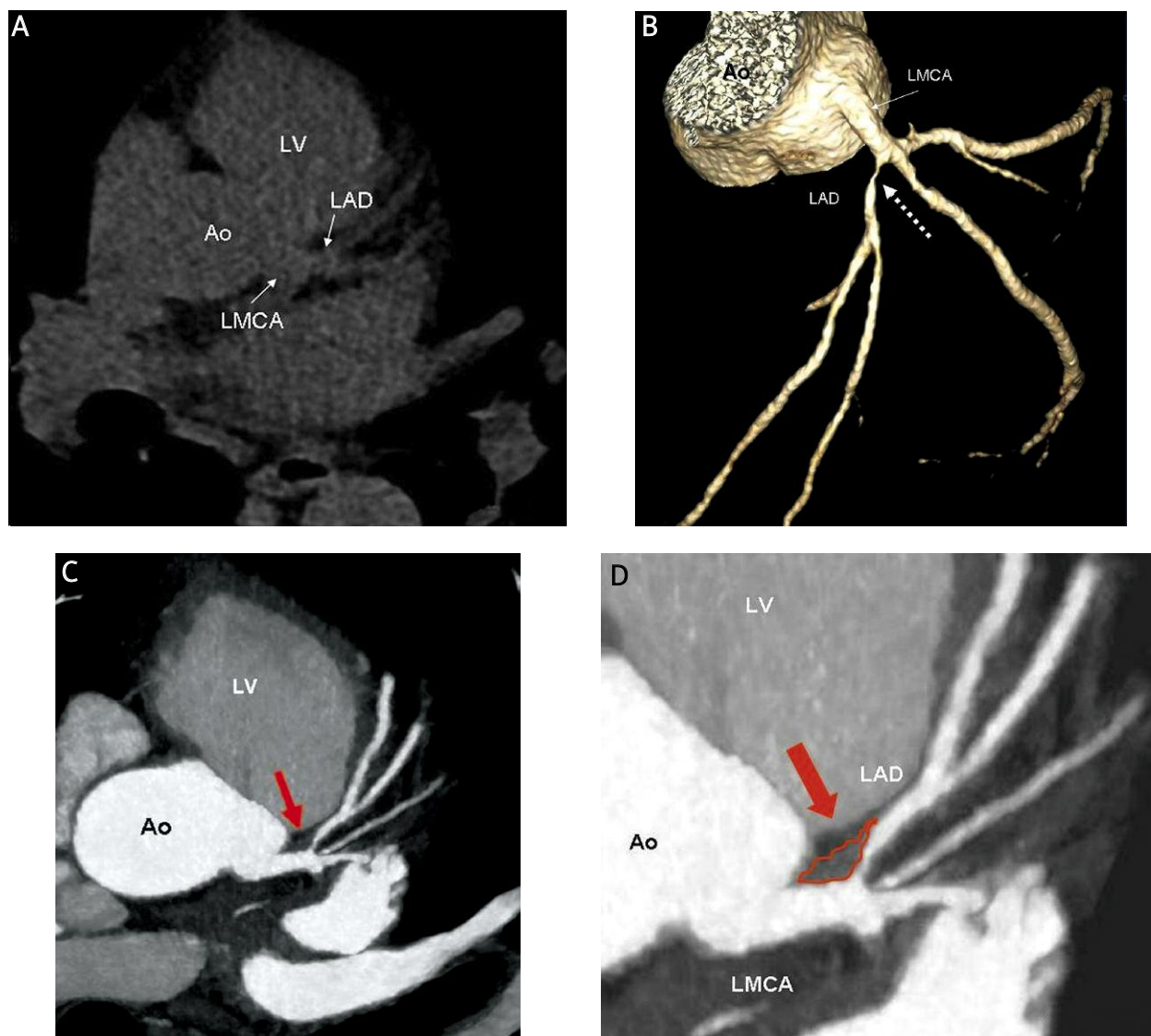


Fig. 3. The CAC score zero (negative coronary artery calcification) and high-grade proximal LAD stenosis presented in CCT angiography. The CAC score zero (A). Multiplanar reconstruction of LMCA and LAD reveals high-grade stenosis of proximal LAD (B, white dotted arrow) in the presence of zero CAC score (non-calcified plaque) (C, D – red arrow)
Ryc. 3. Indeks CAC zero (brak zwapnień w tętnicach wieńcowych) oraz istotne zwężenie proksymalnego odcinka LAD obrazowane w angiografii CCT. Indeks CAC zero (A). Obecność istotnego zwężenia proksymalnego odcinka LAD w wielopłaszczyznowej rekonstrukcji obrazu (B, biała strzałka wykropkowana) u pacjenta z indeksem CAC zero (nieuwapniona blaszka miażdżycowa) (C, D – czerwona strzałka)

Table 3. After adjustment for age, gender, hypertension, hyperlipidemia, and creatinine levels, in both CAC score ≤ 10 and ≤ 100 groups, only age (OR = 1.05, 95% CI: 1.02-1.08, $p = 0.0005$, OR = 1.05, 95% CI: 1.03-1.08, $p < 0.0001$, respectively) and male gender (OR = 3.45, 95% CI: 1.92-6.22, $p < 0.0001$, OR = 3.31, 95% CI: 1.88-5.81, $p < 0.0001$, respectively) were independent predictors of obstructive CAD.

Discussion

The first and most important finding of this study concerns the definition of low CAC score in an intermediate risk

population. A total CAC score ≤ 10 , not as previously proposed < 100 , should be classified as a “low CAC score”. A low CAC score or the absence of coronary calcifications does not mean the exclusion of coronary artery disease, as non-calcified obstructive coronary plaques might coexist with negative Agatston score results. Therefore CAC score ≤ 10 better than CAC score < 100 discriminates patients with low-calcified or non-calcified obstructive plaque. Significant calcification might be interpreted as a kind of plaque stabilization. Consequently, patients with plaques richer in lipids, with more extensive inflammatory processes, with low cal-

Table 3. Relation of cardiovascular risk factors to obstructive CAD in patients with CAC score ≤ 100 and CAC score ≤ 10
Tabela 3. Czynniki ryzyka wystąpienia chorób sercowo-naczyniowych w przewidywaniu CAD w grupie chorych z indeksem CAC ≤ 100 i indeksem CAC ≤ 10

Parameter	Univariate regression analysis		
	OR	95% CI	Value of <i>p</i>
CAC score ≤ 100 (<i>n</i> = 889)			
Age [year]	1.05	1.03-1.07	< 0.0001
Gender (male)	2.01	1.40-2.91	0.0002
Hypertension	1.62	1.12-2.36	0.0106
Hyperlipidemia	1.49	1.03-2.15	0.0329
Creatinine [mmol/l]	1.02	1.01-1.03	0.0001
HDL (< 1.15 mmol/l)	1.73	1.05-2.85	0.0327
CAC score ≤ 10 (<i>n</i> = 668)			
Age [year]	1.04	1.01-1.07	0.0024
Gender (male)	2.56	1.46-4.49	0.010
Hypertension	2.21	1.22-4.00	0.0085
Hyperlipidemia	1.78	1.01-3.15	0.04
Creatinine [mmol/l]	1.03	1.01-1.04	0.001
Fasting glucose level	1.34	1.05-1.71	0.0184

cification or non-calcified, are at risk for plaque rupture. There is growing evidence suggesting that non-calcified plaque might be associated with acute coronary syndrome. An analysis of the composition of vulnerable plaques in acute coronary syndromes has shown that culprit lesions in 29% of cases were exclusively noncalcified. Thus, patients may develop symptomatic CAD or even acute coronary syndrome prior to the accumulation of calcium [13, 16]. In more recent publications, the likelihood of obstructive coronary artery lesions in the absence of calcifications was considered to be in the range of 4% to as high as 29% [10, 17-21]. We conclude that the incidence of CAD in those studies was dependent mainly on the cut-off point of a low CAC score. In our analysis the incidence of CAD was two-fold higher (8.4% vs. 15.7%) when the criterion for a "low" CAC score was upgraded from an Agatston score of 10 to 100. Importantly, when we compare patients with a CAC score of 10-100 to patients with a CAC score ≤ 10 , the incidence of CAD rises significantly (~5-fold). Our results are similar to the previous results of Ueda, who reported that the incidence of CAD increased 6-fold in the CAC 10-100 score group [22, 23]. When a CAC score < 100 is classified as low, the high risk non-calcified obstructive CAD is simply overestimated.

The most important issue is to determine predictors of obstructive CAD with concomitant low CAC score. There have been several studies on the association between cardiovascular risk factors and the presence of non-obstructive calcified or non-calcified coronary plaque among patients with low CAC scores [10, 24-30]. The authors demonstrated that diabetes, hyperlipidemia, and smoking are associated with the presence of non-calcified, non-obstructive plaque, but the results for obstructive non-calcified plaque

are not so obvious [19, 22, 23]. Similarly to our results, the multicenter CONFIRM Registry reported that male gender, age and smoking were independent predictors of CAD at negative CAC score results on CCT [30]. Traditional clinical risk factors, excluding age and gender, have no statistical power to be independent predictors of obstructive CAD among intermediate risk persons with low CAC scores.

Conclusions

The cut-off point of 10 for CAC score determined patients with CAD with the best sensitivity and specificity. Therefore, a total CAC score < 10 should be classified as "low".

Low CAC score is associated with a low risk of obstructive CAD. Nevertheless, low CAC score alone cannot be used as a tool aimed at identifying or excluding obstructive CAD. In patients with low CAC scores obstructive plaques are present and are associated with increasing age and male gender. No additional clinical predictors of CAD in low CAC score patients were found.

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