Prognostic value of coronary artery calcium score in patients with symptoms suggestive of coronary artery disease

Results from the Silesian Calcium Score (SILICAS) study

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INTRODUCTION
Atherosclerosis, in which a degenerative-inflammatory process leads to the development of plaques gradually infiltrated with calcium, is the cause of most cases of coronary artery disease (CAD). The presence of coronary calcifications well reflects the extent of the atherosclerotic process.2–4 Calcium deposits may be a component of both critically stenosed and non-obstructive plaques. High numerical values of the coronary artery calcium score (CACS) are usually present in subjects with high-grade coronary lesions, but may also be found in individuals with extensive atherosclerosis but no critical coronary stenosis. On the other hand, noncalcified plaques may be present, especially in younger subjects, and may be prone to rupture.4–7

The predictive role of CACS for cardiovascular events in asymptomatic subjects has been well studied.8–12 In this group, the absence of coronary calcium identifies the subjects with very low risk of subsequent coronary events,4,13,14 and a CACS of more than 400 Agatston units (AU) is considered
a CAD equivalent, with a 10-year MACE rate of over 20%. The Screening for Heart Attack Prevention and Education (SHAPE) guidelines proposed to use the CACS value as the basis for risk screening in apparently healthy population of men older than 45 years and women older than 55 years. This approach, however, has not been widely accepted.

In symptomatic subjects, the role of calcium scoring is more controversial. Patients with symptoms suggestive of CAD represent a nonuniform group, for whom confirmation or exclusion of CAD diagnosis and assessment of the risk of cardiac events are of key importance for the choice of a management strategy. Classic risk factors, including age, sex, arterial hypertension, smoking, and dyslipidemia, serve as the basis for the most popular risk calculators, such as the Framingham scale and SCORE. Those scales are useful for cardiovascular risk assessment but have important limitations. A substantial proportion of patients at risk of cardiovascular events cannot be identified using the classic risk factors. In addition, in young and middle-aged subjects, the risk of cardiovascular events is low even in the presence of several risk factors, while in the elderly population, a small change in the risk profile may have major prognostic implications.

Currently, the calcium score measurement is not included in the diagnostic algorithm in patients with suspected CAD. However, some studies suggest that CACS may provide more valuable diagnostic and prognostic information than that obtained from exercise testing and single-photon emission computed tomography (CT). On the other hand, other data indicate that up to 20% of symptomatic patients with a negative CACS value may have obstructive coronary lesions. Therefore, the use of coronary calcium scoring in this setting remains controversial and requires further research.

The primary objective of the SILICAS study was to assess the predictive value of coronary calcium on the major adverse coronary events (MACEs) including cardiac death, nonfatal myocardial infarction (MI), and coronary revascularization, in order to establish its usefulness as the first-line noninvasive test in patients with an intermediate probability of CAD. Secondary objectives included the incidence of cardiac death, MI, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG), as well as the number of coronary angiographies and hospitalizations for stable and unstable angina in relation to the CACS.

**PATIENTS AND METHODS** Study design and participants SILICAS was a prospective, single-center observational study, enrolling subsequent patients without a previous diagnosis of CAD, who had symptoms suggestive of CAD and no known coronary anatomy, and were referred by their attending physicians for a CACS examination to the Unit of Noninvasive Cardiovascular Diagnostics of the Upper-Silesian Center of Cardiology in Katowice, Poland.

Subjects meeting the following criteria were included: male and female subjects aged 18 years or older, symptoms suggestive of CAD, intermediate probability of CAD based on clinical data, no established CAD diagnosis, and a written informed consent to participate in the study. The exclusion criteria were as follows: pregnancy, previous invasive coronary angiography (independent of the result); CT angiography performed at the time of CACS assessment, history of an acute coronary syndrome, history of any coronary revascularization; clinical heart failure (New York Heart Association class >1), clinically relevant structural heart disease, cardiac arrhythmias with potential impact on the interpretation of CACS, other contraindications to CACS measurement, presence of a disease likely to affect medium-term prognosis, and lack of informed consent or inability to provide an informed consent.

Clinical history was obtained and physical examination performed in each patient at the initial visit. All patients were prospectively followed up by telephone interviews, for at least 1 year after CACS measurement. In case of any incident event of interest, patients were examined and all medical records were analyzed.

A written informed consent was obtained at the baseline visit from all subjects included in the study. The study was approved by the Ethics Committee of the Medical University of Silesia.

**Computed tomography protocol and data analysis** CACS assessment was performed using a 64-slice CT scanner (Aquilion 64, Toshiba Medical Systems, Tokyo, Japan). A non-contrast-enhanced, prospective, electrocardiogram-gated sequential scan was performed with the following parameters: tube voltage, 120 kV; tube current, 200 mA; rotation time, 350–500 ms; and section width, 2.0 mm. CACS values were determined by 2 experienced physicians blinded to patients’ clinical data, using a dedicated work station (Vitreos2, Vital Images, Minnetonka, Minnesota, United States and Advantage, GE Healthcare, Chicago, Illinois, United States). The quantitative CACS values were calculated according to the Agatston method.

**Statistical analysis** Discrete variables were presented as absolute and percent values. Continuous variables were assessed for normal distribution by means of the Shapiro–Wilk test; for the normal distribution, the data were presented as the mean ± SD, and for other distributions, as the median ± a half of the interquartile gap. The prognostic value of the CACS was assessed using the Cox regression analysis. The initial univariate analysis included all components of the primary endpoint. The hazard ratio and 95% confidence interval was calculated for each variable. The prognostic value of CACS was assessed for the groups with a CACS of 0 and a CACS of 1 or
higher. In addition, the calculations were performed for the following CACS groups: 1–99 AU, 100–399 AU, 400–999 AU, and ≥1000 AU. Sensitivity and specificity of CACS for the prediction of the primary endpoint was calculated using the receiver-characteristic operating curve method. The level of statistical significance was set at a P value of less than 0.05. All data were analyzed by means of the Statistica 7 program (StatSoft, Tulsa, Oklahoma, United States).

RESULTS Clinical characteristics of the study population A total of 906 patients were screened, of whom 259 were excluded because of a CT angiogram done together with the CACS evaluation; 31, because of a prior coronary angiography; and 28, due to insufficient medical records. The final study population comprised 588 patients. Their mean age was 61.1 ±9.7 years, and 36% were male. Arterial hypertension was present in 64%, hyperlipidemia in 57%, diabetes in 15%, and positive family history of CAD in 61% of the patients. In addition, 21% of the patients were current or past smokers, and 69% reported low physical activity. A mean body mass index was 28.18 ±4.14 kg/m². Study group characteristics are presented in Table 1.

Distribution of coronary artery calcium score In 239 patients (40.6%), no coronary calcifications were observed (CACS = 0 AU), while 349 patients (59.4%) had a CACS of 1 AU or higher. Patients with positive CACS more often had hypertension, diabetes, hypercholesterolemia, and positive history of premature CAD (Table 1). Among patients with positive results, the score was in the range of 1 to 99 AU in 172 patients (49.3%; 29.2% of the entire study group), 100 to 399 AU in 105 patients (30.1%; 17.9%), 400 to 999 AU in 38 patients (10.9%; 6.5%), and ≥1000 AU in 34 patients (9.7%; 5.8%). The distribution of CACS results among the subgroups is presented in Figure 1.

Radiation exposure The mean effective radiation dose in our study was 1.32 ±0.39 mSv (range, 0.48–3.30 mSv).

Clinical outcomes Patients were followed up for a mean period of 638 ±261 days (median, 707; Q1–Q3, 587–826). The primary endpoint,
death due to MI, 13 nonfatal MIs, 72 PCIs, and 33 CABG procedures. For the 4 subgroups of patients with positive CACS (1–99 AU, 100–399 AU, 400–999 AU, and ≥1000 AU), an event occurred in 8%, 39%, 68%, and 91% of the patients, respectively. Total and nonfatal MI, PCI, and CABG showed a significant positive relationship with CACS (CACS = 0 vs CACS ≥1; \( P < 0.001 \) for all variables; TABLE 2).

Only patients with a positive CACS required coronary revascularization during follow-up. In patients with a CACS of less than 100 AU, both PCI and CABG were rarely necessary (7% and <1%, respectively). The need for PCI significantly increased with a CACS of 100 AU or higher (33%, 47%, and 44%, for the CACS cut-off values of 100 AU, 400 AU, and 1000 AU), and for CABG, only

**TABLE 2**

<table>
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<tr>
<th>CACS Cut-off</th>
<th>Event Occurrence (%)</th>
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<tr>
<td>0–99 AU</td>
<td>8%</td>
</tr>
<tr>
<td>100–399 AU</td>
<td>39%</td>
</tr>
<tr>
<td>400–999 AU</td>
<td>68%</td>
</tr>
<tr>
<td>≥1000 AU</td>
<td>91%</td>
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**FIGURE 2** Kaplan–Meier curves showing survival without major adverse coronary events (composite of cardiac death, nonfatal myocardial infarction, and revascularization) according to coronary artery calcium score (CACS, expressed in Agatston units [AU]).

**FIGURE 3** Receiver-operating characteristic curve for the use of coronary artery calcium score (CACS) to predict a primary outcome event. For a CACS of 92 Agatston units (white dot), sensitivity was 90.1%; specificity, 82.6%; and the area under the curve, 0.93.
for CACS of 1000 AU or higher (6%, 12%, and 50%, respectively).

Hospitalization for unstable angina was necessary in 45 patients (7.7%), and for stable angina, in 107 subjects (18.2%). In both cases, the majority of the events occurred in patients with a CACS of 1 AU or higher: for unstable angina, the distribution was 0.8% vs 28.9% (P < 0.001) in those with a CACS of 0 AU vs those with a CACS of 1 AU or higher, and for stable angina—2.5% vs 12.3% (P < 0.01). In the group with a CACS of 0 AU, coronary angiography was performed in 3.3% of the patients, and in those with a CACS of 1 AU or higher—in 45.3% (P < 0.001).

**DISCUSSION** In a cohort of 588 consecutive patients at an intermediate risk of CAD, presenting with symptoms suggestive of CAD and with no established coronary anatomy, we found that the presence of coronary artery calcium in general, but in particular in the subgroups with incremental CACS values, is an excellent predictor of MACE at medium term. In our cohort, CACS was treated as the first noninvasive diagnostic test. Any previous noninvasive tests were not taken into consideration.

Notably, in our group, no MACE occurred in patients with a CACS of 0 AU. This is in contrast to the results of the Coronary CT Angiography Evaluation for Clinical Outcomes (CONFIRM) registry, in which symptomatic patients with a CACS of 0 AU had the same MACE rate as those with positive CACS values. It has to be noted, however, that the CONFIRM findings concerned only a small group of patients (1.8%) in whom obstructive coronary lesions were present. The CORE64 study reported a high (19%) proportion of patients with coronary stenosis in the absence of calcium, but their population was different than ours because it only included patients with clinical indications to invasive coronary angiography.

Our findings are compatible with those of Sarwar et al., who reported a low, 1.8% incidence of MACEs during the 42-month follow-up in a large group of symptomatic patients with no coronary calcium. In this group, the relative risk of cardiac events was very low (RR, 0.09; P < 0.0001) when compared with patients with positive CACS values.

The absence of MACE in our group with a negative CACS can be explained by the age of our population. Noncalcified obstructive or nonobstructive plaques are mostly present in patients younger than 45 years, whose contribution to our group was low.

In our study, a CACS of 1 AU or higher was associated with a risk of MACEs. However, only 8% of the patients with a CACS of 1 AU or higher but lower than 100 AU experienced MACEs. We found that in symptomatic subjects, the optimal cut-off value for the prediction of MACE is 92 AU. This is similar to the findings of Keelan et al., who reported a 3-fold increase in the incidence of hard cardiac events in patients with a CACS of more than 100 AU than in those with a CACS of less than 20 AU. Also Schmermund et al. found a significant increase in MACEs in symptomatic subjects with CACS exceeding 100 AU.

Traditionally, subjects with a CACS of less than 100 AU, 100–399 AU, and exceeding 400 AU are classified as being at low, intermediate, and high risk, respectively. These values, however, were established for asymptomatic subjects and were based on the diagnostic rather than prognostic predictors.

We confirmed that these strata are similarly useful for risk stratification in symptomatic patients. Our results are in accordance with the data published by Al-Mallah et al., whose study groups had similar characteristics (symptomatic, mean age of 56 years, 50% of men, 56% of patients with a CACS of 0 AU). They found that a CACS exceeding 400 AU improved prediction of hard cardiac events beyond clinical data. In our study, the introduction of an additional stratum with a CACS exceeding 1000 AU enabled the identification of a very high-risk group, with an almost 100% rate of MACE.

Our results indicate that coronary artery calcium scanning is a useful first-choice noninvasive method for risk stratification of symptomatic patients suspected of CAD. The widespread use of this approach is, however, limited by the radiation exposure, availability, and cost. The effective radiation dose with a coronary artery calcium scan should average at about 1.0 to 1.5 mSv, and should not exceed 3.0 mSv, which is less than the amount of radiation received each year from

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**TABLE 2** Incident primary endpoint component events in relation to the presence of coronary calcification

<table>
<thead>
<tr>
<th>Event</th>
<th>All patients (n = 588)</th>
<th>CACS = 0 AU (n = 239)</th>
<th>CACS ≥1 AU (n = 349)</th>
<th>P value (CACS = 0 AU vs CACS ≥1 AU)</th>
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<tr>
<td>total events</td>
<td>119 (20.2)</td>
<td>0</td>
<td>119 (34.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cardiac death</td>
<td>1 (0.2)</td>
<td>0</td>
<td>1 (0.3)</td>
<td>–</td>
</tr>
<tr>
<td>MI (fatal or nonfatal)</td>
<td>14 (2.4)</td>
<td>0</td>
<td>14 (4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCI</td>
<td>72 (12.2)</td>
<td>0</td>
<td>72 (20.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CABG</td>
<td>33 (5.6)</td>
<td>0</td>
<td>33 (9.5)</td>
<td>&lt;0.001</td>
</tr>
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**Abbreviations:** CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention; others, see **TABLE 1**
natural sources. In our study, these standards have been observed. With current technical improvements, radiation exposure during coronary calcium scanning may be as low as that in mammography (0.8 mSv). Still, it should be stressed that this is not always achievable, and even low radiation doses cannot be neglected.

Our study has certain limitations. Because it is a single-center, medium-sized registry, selection bias is likely, despite the inclusion of consecutive patients. Most importantly, however, coronary revascularization procedures, which are a component of MACEs, might have been influenced by the CACS findings. However, other authors also used MACE as the primary endpoint, since in the intermediate-risk populations, death and MI rates are low, and the outcome is mostly driven by the need for revascularization.

We conclude that in patients with symptoms suggestive of CAD in whom coronary anatomy is not known, and who belong to the intermediate risk group, the CACS measurement may be considered the first-line test to assess the risk of MACE.

Contribution statement MS and ZP contributed to the concept and design of the study. All authors were involved in data collection and analysis. ZP drafted the paper. All authors edited and approved the final version of the manuscript.

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ARTYKUŁ ORYGINALNY

Wartość prognostyczna wskaźnika uwapnienia tętnic wieńcowych u objawowych pacjentów z podejrzeniem choroby wieńcowej

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