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ORIGINAL PAPER

Predictive value of coronary calcifications for future cardiac events in asymptomatic patients: underestimation of risk in asymptomatic smokers

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Abstract

Coronary calcification (CAC) is an established marker for coronary atherosclerosis and has a highly specific predictive value for cardiovascular events. This study aimed to determine the predictive value in the specific group of asymptomatic smokers in comparison to non-smokers. We included 1432 asymptomatic individuals (575 women, 857 men, age 59.2 ± 7.7 years.) in this study. Coronary calcification was calculated by multi-slice computed tomography following a standardized protocol including calcium score (CS). Coronary risk factors were determined at inclusion. After mean observation time of 76.3 ± 8.5 months the patients were contacted and evaluated for cardiovascular events (myocardial infarction, cardiac death and revascularisation). Mean CS was 231 ± 175 in smokers and 239 ± 188 in non-smokers. Cardiovascular events were found in 14.9% of our patients and there were significantly more events in smokers (119 events, 8.3%) than in non-smokers (94 events, 6.6%, p = 0.001). CS > 400 showed a hazard ratio for future cardiac events of 5.1 (95% CI 4.3–7.6) in smokers and 4.4 (95% CI 3.4–6.2) in non-smokers, p = 0.01. Also in smokers determination of CAC is a valuable predictor of future cardiovascular events. In our study smokers showed throughout all score groups a significantly higher risk compared to non-smokers with equal CS. Therefore, CS may underestimate the risk for future cardiac events in smokers compared to non-smokers.

Keywords Coronary calcifications · Agatston score · Smokers · Risk stratification

Abbreviations

ATP III	Adult treatment panel
CS	Coronary calcium score
CAC	Coronary calcium
CAD	Coronary artery disease
COPD	Chronic obstructive pulmonary disease
MI	Myocardial infarction
PROCAM	Prospective Cardiovascular Muenster Study

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Introduction

Coronary artery disease (CAD) is the leading cause of death in western industrialized countries [1]. Accurate identification of patients at risk for cardiovascular events is crucial to establish an effective prevention [2, 3], especially in high risk groups like smokers.

Coronary Calcification (CAC) is an established marker of coronary atherosclerosis. Calcium in the coronary artery is pathognomonic of coronary atherosclerosis, confirmed by histopathology and intravascular ultrasound studies [4, 5]. A simple and reliable quantification of CAC is achieved noninvasively by cardiac computed tomography [2, 3, 6]. This offers a relatively easy possibility to obtain the individual plaque burden of a patient. Several studies showed an association between future cardiovascular events and the amount of CAC [2, 3, 7]. Coronary

calcium screening can therefore be used for risk prediction of cardiovascular events [2, 3]. The determination of the individual amount of CAC by calcium score (CS) provides a more accurate risk prediction for the individual patient than conventional risk factors scores like ATP III score or PROCAM score [3]. The absence of CAC, a CS of 0, is associated with an excellent cardiovascular prognosis [7]. An increasing score, e.g. above the 75. percentile or above 400 reveals a highly elevated cardiovascular risk independent from underlying risk factors [2].

Cigarette smoke as one main risk factor for atherosclerosis causes several effects on the vascular endothelium which leads to endothelial dysfunction and coronary atherosclerosis. These effects differ from other risk factors. Smoking causes reduced nitric oxide bioavailability in the endothelium and leads to an increased vascular inflammation and procoagulant environment [8, 9]. Increased proinflammatory markers, such as tumor-necrosis factor-α, interleukin 1β, C-reactive protein can be found in smokers. Cigarette smoke leads to an increased leucocytes endothelial adhesion, vascular remodeling by matrix metalloproteinases and affects the adaptive and innate immune response [10, 11].

Therefore, this retrospective study addresses the question of reliability of CS as a risk prediction model in smokers in comparison with non-smokers. We evaluated the predictive value of CAC for future cardiovascular events in smokers and non-smokers.

Methods

Study protocol

The research protocol was approved by the local Clinical Institutional Review Board and complies with the declaration of Helsinki. We retrospectively examined 2776 consecutive patients referred to the outpatient department of our hospital by a primary care physician for preventive cardiological examination between 2000 and 2005. All patients underwent clinical examination, ECG, stress ECG, and echocardiography. 1308 patients showed either typical clinical symptoms of CAD or CAD was suspected in the examinations mentioned above, so that a coronary angiography was recommended. As we intended to concentrate on the prognostic value of coronary calcium, not on the diagnostic value of coronary calcium for coronary artery disease we excluded these patients with known or suspected coronary artery disease. The remaining 1468 asymptomatic patients were included in our study after they provided written consent to undergo a multi-slice computed tomography following for determination of the CS and follow-up interview.

Risk factors

For all patients we evaluated conventional cardiovascular risk factors by personal interview and screening of medical records. In addition, arterial blood pressure, LDL cholesterol level, HDL cholesterol level, triglyceride level, and blood glucose level were determined in the fasting state. Smokers were defined as active smokers on the beginning of the observation period. We calculated the 10-year risk of coronary events described by the Adult Treatment Panel III (ATP III risk). The ATP III risk was calculated according to the National Cholesterol Education Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) [12].

Coronary artery calcium scanning

CAC scanning was performed using a Siemens multi-slice CT scanner (Somatron Sensation 4 or 16, Siemens Medical Solutions, Forchheim Germany) in the high-resolution mode. ECG-triggered images of 100 ms duration were acquired at 80% of the R–R interval during one end-inspiratory breath-holding period. A total of 40 3 mm-thick slices were obtained covering the whole heart. Coronary calcifications were automatically defined as lesions with a density > 130 HU in more than 3 adjacent pixels. For quantification of coronary calcium, the Agatston score was calculated, which constitutes the product of the lesion´s surface area and a weighting factor ranging from 1 to 4, which was assigned according to the peak density of the lesion [13].

Clinical follow-up

Study patients were contacted after a mean observation time of 76.3 ± 8.5 months. Cardiovascular events were assessed using a standardized telephone interview. In case of hospital admission or further cardiologic examinations the patient's medical records were reviewed for complaints of chest discomfort, dyspnoea, myocardial infarction, and coronary revascularisation.

Clinical endpoints

The primary endpoint was a combined endpoint of cardiac events containing cardiac death, myocardial infarction, and revascularisation. MI was defined using the WHO-Monica definition as the presence of at least 2 of the following: prolonged chest pain leading to hospital admission, specific ECG changes, elevation of serum creatine kinase levels up to twice the upper limit with an elevated creatine kinase-MB fraction or troponin level without prior coronary

intervention. Death due to coronary artery disease was considered if the death was proved to be due to coronary atherosclerosis by autopsy, occurred within 1 h after onset of prolonged severe chest pain, or occurred during hospital admission because of MI. Revascularisation (percutaneous coronary intervention or coronary artery bypass graft) was evaluated by the standardized telephone interview and the patients' medical records. Coronary interventions had to be confirmed by reports of the performing physician.

Statistics

Statistical analyses were performed using the SPSS software package (version 19.0, SPSS Inc. Chicago, Illinois). CS was expressed as mean score ± standard deviation except where indicated. Because of the non-normality, statistical analysis was performed on the base 10 log of the transformed Agatston score + 1. To compare score values in different risk groups we used the Wilcoxon signed rank test for unpaired data. We performed a two tailed test. A p-value under 0.05 was considered to indicate statistical significance.

We used logistic regression analysis in a univariate and multivariate model to calculate the risk ratio estimates and 95% confidence intervals for cardiac death, MI and revascularisation in dependence of different score groups (patients with a score of 0 served as the reference group) and to calculate the risk ratio of cardiovascular risk factors (patients without cardiovascular risk factors served as the reference group) for calcium scores above 400.

Additionally, we calculated the risk ratio estimates and 95% confidence intervals for different score groups in smokers and non-smokers adjusted for sex, age, and coronary risk factors including hypertension, hypercholesterolemia and diabetes. To verify the assumption of proportional hazards we performed an analysis of the calculated risk ratios as described by Hosmer and Lemeshow. To account for the inflation of the type I error due to multiple testing we performed the Bonferroni adjustment. The significance level was set at 0.05/4 = 0.0125.

Results

1432 individuals (575 female and 857 male, age 59.2 ± 7.7 years) of the initially 1468 included patients completed the follow up. 36 patients (17 of 748 non-smokers and 19 of 720 smokers) could not be contacted for follow-up examination. 8 of these patients died of non-cardiac death (5 non-smokers and 3 smokers). The mean observation time was 74.3 ± 9.3 months. The baseline characteristics and distribution of cardiovascular risk factors are shown in Table 1. The mean number of risk factors was 1.5 in non-smokers and 2.6 in smokers. There was no difference in age, risk factor distribution, and CAC score between these patients that completed the follow up and those that did not finish the study.

The mean CAC score was 238 ± 180 in all patients. Figure 1 depicts a CT scan of a patient with a CAC score of 518. There was no difference in CAC score between smokers and non-smokers (231 ± 175 and 239 ± 188, p = 0.25). Coronary calcifications could be excluded in 233 individuals (110 smokers and 123 non-smokers, p = 0.15). During the observation period no patient with exclusion of coronary calcifications died because of cardiac death or suffered from MI.

213 cardiovascular events could be observed. There was a significant higher rate of all cardiovascular events in smokers than in non-smokers (119 events vs. 94 events, p = 0.001). 19 smokers and 15 non-smokers died of cardiac death (p = 0.03). 49 patients suffered from MI. A significant

Table 1 Baseline characteristics of 1432 patient included in the study

	All patients		Non-smokers		Smokers		p-value
	n	%	n	%	n	%	
Patients	1432		731	51	701	49	
Male	857	59.8	421	29.4	436	30.4	0.28
Female	575	40.2	310	21.6	265	18.5	0.31
Age (years)	59.2 ± 7.7		58.9 ± 7.8		59.7 ± 7,5		0.39
BMI (kg/m)	27.1 ± 5		26.9 ± 4.8		27.4 ± 5		0.21
Arterial hypertension	759	53	380	26.5	379	26.5	0.2
Hyperlipidemia	592	41.3	307	21.4	285	19.9	0.31
Diabetes	209	14.6	109	7.6	100	7	0.19
Family history of CAD	688	48	328	22.9	360	25.1	0.17
Mean number of risk factors	2		1.5		2.6		< 0.001
ATP III risk score	12.6 ± 4.6		10.6 ± 4.0		14.7 ± 5.2		< 0.01
CAC-score	238 ± 180		239 ± 188		231 ± 175		0.25

CAD coronary artery disease, ATP III risk score

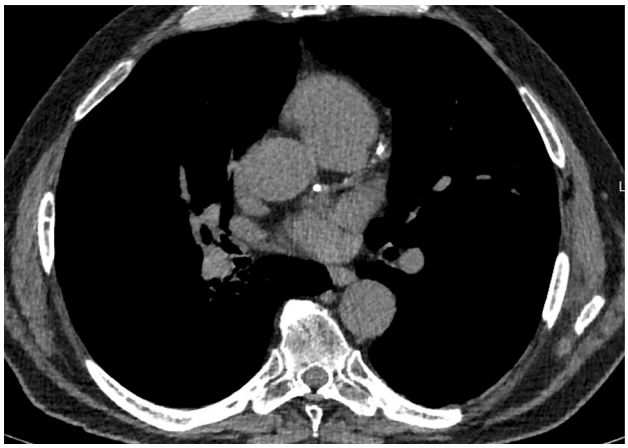

Fig. 1 Extended coronary calcification in a smoker. Calcium score was 518

higher frequency could be observed in smokers than in non-smokers (29 MI in smokers, 20 in non-smokers, p = 0.01). Myocardial revascularisation was performed in 130 patients and smokers had a higher frequency in comparison to non-smokers (71 patients vs. 59 patients, p = 0.01). All events are depicted in Table 2.

Table 3 depicts the risk ratio of different risk factors for a calcium score above 400 in a multivariate analysis. We could calculate a significant correlation between a score above 400 and age, male sex, hyperlipidaemia, diabetes, smoking, and hypertension. Thereby age (0.201 ± 0.03), male sex (0.227 ± 0.07), and also smoking (0.283 ± 0.028) had a relatively small risk ratio compared to hyperlipidaemia (0.748 ± 0.158), diabetes (0.440 ± 0.074), and hypertension (0.39 ± 0.077).

Table 4 shows the hazard ratio for cardiovascular events in different score groups adjusted for sex, age, and coronary risk factors including hypertension, hypercholesterolemia and diabetes. We found a strong correlation between an increasing CAC score and the rising hazard ratio for cardiovascular events within in the study collective. We had a very high negative predictive value for a CAC score of 0. No events could be observed in non-smokers and 1 event in smokers with exclusion of coronary calcium (CAC score 0). The hazard ratio for cardiovascular events increases

Table 3 Risk ratio of different risk factors adjusted for age, sex, hyperlipidaemia, diabetes, hypertension and smoking for a calcium score above 400 in a multivariate analysis

	Risk ratio	p-value
Age	0.201 ± 0.03	< 0.001
Male sex	0.227 ± 0.07	< 0.001
Hyperlipidaemia	0.748 ± 0.158	< 0.001
Diabetes	0.440 ± 0.074	< 0.001
Hypertension	0.390 ± 0.077	< 0.001
Smoking	0.283 ± 0.028	< 0.001

constantly with the CAC score in both groups (see Fig. 2). In patients with a low CAC score between 1 and 100 we calculated a hazard ratio of 1.3 (CI 0.9–1.9) for non-smokers and 1.5 (CI 1.0–2.2) for smokers. The hazard ratio increased up to 4.4 (CI 3.6–6.2) for non-smokers and 5.1 (CI 4.3–7.6) for smokers for CAC score above 400 (p = 0.01).

In all score groups we found a significant higher hazard ratio in smokers compared to non-smokers. The difference increased with the CAC score and hazard ratio.

Discussion

The determination of coronary calcification is an established method for the individual evaluation of cardiovascular risk [14–17].

It is the strength of CAC scoring, that the individual extent of CAC reflects not only the individual extent of atherosclerosis and but also reflects the individual risk of future cardiovascular events, independent of the underlying risk factors. Therefore, CAC scoring has been shown to be superior in risk stratification compared to score systems using cardiovascular risk factors like ATP II risk score or PROCAM score [2, 3].

The independence of CAC and cardiovascular risk from individual risk factors could be shown very clearly by Silverman et al. [18]. As expected, they found a high correlation between the CAC and coronary heart disease. The risk of cardiovascular events increased with CAC, independent from the number of underlying risk factors. Even in patients

Table 2 Event rates of 1432 patient included in the study

	All patients		Non-smokers		Smokers		p-value
	n	%	n	%	n	%	
CV events (n)	213	14.9	94	6.6	119	8.3	0.001
Myocardial infarction (n)	49	3.4	20	1.4	29	2	0.01
Cardiac death (n)	34	2.4	15	1	19	1.3	0.03
Revascularisation (n)	130	9.1	59	4.1	71	5	0.01

Table 4 Cox proportional hazards model predicting cardiovascular events in different calcium score groups for non-smoker and smoker adjusted for age, sex, hyperlipidaemia, diabetes, hypertension

Calcium-score	Non-smokers				Smokers				
	Patients (n)	Events (n)	Hazard ratio	95% CI	Patients (n)	Events (n)	Hazard ratio	95% CI	p-value
0	123	0	1		110	1	1		
1–100	146	9	1.3	0.9–1.9	138	10	1.5	1.0–2.2	0.03
101–400	245	32	2.9	2.2–4.0	240	41	3.5	2.4–4.2	0.01
> 400	217	53	4.4	3.4–6.2	213	67	5.1	4.3–7.6	0.01

CI confidence interval

with three conventional risk factors and a CAC score of 0 the hazard ratio was only 1.4 for future cardiovascular events. In contrast, patients with no conventional risk factors and a CAC-score > 300 the hazard ratio for hard cardiovascular events was 8.1 [18]. This again demonstrates the high accuracy of CAC in the prediction of cardiovascular events compared to conventional risk stratification. Similar results were found in several studies [19–21]. Based on these findings an almost identical number of cardiovascular events can be assumed in patient with similar scores.

Because of the special pathophysiological mechanisms in vascular disease induced by smoking, we wanted to examine, if this risk factor independent prediction of cardiovascular events is also reliable in smokers [9].

We examined an asymptomatic population without known cardiovascular diseases on study entry. The risk factor distribution was comparable to former studies on CAC and typical for a population in a western industrialized country.

Apart from smoking there was no difference in risk distribution between smokers and non-smokers [17, 19, 22, 23].

As expected, we could identify age, male sex, and conventional risk factors (hyperlipidaemia, hypertension, diabetes and smoking) as independent risk factors for an elevated CAC. It was conspicuous, that smoking possesses a relatively small risk ratio (0.283 ± 0.028) for a CAC above 400 compared to hypertension, diabetes, and hyperlipidaemia.

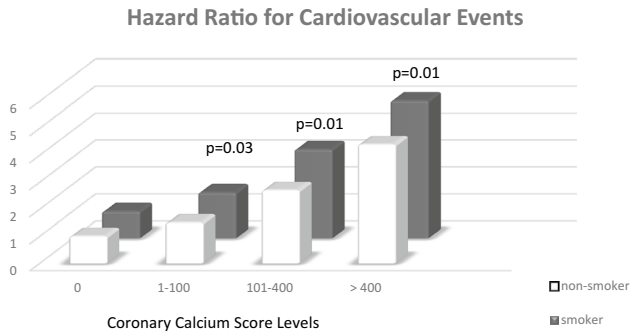

Fig. 2 Cox proportional hazard radio for cardiovascular events associated to coronary calcium score levels in smoker and non-smoker

This already indicates, that CAC might not fully reflect the clinical impact of smoking on atherosclerosis (Table 3).

Regarding the prediction of cardiovascular events coronary calcifications reflected the cardiovascular risk in both smokers and non-smokers: Patients without coronary calcification had an extremely low risk of cardiovascular events during the whole observation period. With an increase of CAC also the risk for future cardiac events increased, independent of underlying cardiovascular risk factors (Table 4).

Thus, risk stratification by coronary calcium is also reliable in smokers. These finding comply with a prior study in patients with COPD undergoing lung cancer screening with low dose chest CT and determination of coronary calcification [24, 25].

However, smokers showed throughout all score groups a significantly higher risk compared to non-smokers with equal scores, also after correction from concomitant risk factors (see Fig. 2). Coronary calcium score alone underestimated the cardiovascular risk in smokers. This finding stands in contrast to the previous assumption, that equal scores are associated with an equal risk for future cardiovascular events.

Several studies have analysed the predictive value of CAC. Although a specific evaluation for each risk factor is not available, similar effects as described above for smoking have not been described for diabetes or hyperlipidaemia. All studies found a strong correlation of CAC and future events illustrated the specific strength of CAC screening: the reliable quantification of the individual cardiovascular risk, independent of the underlying known or unknown risk factors [19, 26]. More detailed analysis should be performed to assess possible under- or overestimation in specific risk groups.

The further increased risk in smokers compared to non-smokers with equal scores might be attributed to the specific effects of smoking in addition to the enhancement of conventional atherosclerosis. For example, cigarette smoking induces differential inflammatory signals to the endothelium and activates procoagulant factors [9, 10, 27].

Limitations

The study population consisted of a Caucasian population sent to our institution for a preventive cardiovascular medical check-up and is therefore pre-selected and may not applicable to the general population. However, due to distribution of risk factors and coronary calcification our study population reveals a typical population with cardiovascular risks in Europe. Only few patients were lost to follow-up. There was no difference in smokers and non-smokers in patients who were lost to follow-up. Patients were informed about their calcium score and the authors couldn´t exclude a possible change in patients' risk behaviour after this information. However, this specific effect might be equal for all groups. Smoking was not quantified by packyears and therefore, only information of the cumulative influence of smoking could be offered.

Conclusion

Coronary calcium is a highly predictive marker of future cardiovascular events in smokers. As described in non-smokers coronary calcium is superior to conventional cardiovascular risk factors and cardiovascular risk score like the ATP III score in the prediction of cardiovascular events. Still the event rate in smokers is significantly higher compared to non-smokers with equal calcium scores, indicating that coronary calcium alone underestimates the cardiovascular risk in smoker.

Compliance with ethical standards

Conflict of interest Author GSZ has received research grant by Actelion pharmaceutical. Author GSZ has received a speaker honorarium from Novartis, BerlinChemie, Roche and Boehringer Ingelheim. The other Authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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