Calcium score in the Prediction of Adverse Events in Patients with Suspected Coronary Artery Disease

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Abstract

Background: Coronary Artery Disease (CAD) is an important cause of morbidity and mortality worldwide, and models to predict events based on risk factors have limited capacity. Among the new markers available in clinical practice, the Calcium Score (CS) is characterized as a potential tool for predicting adverse events and can add value to existing models.

Objective: Determine the value of CS in predicting adverse clinical outcomes in patients with suspected CAD.

Methods: The study prospectively evaluated 380 consecutive patients with a mean age of 57.5 years, including 114 men with suspected CAD from January 2008 to June 2012. Adverse event was defined as the presence of cardiovascular death, coronary artery bypass grafting and hospitalization for Acute Myocardial Infarction (AMI).

Results: During a mean follow-up of 15 months, there were 57 cardiac events. In the multivariate analysis, using the Cox regression model, NYHA functional class — class II, III and IV (HR 2.18 95% CI 1.28 — 3.72), smoking (HR 2.72 95% 1 , 54 to 4.83) and CS (HR 8.62 95% CI 3.16 — 23.51) were predictors of adverse clinical outcome.

Conclusion: CS in patients with suspected CAD presented a value independent from conventional risk factors in the prediction of adverse clinical events and may prove useful in risk stratification of patients. (Arq Bras Cardiol: Imagem cardiovasc. 2014;27(3):191-196)

Keywords: Probability; Coronary Artery Disease/mortality; Calcium/adverse effects; Prognosis.

Introduction

According to the World Health Organization (WHO), cardiovascular disease is the leading cause of mortality worldwide, with significant socioeconomic impact[1]. Diagnosis of Coronary Artery Disease (CAD) takes into account the presence of symptoms, risk factors and complementary diagnostic methods, which generally use stress mechanisms, with the goal of diagnosing the presence of myocardial ischemia. A recent multicenter study demonstrated that, based on current algorithms used for the evaluation of patients with suspected CAD, about 40% of patients undergoing coronary angiography showed no coronary obstruction[2]. Calcium score (CS) stands out as a method for risk stratification and prediction of adverse cardiac events in asymptomatic patients, especially in intermediate-risk groups[3-5]. However, the addition of CS to traditional risk factors in symptomatic patients with suspected CAD is not yet fully established in the Brazilian population[6].

This study evaluates the calcium score potential in predicting adverse events in patients with suspected Coronary Artery Disease (CAD) to Computed Tomography Angiography (CTA).

Material and Methods

Study population

From January 2008 to December 2012, 430 patients with suspected coronary artery disease were enrolled in a cohort with prospective data collection. Patients were referred for the test for various indications, including evaluation of symptoms and signs of heart disease (abnormal resting ECG or positive stress test). Patients with a prior diagnosis of coronary artery disease (patients who underwent angioplasty, coronary artery bypass grafting or who were hospitalized due to acute myocardial infarction), pregnant patients, patients allergic to contrast and with renal failure were excluded from the study. The study was submitted and approved by the ethics committee of the institution.

Data collection

On admission, standardized data about the presence of cardiac risk factors were collected for each individual. Hypertension was defined as a documented history of high

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blood pressure or treatment with antihypertensive drugs. Diabetes mellitus was defined by means of previous diagnosis of diabetes and/or use of insulin or oral hypoglycemic agents. Dyslipidemia was defined as a history of dyslipidemia or current treatment with lipid-lowering drugs. Smoking was considered the current habit of smoking or smoking cessation within three months before the test. To define the functional class, the classification based on the New York Heart Association (NYHA) was used. Family history of coronary artery disease was defined as the presence of CAD in first-degree relatives younger than 55 (men) or 65 (women).

Adverse clinical outcomes of the patients were obtained through telephone interview and were classified as the occurrence of: 1) death; 2) coronary artery bypass grafting; and 3) hospitalization for Acute Myocardial Infarction (AMI).

Calcium Score

The study used 64-channel computer tomography scanner (Aquilion, Toshiba Medical Company, Japan), and images of the entire heart were acquired in apnea of 6 to 8s. Calcification was defined as a hyperattenuating lesion with signal intensity above 130 Hounsfield units (HU) and an area ≥ 3 adjacent pixels (at least 1 mm^2) calculated from the weighted sum of densities above 130 HU (Agatston score). CS was stratified into groups: 1 = zero; 2 = 1 to 99; 3 = 100 to 399 = 4 and ≥ 400.

Statistical Analysis

Initially, the patient data were analyzed using descriptive statistical techniques, with calculation of means and Standard Deviations (SD) for quantitative variables and calculating percentages for qualitative variables. For each explanatory variable (age, sex, family history, coronary syndrome, NYHA class, smoking, dyslipidemia, high blood pressure (HBP), diabetes, atherosclerosis, physical inactivity and calcium score) univariate analysis was performed. The Cox regression model was used to assess the value of clinical variables and calcium score in predicting cardiac events. Initially, univariate analysis of clinical variables and CS variables was performed to identify potential predictors. Hazard ratio was calculated with a confidence interval of 95% as an estimate of the risk associated with a particular variable. Subsequently, multivariate analysis was performed including all variables selected in the univariate analysis. Kaplan-Meier curves were used for analyzing the rate of events in time. Statistical analyzes were performed using the software SPSS (version 18.0, SPSS Inc., Chicago, Illinois) and $p < 0.05$ were considered statistically significant.

Results

During the study period, 430 patients were initially selected, and 21 were excluded for indication of post coronary artery bypass grafting evaluation and 29 were excluded for indication of post-angioplasty evaluation, providing a final sample of 380 patients. The mean age was 57.5 ± 12.2 years, and 266 men (70%) were evaluated. Among the patients evaluated, 113 were smokers (30%); 229 had dyslipidemia (60%); 205 were hypertensive patients (54%); 53 had diabetes (14%); and 153 were not physically active (40%). The main indications were chest pain (31.4%), altered exercise test (14.9%), check-up (13.9%), altered myocardial scintigraphy (27.6%), and altered stress echocardiography (11.3 %). Mean follow-up was 15 months (range of 3 - 43 months) in 345 patients (90.4%), during which 57 patients had some type of adverse cardiac event (15%).

During follow-up, 57 events occurred. Only adverse clinical outcomes occurring after three months of follow-up were selected. There were three deaths, seven myocardial infarctions, 15 episodes of unstable angina, 26 angioplasties and six coronary artery bypass grafting surgeries. Overall patient characteristics are summarized in Table 1. The variables that were significant in the univariate analysis were included in multivariate analysis. Independent predictors of adverse cardiac events obtained in the multivariate analysis are shown in Table 2. We can observe that the NYHA functional class, comparing the functional class I with classes II, III and IV (HR 2.18 95% CI 1.28 — 3.72), smoking (HR 2.72 95% CI 1.54 — 4.83) and calcium score comparing groups 1 and 3 (HR 6.15 95% CI 2.19 — 17.25) and between groups 1 and 4 (HR 8.62 95 % 3.16 — 23.51) were predictors of adverse clinical outcome. Figure 1 shows the different curves related to event-free survival compared to CS (log-rank = 0.001)

Discussion

Our study demonstrated that CS has an independent role in the prediction of adverse events in patients with suspected CAD, compared with traditional risk factors.

The reference standard test for diagnosing the presence and extent of CAD is Invasive Coronary Angiography (ICA), but it has some non-negligible risks — with risk of complications of 1.7% and mortality of 0.11[7].

Other noninvasive tests also provide useful prognostic information for risk stratification. Myocardial scintigraphy showed an annual mortality or infarction rate smaller than 1% per year in normal studies. Stress echocardiography has an excellent negative predictive value for the occurrence of adverse cardiac events[8-11]. CTA has recently demonstrated an excellent prognostic value in predicting events[12-14].

The presence of calcification in the coronary arteries is equivalent to the presence of atherosclerosis, which can be measured noninvasively using computed tomography[15]. The evaluation of CS is based on a non-contrast acquisition of a series of axial computed tomography 3-mm thick sections covering the whole extension of the heart, with radiation doses ranging from 0.9 to 1.1 mSv defined as a hyperattenuating lesion with signal intensity above 130 HU and an area of (at least 1 mm^2). Several population studies have shown that CS has a significant association with the occurrence of major cardiovascular events in medium and long term follow-up.[16-20] Its use as a diagnostic tool, however, is more controversial, with studies showing that, particularly in younger patients or in populations with high prevalence of CAD, as well as inappropriate positive VPP, CS also features VPN insufficient to rule out the presence of significant obstructive disease.[21].

Our study showed that only 3.1% of patients with zero CS presented adverse events, with VPN of 98.1%, and values equal to or greater than 400 showed HR of 8.63

(95% CI 3.164 — 23.514), demonstrating the excellent stratification capability of the CS. Blaha et al. noted that zero CS predicts an excellent survival with event rates of approximately 1% in 10 years, and HR for all-cause mortality among patients with CS greater than 400 compared with zero CS was 9.65 (95% CI 7.46 —12.5)[22]. Hou et al. found probability of events in three years, a value of 33.8% for CS greater than 400 and only 2.1% for zero CS. HR for CS of 100 to 400 and greater than 400 compared to zero CS were 9.21 (95% CI 6.5 — 13) 22.22 (95% CI 16.08 — 30.71), respectively[23].

Keelan et al.[24], in a study with 288 symptomatic persons undergoing CTA (computed tomography angiography) in a follow-up of 6.9 years, showed that age and CS were the only independent predictors of future coronary events (RR 3.20, 95% CI 1.71 — 8.71). In our study, we found independent risk factors for adverse events such as smoking and NYHA. These results demonstrate the limitation of traditional risk factors in the determination of adverse events in patients with suspected coronary artery disease events, demonstrating the additive role of CS.

Although CS is associated with an increased risk of coronary events, its ability to predict cardiovascular events is not absolute. However, the absence of coronary calcification is associated with a very low probability of cardiovascular events. A systematic review of 49 manuscripts revealed the frequency of cardiovascular events among patients with zero CS, revealing the value of 0.56% for asymptomatic patients and 1.8% in symptomatic patients[25]. In our study, the frequency of adverse events with zero CS was 3.1%, confirming that our patients had moderate pretest probability in general.

Among the limitations of this study, we can mention the low rate of events, as well as a wide spectrum of different conditions associated with the referral for the test.

Table 1 – Baseline characteristics of the study population according to the occurrence of adverse clinical outcomes

	Patients without events n = 323	Patients with events n = 57	Hazard Ratio (95% CI)	P-value
Age	57.45 ± 12.19	63.31 ± 11.27	1.02 (1.00 — 1.04)	0.05
Male (n/%)	222 (68.7%)	44 (77.2%)	1.26 (0.70 — 2.29)	0.42
Family History	189 (58.5%)	33(57.9%)	1.10 (0.65 — 1.86)	0.731
Dyslipidemia	194 (61.4%)	35 (60.1%)	1.03 (0.61 — 3.54)	0.903
Smoking	13 (4%)	10 (17.5%)	3.49 (1.76 — 6.91)	<0.001
Hypertension	163 (50.5%)	42 (73.7%)	2.62 (1.45 — 4.74)	0.001
Diabetes	40 (12.4%)	13 (22.8%)	1.91 (1.03—3,54)	0.037
Atherosclerosis	49 (86%)	142 (44%)	7.07 (3.35—14.93)	<0.001
Physical inactivity	133 (41.2%)	20 (35.1%)	0.79 (0.46—1.35)	0.464
NYHA Class II / IV (n/%)	31 (11.2%)	25 (44.6%)	5.15 (3.04—8.74)	<0.001
Calcium Score				
0	157 (48.6%)	3 (5.2%)		<0.001
1 and <100	87 (26.9%)	9 (15.8%)	3.2 (1.07—9.54)	
≥ 100 and <400	44 (13.6%)	16 (28.1%)	9.73 (3.56—26.55)	
≥ 400	35 (10.8%)	29 (50.9%)	16.8 (6,48—43,74)	

NYHA: functional classification of Cardiac Failure of the New York Heart Association.

Table 2 – Multivariate analysis in the prediction of adverse clinical events

Variable	Hazard Ratio	95% confidence interval	Coefficient	Standard error of the coefficient	P-value
Calcium score group (1/2)*	2.49	(0.83—7.50)	0.916	0.56	0.103
Calcium score group (1/3)	6.15	(2.19—17.25)	1.817	0.52	0.001
Calcium score group (1/4)	8.63	(3.16—23.51)	2.155	0.51	0.000
Smoking	2.18	(1.28—3.72)	0.78	0.27	0.004
NYHA	2.73	(1.54—4.83)	1.00	0.29	0.001

*NYHA: functional classification of Cardiac Failure of the New York Heart Association; *Analysis of the calcium score groups was performed by comparing groups 2, 3 and 4 to group 1.*

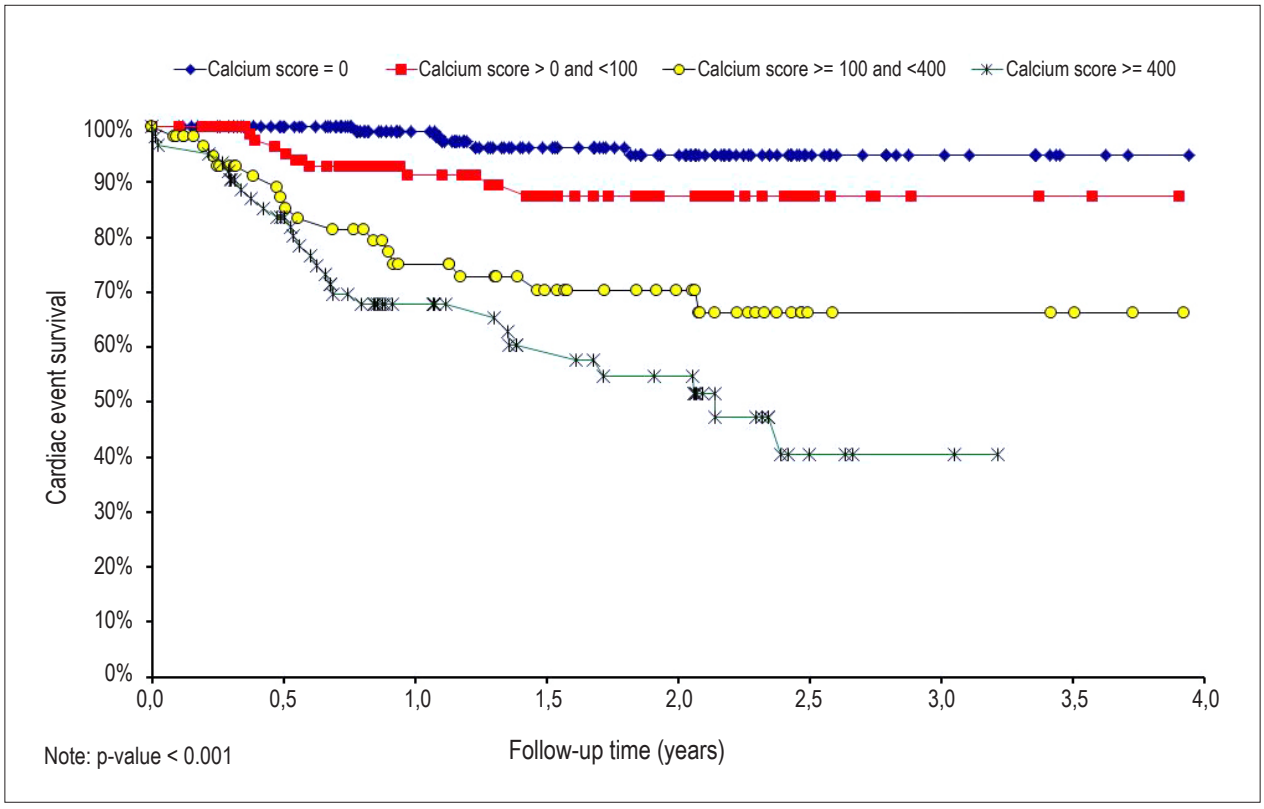

Figure 1 – *Comparison of event-free survival: analysis of calcium score.*

Future studies should address the prognostic role of CS in more homogeneous populations. Besides this, the study population was small. Studies in larger cohorts (with longer follow-up time) are clearly needed to confirm these results. The TCA results have the potential to influence the decision of referring the patients for coronary artery bypass grafting and may change the outcome in this study. However, we consider adverse clinical outcomes only those that occurred after three months' follow-up (15 months on average, ranging from 3 to 43 months).

In conclusion, the calcium score presented an independent value of conventional risk factors in the prediction of adverse clinical outcomes in patients with suspected CAD and may prove useful in risk stratification of these patients.

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