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Cardiac calcification by transthoracic echocardiography in patients with known or suspected coronary artery disease

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Abstract

Objectives: To estimate the correlation between the total heart calcification score index (CSI), assessed by echocardiography, left ventricle mass index (LVMI), Framingham risk score (FRS), and angiographically assessed coronary artery disease (CAD).
Background: Aortic valve and root sclerosis (AVS, ARS) and mitral annular calcium (MAC) detected by echocardiography have been associated with atherosclerosis. FRS is recommended for estimation of total coronary heart disease risk over the course of 10 years. The anatomic extent of CAD can be assessed with coronary angiography. Total and cardiovascular mortality risk increases with increasing LVMI.
Methods: 167 consecutive in-hospital patients (mean age 66.6±9.7 yrs, 119 men) underwent: 1) complete transthoracic echocardiography (TTE), with CSI assessment (from 0=normal to 10=diffuse calcification of aortic valve, mitral annulus and aortic root), 2) the FRS evaluation (FRS ≤ 10=low, FRS ≥ 11 and ≤20=average risk, and a FRS ≥ 21=high risk), and 3) coronary angiography (with Duke score evaluation, from 0=normal to 100=severe left main disease).
Results: The mean CSI of the entire population was 3.94±2.1, with a mean of 2.75±2 in patients at low risk, with a progressive increase in patients at average risk (4.11±2.2), at high risk (4.7±1.7), respectively. CSI was associated with the presence of CAD ($p=0.003$) and the presence of abnormal LVMI ($p=0.002$).
Conclusions: Echocardiographically assessed CSI is correlated to FRS, Duke score and LVMI and can provide a simple, radiation-free index of cardiovascular risk.

Keywords: Calcification; Echocardiography; Framingham risk score; Coronary artery disease

1. Background

Atherosclerotic disease is characterized by the accumulation of lipid material in the arterial wall resulting from autoimmune and inflammatory mechanisms [1]. More than 90% of these fatty plaques undergo calcification [2]. Vascular calcification is an active, cell-mediated process. Vascular smooth muscle cells retain pluripotential capability and can transform into osteoblast-like cells [3].

Calcified plaque in the coronary arteries is a marker of atheromatous-plaque burden and is predictive of future risk of cardiovascular events [4], which is frequently used in intervention trials, usually assessed with cardiac Computed Tomography or electron-beam tomography through coronary-artery calcium (or Agatston) score [5]. A recent consensus conference concluded that a calcification index should be developed, to facilitate the ability of the clinician to diagnose vascular and valvular calcification in order to predict which patients would have adverse cardiovascular outcomes [6]. Echocardiography is a low cost, portable, facile and

Abbreviations: AVS, aortic valve sclerosis; ARS, aortic root sclerosis; CAD, coronary artery disease; CSI, calcification score index; EF, ejection fraction of the left ventricle; FRS, Framingham risk score; LVMI, left ventricle mass index; MAC, mitral annulus calcification; TTE, transthoracic echocardiography.

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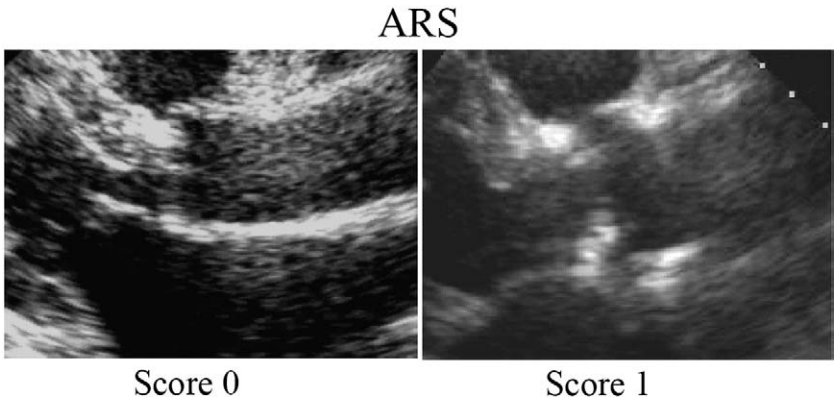

Fig. 1. Quantification of ARS — transthoracic parasternal long axis view; score 0 — normal aortic root, score 1 — enhanced echogenicity of the aortic root.

radiation-free technique with obvious potential to detect and quantify vascular and valvular calcifications.

The attachment points of the aortic and mitral valves to their respective annuli are sites of turbulent blood flow, where there is a tendency for atherosclerosis to initiate [7,8]. Mitral annulus calcification (MAC), aortic valve sclerosis (AVS), and aortic root sclerosis (ARS) detected by echocardiography, have been associated with atherosclerosis [9–11].

The aim of the present work is to evaluate a single and simple objective semi-quantitative echocardiographic cardiovascular Calcium Score Index (CSI), a new algorithm using the simple transthoracic echocardiography parameters (MAC, AVS, ARS), that could be used in the clinical routine for a better characterization of the risk of developing cardiovascular disease.

This echocardiography-based cardiovascular calcification index (CSI) was compared to time-honored clinical predictors of coronary artery disease, such as the Framingham Risk Score (FRS) [12], with established echocardiographic markers of risk, such as left ventricle mass index (LVMI) [13,14], and coronary angiographic descriptions of anatomic coronary artery disease, such as the angiographic Duke score [15].

2. Methods

2.1. Study population

We enrolled a total number of 214 consecutive patients, with suspected or known coronary artery disease, hospitalized in our Institute between February 2006 and March 2007. All these patients underwent: 1) complete transthoracic echocardiography in the first 24 h before reperfusion treatment in all the patients with a clinically stable condition, and in the previous 2 h in patients who needed urgent revascularization, 2) the Framingham risk score evaluation, and 3) coronary angiography. Patients with valvular stenosis (rheumatic or degenerative), prosthetic valves, or poor transthoracic acoustic window were excluded. 15 patients (7%) were excluded from the study due to a poor transthoracic acoustic window which did not allow an optimal visualization of the aortic root, the aortic valve and the mitral annulus. The presence of valvular stenosis (rheumatic or degenerative) and of a prosthetic valve was found in 32 patients (15%) who were excluded from the study population.

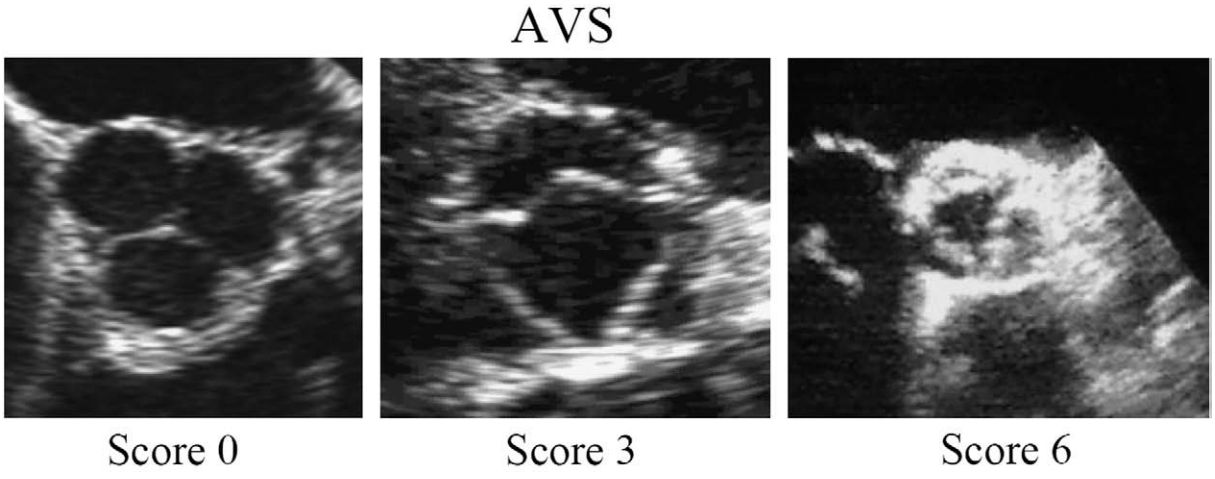

Fig. 2. Quantification of AVS — transthoracic parasternal short axis view at the level of the great vessels; score 0 — normal aortic valve; score 3 — enhanced echogenicity of all aortic cuspids; score 6 — calcification of all aortic cuspids.

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2.2. Transthoracic echocardiography (TTE)

Two-dimensional complete echocardiographic studies were performed in all patients by use of a commercially available system (Biosound Esaote MyLab; Hewlett-Packard SONOS 7500; Philips iE33), and emphasising the study of the aortic valve, aortic root and mitral annulus using the classical views: the parasternal long axis for the assessment of the aortic root (Fig. 1), the parasternal short axis at the level of the great vessels for the aortic valve (Fig. 2), and the apical four-chamber view and parasternal long axis for the mitral annulus, respectively (Fig. 3) [16]. In all cases, pre and post processing settings in each patient were tailored to optimize the display of cardiac structures at the beginning of each examination and thereafter were left unchanged throughout the study [17].

The aortic root sclerosis (ARS) was defined by an increased echogenicity and/or by thickening of the walls (≥2.2 mm), following the criteria proposed by Tolstrup et al. [18]. An enhanced echogenicity and thickening of the cuspids or the presence of the calcifications characterized the aortic valve sclerosis (AVS) [11]. The TTE criteria for mitral annulus calcification (MAC) included an intense echo-producing structure located at the junction of the atrioventricular groove and posterior mitral leaflet. MAC was quantified from mild to severe, considering its thickness and length [19].

We designed an algorithm to quantify the progression of atherosclerosis at the level of aortic root, aortic valve, and mitral annulus, which is illustrated in Fig. 4. The sum of the points obtained was called the calcification score index (CSI),

ARS - (0-1)
Score: **0-** normal echogenicity, wall thickness < 2.2 mm
1- enhanced echogenicity, wall thickness ≥ 2.2.mm

AVS – (0-6)
Score: **0-** normal echogenicity
1- enhanced echogenicity
2- calcification

	0	1	2	**CSI= ARS+AVS+MAC**
RC	□	□	□	**(0-10)**
LC	□	□	□	
NC	□	□	□	

MAC – (0-3)
Score: **0-** normal echogenicity
1- mild calcification (thickness < 2mm, length < 5mm)
2- moderate calcification (thickness >2mm, length >5mm)
3- severe calcification ("shadowing")

Fig. 4. The quantification of CSI (calcification score index) — RC = right coronary cuspid, LC = left coronary cuspid, NC = non-coronary cuspid, ARS = aortic root sclerosis, AVS = aortic valve sclerosis, MAC = mitral annulus calcification.

with a range from 0 (normal) to 10 (diffuse calcification of the aortic root, aortic valve and mitral annulus).

All other echocardiographic variables were measured following recommendations of American Society of Echocardiography [16], in particular ejection fraction (EF) and LVMI.

2.3. Framingham risk score (FRS)

FRS is a simple coronary disease prediction algorithm encompassing the well-known risk factors [20]. To calculate it

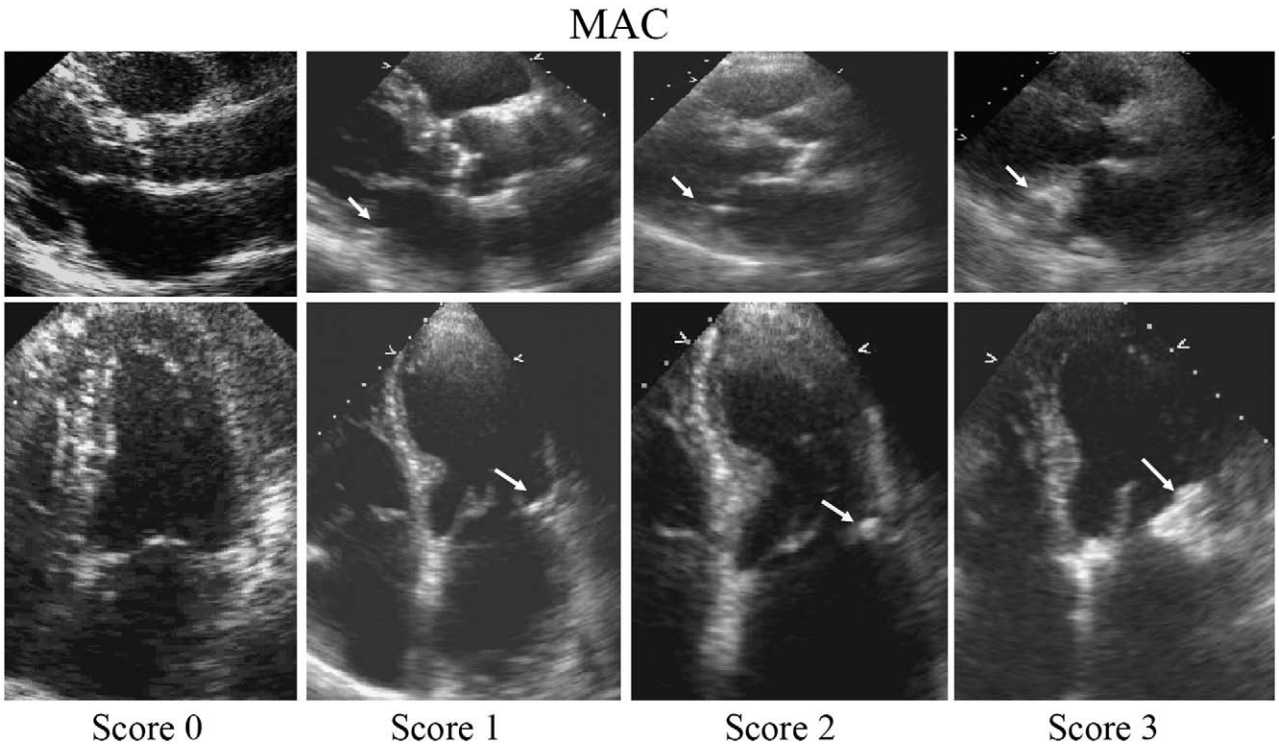

Fig. 3. Quantification of MAC transthoracic parasternal long axis view (top) — transthoracic apical four-chamber view (bottom); score 0 — normal mitral annulus, score 1 — mild calcification of the mitral annulus, score 2 — moderate calcification of the mitral annulus, score 3 — severe calcification of the mitral annulus.

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Table 1
The inter- and intra-observer variability on CSI

	Inter	Intra
Bias	0.13	0.40
Limit of agreement (+)	1.41	1.87
Limit of agreement (−)	−1.15	−1.07

we used the following variables: age, gender, systolic blood pressure, diastolic blood pressure, history of smoking, diabetes mellitus, HDL cholesterol and total cholesterol, considering a FRS ≤ 10 to characterize the patients at low risk to develop a cardiovascular disease, a FRS ≥ 11 and ≤ 20 at average risk, and a FRS ≥ 21 at high risk.

2.4. Coronary angiography

All the patients underwent the coronary angiography, using Duke score for the estimation of the extent of the coronary artery disease (CAD), with a range from 0 (no CAD ≥ 50%) to 100 (left main disease ≥ 95%) [15]. This index takes into account not only the number of major diseased vessels, but also any significant involvement of the left anterior descending coronary artery, particularly when there is involvement of the proximal segment and/or proximal segment stenosis is severe (i.e., ≥ 95%).

2.5. Statistical analysis

Parametric data are expressed as mean ± SD and nonparametric data were given as frequency and percentage. Groups were compared for categorical data or frequency of events using the χ^2 test and for continuous variables using unpaired Student's *t*-test, Anova *F*-test and Kruskal–Wallis test. All tests were 2-sided, and $p < 0.05$ was considered statistically significant. Roc-curve analysis was used to determine the best cut-off for CSI and after that univariate descriptive and logistic regression analysis was used to determine which variable might have predicted CSI. Stata v9.0 for Windows was used for data analysis. Anova *F*-test was also used to determine if different index values of CSI might have predicted LVMI, FRS and Duke score. Logistic regression models were computed to examine the level of association between CSI score on CAD status, checking for all other risk factors. Independent variables significantly related to the dependent variable on a bivariate level were entered into the model. An additional stepwise selection logistic regression was used to identify these seven variables that significantly related to the CAD (hypercholesterolemia, familiarity, hypertension, smoke history, diabetes, age, gender and CSI index).

The inter- and intraobserver reproducibility of CSI was evaluated using Bland–Altman analysis by calculating the bias (mean difference) and the 95% limits of agreement (2 SD around mean difference) [21].

3. Results

3.1. The inter- and intraobserver variability

The inter- and intraobserver variability on CSI has been evaluated separately on a set of 15 consecutive patients (Table 1). The Bland–Altman analysis resulted in a nonsignificant bias in interobserver (0.13) and intraobserver (0.40) measurements and the 95% limits of agreement are respectively 1.28 (inter) and 1.47 (intra) (Fig. 5).

The coefficient of variation for intra- and interobserver reproducibility was <6% for the left ventricle diameter, <10% for the left ventricle wall thickness and <25% for the LVMI, data comparable with those already published by our laboratory [22].

3.2. Population characteristics

The receiver operator characteristic analysis of CSI=4 served as the best cut-off for CAD identification (Fig. 6). We divided the study population in 2 groups: Group I encompassing the patients with a CSI ≤ 4, and the Group II of those with a CSI > 4.

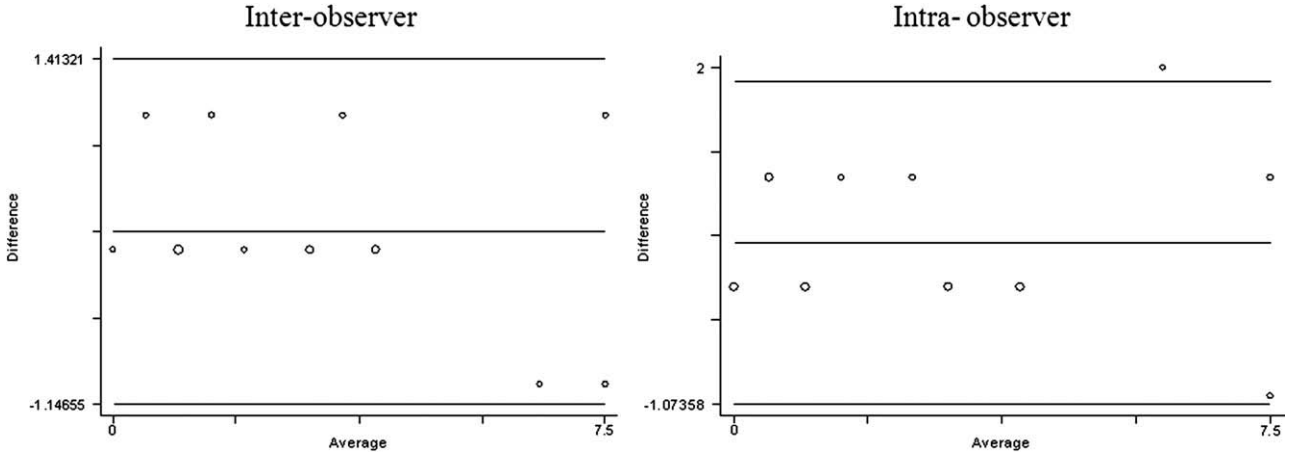

Fig. 5. Bland–Altman analysis of CSI, the difference plotted against the average of the two measurements.

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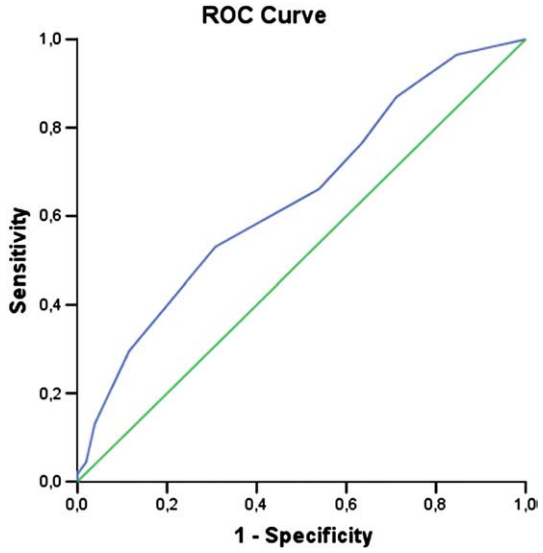

Fig. 6. Receiver operating curves (ROC) of CSI in predicting CAD.

The study population consisted in 167 consecutive in-hospital patients (mean age 66.6±9.7 yrs, 119 men) with the main characteristics that are presented in Table 2. There was a statistically significant inter-group differences in age (OR=2.04: $p<0.001$), systolic blood pressure (OR=1.02; $p<0.03$), presence of diabetes mellitus (OR=3.95; $p<0.001$), presence of nitrate treatment (OR=2.18 $p<0.02$) and insulin treatment (OR=3.97; $p<0.02$). The data regarding the revascularization treatment and clinical characteristics are shown in Table 3.

Table 3
Clinical characteristics and revascularization treatment of the population

	Total	Group I (CSI ≤ 4)	Group II (CSI>4)	
	$n=167$	$n=90$	$n=77$	
Unstable angina	29 (17.3%)	16 (17.8%)	13 (16.9%)	n.s.
Exertional angina	75 (45%)	39 (43.4%)	36 (46.8%)	n.s.
AMI	19 (11.4%)	10 (11.2%)	9 (11.7%)	n.s.
Heart failure	27 (16.2%)	15 (16.7%)	12 (15.5%)	n.s
Previous AMI	56 (33.5%)	28 (31.2%)	28 (36.45)	n.s.
PTCA	56 (33.5%)	28 (31.2%)	28 (36.45)	n.s.
Previous PTCA	37 (22.1%)	16 (17.8%)	21 (27.3%)	n.s.
CABG	16 (9.6%)	6 (6.8%)	10 (13%)	$p<0.05$
Previous CABG	22 (13.2%)	11 (12.2%)	11 (14.3%)	n.s.

AMI = acute myocardial infarction, PTCA = percutaneous transluminal coronary angioplasty, CABG = coronary artery bypass graft surgery; n.s. = no significant differences.

3.3. Echocardiographic findings

The principal echocardiographic parameters assessed, including CSI, the FRS, and the Duke score are presented in Table 4., where it is showed that CSI, FRS, Duke Score and LVMI were significantly different between groups.

When the population was divided in 3 groups using FRS to identify the patients at different risk to develop a cardiovascular disease, the presence of aortic root sclerosis (ARS) and of mitral annulus calcification (MAC) was higher in patients with a FRS ≥ 21 ($p<0.0001$ for ARS, $p<0.027$

Table 2
Main characteristics of the population

	Total	Group I (CSI ≤ 4)	Group II (CSI>4)	
	$n=167$	$n=90$	$n=77$	
Age (yrs)	66.6±9.7	64.2±10.5	69.5±8.0	$p<0.001$
Men	119 (71.3%)	62 (78.9%)	57 (74.0%)	n.s.
Systolic BP	135.4±21.5	131.9±21.4	139.6±21.1	$p<0.03$ (0.021)
Diastolic BP	72.1±9.8	73.3±11.6	73.4±12.0	n.s.
BSA (m^2)	1.86±0.18	1.86±0.19	1.87±0.18	n.s.
HDL cholesterol (mg/dl)	40.8±17.9	42.8±18.4	38.5±17.3	n.s.
Total cholesterol (mg/dl)	177±42.8	181.6±42.9	171.6±42.5	n.s.
Smoke history	86 (51.5%)	42 (46.7%)	44 (57.1%)	n.s.
Hypertension	106 (63.4%)	52 (57.8%)	54 (70.1%)	n.s.
Diabetes mellitus	46 (27.5%)	14 (15.6%)	32 (42.1%)	$p<0.001$
Ca channels antagonists	45 (26.9%)	23 (25.6%)	22 (28.6%)	n.s.
Beta-blocker treatment	100 (59.8%)	49 (54.4%)	51 (66.2%)	n.s.
ACE inhibitor treatment	86 (51.5%)	41 (45.6%)	45 (58.4%)	n.s.
Lipid lowering drug treatment	108 (64.6%)	57 (63.3%)	51 (66.2%)	n.s.
Aspirin treatment	102 (61%)	52 (57.8%)	50 (64.9%)	n.s.
Nitrate treatment	56 (33.5%)	23 (25.6%)	33 (42.9%)	$p<0.02$
Ticlopidine treatment	31 (18.5%)	17 (18.9%)	14 (18.2%)	n.s.
Insulin treatment	16 (9.5%)	4 (4.4%)	12 (15.6%)	$p<0.02$
Oral hypoglycemic agents	29 (17.3%)	11 (12.2%)	18 (23.4%)	n.s.

BP = blood pressure, BSA = body surface area, ACE = angiotensin-converting enzyme; n.s. = no significant differences.

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Table 4
The principal echocardiographic parameters, FRS, and Duke score

	Total $n=167$	Group I (CSI ≤ 4) $n=90$	Group II (CSI>4) $n=77$	
LVEF (%)	51.1±10.9	52.4±10.6	49.7±11.2	n.s.
LVEF<50%	44 (26.3%)	19 (21.1%)	25 (32.5%)	n.s.
LVEDD (cm)	5±0.75	5±0.77	5±0.71	n.s.
LVEDD/BSA (cm/m^2)	2.7±0.05	2.6±0.56	2.7±0.45	n.s.
LVESD (cm)	3.6±0.96	3.5±0.97	3.6±0.95	n.s.
LVESD/BSA (cm/m^2)	1.9±0.56	1.9±0.56	1.9±0.44	n.s.
LA diameter (cm)	4±0.63	3.9±0.66	4.05±0.57	n.s.
LA diameter/BSA (cm/m^2)	2.1±0.33	2.1±0.31	2.1±0.35	n.s.
LA volume (ml)	48±20	45±21.1	51±18	n.s.
LA volume/BSA (ml/m^2)	25±10.2	24±10.5	27.3±10	n.s.
LVM (g)	194.34±58.5	185.4±61.4	204.6±53.6	$p<0.04$
LVMI (g/m^2)	104.7±26.6	99.1±25.1	111.1±29.2	$p<0.006$
Abnormal LVMI	58 (34.7%)	24 (27%)	34 (44.2%)	$p<0.03$
MR presence	133 (79.6%)	70 (77.8%)	63 (81.8%)	n.s.
CSI	3.94±2.1	2.32±1.4	5.84±1.0	$p<0.0001$
FRS	20.8±14.3	16.8±12.6	25.5±14.9	$p<0.0001$
Duke Score	29.7±23.7	24.1±23.6	35.9±22.5	$p<0.002$

LVEF = left ventricle ejection fraction, LVEDD = left ventricle end-diastolic diameter, LVESD = left ventricle end-systolic diameter, BSA = body surface area, LA = left atrium, LVM = left ventricle mass, LVMI = left ventricle mass index, MR = mitral regurgitation, CSI = calcification score index, FRS = Framingham risk score; n.s. = no significant differences.

for MAC) comparing to those at low risk. Considering at least one calcification of at least one cuspid of the aortic valve, the presence of calcification was more represented in patients at a high risk ($p<0.0001$). The mean CSI showed a progressive statistically significant increase from a mean of 2.76±2.1 in patients at low risk to a mean of 4.11±2.3 in patients at average risk and 4.71±1.7 at high risk ($p<0.001$ low risk vs. high risk, $p=0.02$ low risk vs. average risk) (Fig. 7).

Similar results are observed dividing the population in 2 groups using Duke Score to identify the patients with the presence of coronary artery disease (CAD): the presence of ARS, MAC and calcification of at least one aortic cuspid were significantly different in patients with CAD ($p<0.001$ for ARS, $p<0.022$ for MAC, and $p<0.013$ for cuspid calcification).

The mean CSI showed a progressive statistically significant increase from a mean of 3.2±2.1 in patients without the presence of coronary artery disease to a mean of 4.3±2.1 in patients with the presence of coronary artery disease ($p=0.003$) (Fig. 8). There was a significant difference between CSI in patients with single vessel CAD compared with those double and triple vessel CAD ($p<0.002$).

We performed multivariate logistic regression using those variables that were found to differentiate between CAD and

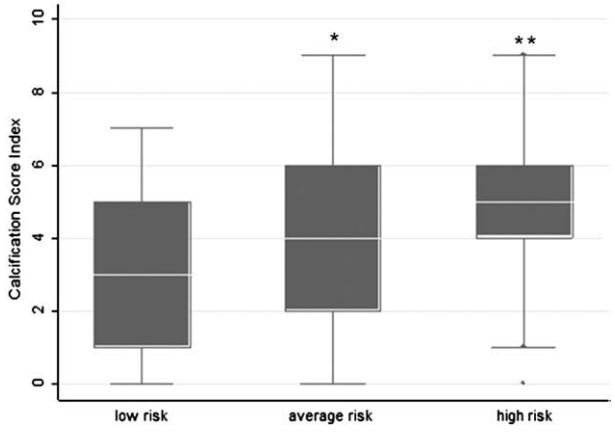

Fig. 7. CSI in different risk groups — CSI showed a progressive statistically significant increase from average risk group to moderate and high risk groups. * $p=0.02$ low risk vs. average risk; ** $p<0.001$ low risk vs. high risk.

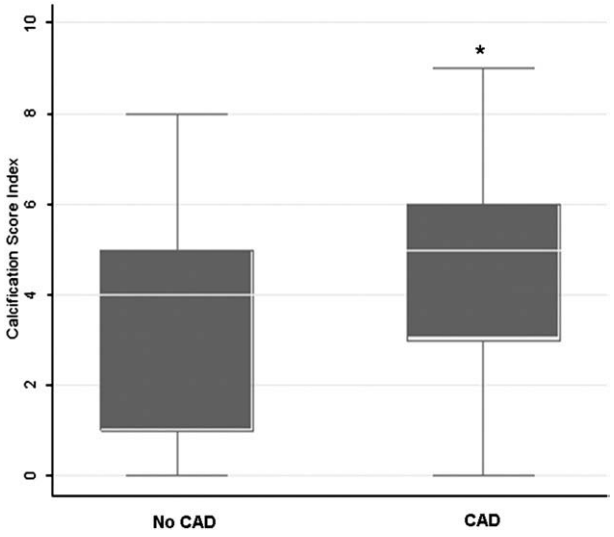

Fig. 8. CSI association with the presence of CAD — the mean CSI was significantly higher in patients with CAD. * $p=0.003$.

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Table 5
Predictors of CAD

	Univariate			Multivariate		
	OR	95%CI	p	OR	95%CI	p
Hypercholesterolemia	3.2	1.499–6.831	<0.05	3.74	1.667–8.529	<0.002
Familiarity	0.81	0.416–1.587				
Hypertension	1.46	0.747–2.878				
Smoke history	1.09	0.567–2.101				
Diabetes	3.343	1.379–8.103	<0.05	2.84	1.101–7.717	<0.036
Age	1.01	0.979–1.047				
Gender	0.3	0.152–0.624	<0.05			
CSI	1.26	1.080–1.486	<0.05	1.2	1.010–1.431	<0.038
LVMI	1.1	0.552–2.223				
LA diameter	0.881	0.456–1.705				

no-CAD at a significant level of 0.05. Of the eight variables (hypercholesterolemia, familiarity, hypertension, smoke history, diabetes, age, gender and CSI), only hypercholesterolemia, diabetes, gender and CSI were individually significant predictors of CAD status ($p<0.05$). There was a statistically significant inter-group difference in the presence of hypercholesterolemia (OR=3.74; $p<0.002$), presence of diabetes mellitus (OR=2.84; $p<0.036$), and in the CSI score (OR=1.20; $p<0.038$) (Table 5). The CSI score odds ratio (OR), reflects the positive response relative to increase of one unit in the CSI after checking for all other effects in the model.

The fit of this model suggest that the model with CSI, hypercholesterolemia and diabetes is preferable to the restricted model with hypercholesterolemia and diabetes, also comparing the two models with the LR test for nested models (LR chi2(1)=4.42; $p=0.036$). We built also the model including the global risk assessed by FRS which showed the additive value of CSI to the FRS for the prediction of coronary artery disease (LR chi2(1)=5.85; $p=0.015$).

Analyzing differences in patients with increasing left ventricle mass index (LVMI), the mean CSI showed a progressive statistically significant increase from a mean of 3.6±2.2 in patients with normal LVMI to a mean of 4.7±2.0 in patients with abnormal LVMI ($p=0.002$) (Fig. 9).

An abnormal CSI (>4) result in a 72% chance of predicting a medium-to- high FRS, a 77% chance of predicting the presence of CAD, and a 61% chance of predicting an abnormal LVMI.

4. Discussion

Previous reports have noted an association between ARS, AVS, MAC and atheroscleorsis [9–11,23]. To our knowledge, this study is the first to develop a unique index, encompassing all three echocardiographic parameters, called calcification score index. The major findings of this study is that the calcification score index, expressed by the sum between ARS, AVS and MAC, assessed by transthoracic echocardiography, is associated with Framingham risk score, Duke score and LVMI.

4.1. Comparison with previous studies

Several pathologic and echocardiographic studies have demonstrated a strong association between AVS [24,25], ARS [24], MAC [18,26] and risk factors such as age, male gender, hypertension, cholesterol, diabetes, and smoking. Previous studies have also shown that patients with AVS and MAC undergoing coronary angiography have a higher prevalence of CAD [24,25,27]. Our study showed the association between ARS, AVS, MAC and the presence of coronary artery disease and the cardiovascular risk, confirming data presented by the previous studies, but also the fact that summing all three parameters (ARS, AVS and MAC) in so-called "calcification score index-CSI" preserves the significantly association.

Systemic endothelial dysfunction and increased common artery intima-media thickness (IMT) are implicated as early events of atherosclerosis. Sgorbini et al. [23] reported that the mean of IMT increases linearly with increasing valvular calcification score (MAC and AVS), and Poggianti et al. [28] showed that AVS is associated with systemic endothelial dysfunction.

Aortic sclerosis is common in the elderly and is associated with an increase of approximately 50% in the risk of death from cardiovascular causes and the risk of myocardial infarction, even in the absence of hemodynamically significant obstruction of the left ventricle outflow [11]. It is also known that total and cardiovascular mortality risk increases with the increasing left ventricle mass index (LVMI), independent of other cardiovascular risk factors [14]. CSI was significantly correlated with LVMI, suggesting that our index could have a prognostic value.

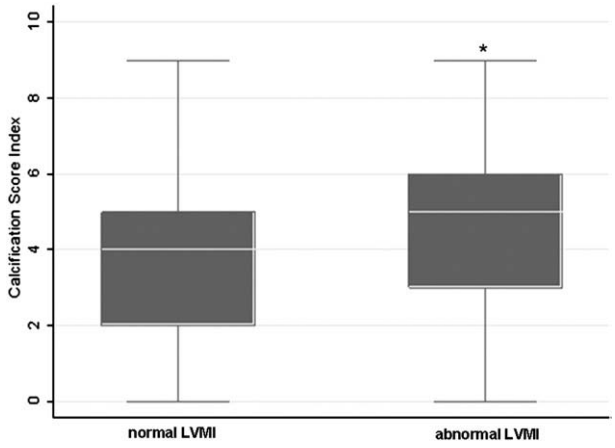

Fig. 9. CSI association with LVMI — in patients with abnormal LVMI the mean CSI was significantly higher comparing to the mean CSI in patients with normal LVMI. * $p=0.002$.

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4.2. Study limitations

The sample for this study may not be representative of the general population. The selected patients were scheduled to undergo coronary angiography for a clinical indication; this inclusion criterion might have skewed the spectrum of the population toward advanced forms of CAD. We did not use a digitized method to identify AVS, ARS and MAC. This could have caused a verification bias and may affect the reproducibility in identifying cardiac calcifications. Nevertheless, the semi-quantitative "eyeball" method is the one currently adopted in everyday clinical echocardiographic practice, and our intention was to find a very simple instrument that could be at hand to everybody, without the necessity of further supplementary analysis.

The inter- and intraobserver agreement of CSI was very good, and therefore acceptable for a simple method which does not increase the analysis time of a standard transthoracic echocardiography.

Major advances in imaging techniques using multislice detector CT and EBCT have facilitated the diagnosis of arterial calcification in vivo [29]. In patients on hemodialysis, the measurement of cardiovascular calcification can be greatly simplified with the use of echocardiography [30]. In our study we propose an alternative to EBCT for calcification assessment. When comparing the different imaging modalities, however, one must keep in mind that echocardiography is radiation free and is more cost-effective than other techniques [29].

The missing data concerning a possible value of CSI in predicting the risk for a subsequent cardiovascular event is one of the biggest limitation of our study, which needs to be studied in more depth. Additionally, whether our findings are sufficient to indicate a widespread use of echocardiography in those patients for risk stratification requires further studies. At present, we can consider CSI as a "promising" or "developing" biomarker, with known accuracy and reproducibility under highly controlled conditions.

5. Conclusions

Calcification score index calculated as the sum of aortic root sclerosis, aortic valve sclerosis, and mitral annulus calcification, is associated with risk factor profile, coronary atherosclerosis and left ventricle mass index. This observation may provide a new tool useful for the cardiovascular risk stratification with standard transthoracic echocardiography. The low cost, portable, facile and radiation free nature of the ultrasound approach make CSI an attractive candidate in the ongoing search for the ideal marker of vascular and valvular calcification.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [31].

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