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Prognostic Value of Percentage Segment Involvement Score Adjusted to Age as measured by Coronary Computed Tomography: A potential marker of vascular age

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ABSTRACT

Introduction: Extent of coronary atherosclerosis burden on coronary computed tomography angiography (CCTA) as measured by segment involvement score (SIS) has prognostic value. Atherosclerotic progression has been advocated as a superior predictor of outcomes; as such methods of adjusting plaque burden to age may be a marker of premature atherosclerosis and vascular age. We sought to investigate the incremental the prognostic value of %SIS/age over routine clinical measures, calcium score and obstructive coronary artery disease (CAD).

Methods: Consecutive patients were prospectively enrolled into the CONFIRM (Coronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) multinational observational study. Patients were followed for the outcome of all-cause death. %SIS/age was calculated on CCTA for each patient, and its incremental prognostic value was evaluated.

Results: A total of 22,211 patients (mean age 58.5±12.7years, 55.8% male) with median follow up of 27.3 months [IQR 17.8, 35.4]) were identified. After adjustment for clinical factors and presence of obstructive CAD, higher %SIS/age was associated with increased death on multivariable analysis (Hazard Ratio [HR]: 2.40(1.83-3.16), p <0.001, C-statistic: 0.723 (0.700-0.756), and net reclassification improvement (NRI): 0.36 (0.26-0.47), p <0.01). A subanalysis of patients with available Agatston score (n=15,186) was performed. %SIS/age was an independent and incremental predictor of all-cause mortality (HR: 1.82 (1.30-2.55) and Harrell C-statistic 0.758 (0.728-0.789).

Conclusion: %SIS/age has incremental prognostic value to traditional risk factors, calcium score and obstructive CAD, and enhances CCTA risk stratification.

List all abbreviations

Segment involvement score (SIS)

Coronary computed tomography angiography (CCTA)

Annual event rate (AER)

Coronary artery disease (CAD)

Major adverse cardiac events (MACE)

Left ventricular ejection fraction (LVEF)

Myocardial infarction (MI)

National Cholesterol Education Program (NCEP)

Net reclassification index (NRI)

Coronary artery calcium (CAC)

INTRODUCTION

Coronary computed tomography angiography (CCTA) is recommended in symptomatic individuals for the detection and exclusion of coronary artery disease (CAD) , and has prognostic value . Increasing extent of coronary atherosclerosis, as quantified by segment involvement score (SIS) or the synonymous total plaque score (TPS), has been shown to be a predictor of clinical events . Rate of atherosclerosis progression has been shown to be a better predictor of adverse clinical outcomes . Hence we devised a score (%SIS/age), which adjusts SIS to the number of evaluable segments and normalizes it to patient age. We hypothesize that %SIS/age is a surrogate marker of 'vascular age', as it gives greater weighting to segments involved in those who are younger, and so may account for premature atherosclerotic disease.

Previous work demonstrated that %SIS/age (or %TPS/age) had incremental prognostic value over risk factors and obstructive CAD for MACE . We sought to externally validate the prognostic value of %SIS/age in the large prospective multinational CONFRIM **(**COroNary Computed Tomography Angiography Evaluation for Clinical Outcomes: An InteRnational Multicenter Registry) cohort, and to determine if %SIS/age was incremental to coronary artery calcification (CAC).

METHODS

Study Population: Consecutive patients undergoing CCTA were prospectively enrolled into the CONFIRM (Coronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) Registry. The design of this study has been described in depth previously . Inclusion criteria were adults (≥ 18 years) referred for clinically suspected CAD who underwent ≥ 64-detector row CCTA examination between February 2003 and September 2010 in twelve centers in six countries (Canada, Germany, Italy, Korea, Switzerland, and the United States). All centers had institutional review board approval for patient enrollment and follow-up.

Those with a history of coronary revascularization, heart transplantation, congenital heart disease and those who had <11 segments reported on CCTA were excluded. As well, to ensure there was no overlap of patients, we excluded patients used in our previous study . After excluding 7,410 patients, a total of 22,211 patients were analyzed.

Clinical Data: Patient demographic data, medical history, risk factors, physical data, and indications for CCTA were collected before each CCTA examination in site-specific case report forms. Standardized definitions for cardiovascular risk factors were used . Both pre-test probability for obstructive CAD (using the Diamond Forrester Score) and National Cholesterol Education Program (NCEP) risk were calculated using age, gender, symptoms and risk factors [smoking, hypertension, dyslipidemia, diabetes, family history of premature CAD] .

CCTA Image Acquisition and Analysis: CCTAs were performed with ≥ 64-detector row scanner, and included both single-source and dual-source scanners. Image acquisition, postprocessing and interpretation for CCTAs and coronary artery calcium (CAC) scores in the CONFIRM cohort were in compliance with each site's institutional policy or SCCT guidelines . CAC scores were calculated by the method of Agatston . Standard post-

processing techniques were used to determine the presence and extent of CAD, with obstructive CAD defined as a luminal diameter stenosis ≥50%. Coronary artery anatomy and the extent of atherosclerotic plaque were assessed using a 17-segment model of the coronary arteries (Figure 1) .

Calculation of %SIS**/age:** SIS was calculated as the total number of coronary segments with atherosclerotic plaque (irrespective of severity). %SIS was calculated as the quotient between SIS and the total number of segments that were evaluable for plaque, multiplied by 100 (20). % SIS was adjusted to age by dividing the %SIS by patient age (%SIS/age = ([SIS / total number of evaluable segments] x 100) / age). In order to obtain clinically applicable categorization, the cohort was divided into four categories of %SIS/age. All %SIS=0 (no atherosclerosis) were assigned into the first category, and the remainder were divided into 3 categories based on cutoffs derived from our previous single center study . Four categories were used to enable adequate evaluation of events for each group, yet allow sufficient stratification of patients to enable this measure to be clinically applicable.

Patient Follow-up and Outcome Measure: All patients were followed for all cause death by each local institution by a dedicated physician or research nurse or both. Death was ascertained by query of the national death index in US sites, and in non-US sites by direct interview or telephone contact with the patient's immediate family or primary physician or review of medical records .

Statistical Analysis: SAS Version 9.3 software (SAS Institute Inc., Cary, North Carolina) was used to perform statistical calculations, with statistical significance defined as $P < 0.05$. Absolute counts and percentages were presented for categorical variables, and continuous variables were presented as means ± standard deviation (SD) for normally distributed data and medians (interquartile range [IQR]) for skewed data. The Wilcoxon rank sum test was used for continuous variables and Chi-square test for categorical variables.

Univariable and multivariable analyses were performed to assess the prognostic value of %SIS/age for all-cause death. Any risk factor or CT parameter that had statistically significant ($p < 0.05$) association for mortality on univariable analysis was included in the subsequent multivariable modelling. Cox proportional hazard models were performed for risk-adjusted analyses to evaluate the independent prognostic value of %SIS/age and construct adjusted survival curves. Statistically significant increases in the global chi-square value and comparisons with global model fit using likelihood ratio tests were used to assess the incremental prognostic value of models with and without %SIS/age. C-index of Harrell was assessed to determine the ability of models with %SIS/age to predict mortality .

Improvement in the prediction performance for mortality of a model that adds %SIS/age to clinical risk factors and presence of obstructive CAD was evaluated with the net reclassification improvement (NRI) index . Category free NRI which defines upward and downward movement as any change in the predicted probabilities was reported as a measure of discrimination with 95% confidence intervals, as it is not influenced by correct scaling of the model and is more generalizable .

As not all patients included in the study had concomitant calcium score measured along with CCTA, we performed a subanalysis in the portion of the cohort that did (n=15,186). Hazard ratios in univariable and multivariable analyses were calculated for 100 point increase in calcium score.

RESULTS

Patient characteristics: A total of 22,211 patients (mean age 58.5±12.7 years, 55.8% male) were identified with median follow-up time of 27.3 months (IQR 17.8, 35.4) (Table 1). The median %SIS/age was 0.16 (IQR 0.00, 0.47), and median SIS was 1.0 (IQR 0.0, 4.0).

There was no visible coronary atherosclerosis (SIS and %SIS/age = 0) in 8,763 (39.5%) patients.

Based on our previous work, patients were stratified into 4 categories (%SIS/age=0, 0.001-0.314, 0.314-0.699, ≥0.700) . Patients falling into respectively higher %SIS/age category had increasing rates of cardiovascular risk factors (diabetes, hypertension, hypercholesterolemia, smoking and family history) and were more likely to be male (Table 1). Additionally, those in the highest %SIS/age category (≥0.700) were more likely to have higher Agatston score (735.7±907.4) and obstructive CAD (72%).

Clinical outcome: A total of 368 patients had the clinical outcome of death (Figures 2 and 3). Forty-nine (0.6%) events were observed in the %SIS/age=0 category (AER=0.20%). 106 events (2.0%) were observed in the %SIS/age <0.314 category (AER=0.61%), 116 (2.3%) in the %SIS/age 0.314–0.699 category (AER=0.78%) and 97 (3.2%) in the %SIS/age ≥ 0.700 category (AER=1.08%) (Figure 2).

Univariable Analysis: Comparing patients with and without the clinical outcome, those who died were more likely to have hypertension (HR 1.93 [1.56-2.40], p <0.001), diabetes (HR 1.74 [1.38-2.19], p <0.001), and smoking history (HR 1.88 [1.52-2.32]). Patients who died were more likely to have higher %SIS/age with HR 3.68 [2.97-4.56], p <0.001, and have obstructive CAD, with HR 3.11 [2.54-3.82], p <0.001 (Table 2). History of dyslipidemia and chest pain appeared to have lower risk of mortality, which is likely explained by treatment with statins for the former and medical and revascularization therapy for the latter, which would be protective. In subjects ≤50 years of age (n=5702, 36 deaths) %SIS/age had HR 4.62 (2.62-8.15), whereas in those >50 years old (n=16509, 332 deaths) HR was 3.22 (2.53-4.11), both p<0.001; the higher hazard ratio in the younger bracket may support the hypothesis that %SIS/age is a marker of premature atherosclerosis.

Multivariable Analysis: Cox proportional hazard modelling was performed to assess the prognostic value of %SIS/age over clinical predictors and obstructive CAD (Table 3). %SIS/age had HR 2.40 [1.83-3.16] for all cause death, p <0.001, and Harrell C-statistic 0.723(0.700-0.756) when applied in addition to clinical risk factors and obstructive CAD (≥50%). Use of %SIS/age category to predict all cause death was associated with HR of 1.52 (1.36-1.71), p <0.001 and Harrell C-statistic 0.735 (0.707-0.762).

Category-Free Net Reclassification Index (NRI): To examine the ability of %SIS/age to appropriately reclassify patient risk for death, the category free NRI was calculated. %SIS/age had a category free NRI of 0.36 (0.26-0.47), p <0.001, for all cause death when used in addition to clinical predictors and obstructive CAD. Higher %SIS/age category was also incremental over clinical predictors and obstructive CAD with NRI of 0.34 (0.24-0.44), p <0.001. In 2 separate models used to compare risk reclassification in addition to traditional clinical risk factors, %SIS/age demonstrated similar ability to reclassify patient risk as the presence of obstructive CAD, with NRI of 0.46 (0.36-0.56) for the model 'Clinical risk + %SIS/Age' versus 0.48 (0.37-0.58) for the model 'Clinical risk + obstructive CAD', p <0.001.

Calcium Score Subanalysis: A subanalysis was performed in patients with available calcium score (n=15,186). These patients had similar characteristics as the overall cohort, except for lower proportion of smoking and diabetic patients, and a greater proportion of patients having chest pain (Supplementary table 1). The clinical outcome of death was present in 273. On univariable analysis, calcium score had HR of 1.06 (1.05, 1.07) for mortality, compared to %SIS/age HR of 4.20 (3.28-5.37) and obstructive CAD HR of 3.46 (2.72-4.40), all p <0.001 (Table 4).

In a Cox proportional hazard model that included clinical risk factors, Agatston score, presence of obstructive CAD and %SIS/age as a continuous variable, %SIS/age had the

highest HR for mortality [1.82 (1.30-2.55)], followed by obstructive CAD [1.77 (1.30-2.41)], whilst Agatston score had HR of 1.04 (1.03,1.05), all p <0.001, Harrell C-statistic 0.758 (0.728-0.789) (Table 5). In a similar Cox proportional hazard model that included %SIS/age category instead, %SIS/age category had HR 1.41 (1.24-1.62), obstructive CAD had HR 1.49 (1.10-2.03) and Agatston 1.04 (1.03-1.05), all p <0.001, Harrell C-statistic 0.762 (0.731-0.793).

DISCUSSION:

Using the CONFIRM registry, we validate the independent and incremental prognostic value of %SIS/age over routine clinical measures, obstructive CAD and Agatston score. Higher %SIS/age categories were associated with increased risk of all-cause mortality (HR 2.40 (1.83-3.16), p <0.001 and NRI of 0.36 (0.26-0.47), p <0.01).

Our previous work demonstrated that %SIS/age (also termed %TPS/age) score has incremental prognostic value for MACE over traditional risk factors and conventional CCTA assessment of coronary atherosclerosis . We hypothesized that this novel measure, which can be quickly and easily derived from routine clinical CCTA, and may be a surrogate marker of coronary vascular age. Although the prevalence of traditional risk factors and obstructive CAD increased with %SIS/age category, two-thirds of patients in the highest %SIS/age category had low or intermediate NCEP risk (Table 1); hence confirming the potential limitations of routine clinical risk predictors and the potential utility of %SIS/age to reclassify patient risk.

CCTA, extent of CAD, and prognosis: Framingham risk factors have only moderate correlation with atherosclerosis burden; a significant proportion of patients with low and intermediate Framingham risk have coronary atherosclerosis demonstrated by CCTA (47.6 and 72.7%, respectively) . Anatomic evaluation of coronary arteries by CCTA allows early

identification of coronary artery disease that may be subclinical and undetectable by functional testing, but is often the substrate of MACE . The presence of non-obstructive CAD on CCTA is associated with higher mortality even adjusting for CAD risk factors, with highest risk seen in those with greater extent of non-obstructive CAD . SIS is a simple and reproducible semiquantitative measure quantifying the extent of CAD burden on CCTA (irrespective of degree of stenosis). Extent of CAD is a strong predictor of events , and SIS ≥5 on CCTA has been shown to have worse prognosis that is comparable to the presence of obstructive CAD .

Coronary vascular age and atherosclerosis that is extensive for age: SIS and extent of CAD increase with age . Atherosclerosis begins in the early decades of life , and may remain clinically silent for decades until plaque erosion and rupture result in clinical events or lesions become obstructive resulting in ischemia. However, individuals with more rapid progression of coronary atherosclerosis have an increased rate of MACE , and progression of CAD is a strong predictor of outcomes . Absolute plaque measurements may estimate 10 year risk which is independent of age, however adjusting plaque burden to age gives a greater weighting for each involved segment if younger and may be a potential estimate of lifetime risk. For example, a 30 year old and 60 year old who have the same plaque burden and CAC theoretically may have the same 5-10 year risk; however the 30 year old would have atherosclerotic disease that is more rapidly progressive and more extensive for their age, and lifetime risk would be greater. Hence %SIS/age may be a marker of vascular age and provide enhanced prediction of lifetime risk.

Coronary artery calcium: CAC assessment is widely used in asymptomatic individuals as a surrogate for atherosclerotic burden, and is a robust method for prognostication . CAC reclassifies risk for adverse cardiovascular events and provides incremental prognostic value to Framingham risk evaluation . However it does not account for the presence and extent of

non-calcified plaque burden. CCTA further refines risk stratification over conventional risk assessment , and has the ability to determine the total extent of atherosclerosis (calcified and non-calcified), degree of luminal obstruction, plaque characteristics, and has incremental value over CAC .

Atherosclerosis development is a continuum, and the presence CAC reflects more advanced stages of disease . In younger patients (< 55 years) soft plaque may be more common and so CAC may underestimate overall extent of atherosclerosis burden . Thus CCTA measures including SIS take into account non calcified plaque that is not detected by CAC score ; therefore SIS enables the detection of earlier stages of atherosclerotic disease , and adds discrimination for risk of death and MI over CAC, particularly when CAC is 0 .

In a sub-analysis of patients with concomitant CAC measurements (n=15,186), %SIS/age was a better predictor for mortality. A multivariable model with %SIS/age was associated with the highest Harrell C-statistic and HR 1.82 (1.30-2.55), p <0.001.

Clinical implications: %SIS/age may offer a method of enhanced risk stratification and prognostication by CCTA. With advancements in CT technology and novel scanning algorithms promising ongoing reduction in radiation dose and increasing use of CCTA, %SIS/age uses information readily available and easily calculable from clinical scans that may identify patients with ‘greater vascular age’ or atherosclerosis that is more extensive for age, and at greater risk of mortality. Additionally, %SIS/age may be a more sensitive marker of subclinical disease than CAC, removing a false sense of security for some at risk patients, and so improve adherence to preventative measures.

Observational data have shown that CCTA impacts downstream testing and management, influences physician behavior and resulting in better risk factor modification and increased medical therapy . The use of statins has been associated with reduced risk for mortality in patients with non-obstructive disease on CCTA . Whilst there is a lack of

prospective data, %SIS/age could be a useful tool for triaging medical therapy. Further studies are needed to understand the clinical role of %SIS/age.

Limitations: Calculation of %SIS/age assumes that plaque is absent at birth and increases in a linear fashion with age. Ideally direct measures of plaque progression would provide us with information regarding true rates of change and how they may be attenuated with medical therapy. In the absence of such tests, %SIS/age may be a reasonable marker of premature atherosclerosis that is extensive for age. Age was removed from the multivariable analysis to avoid collinearity with %SIS/age, as age is part of the score; however, in the univariable analysis, %SIS/age score was a superior predictor of mortality than age, SIS or %SIS alone with much higher hazard ratios. Further studies are needed to better understand how such measures can be used to guide medical therapy.

CONCLUSION:

%SIS/age may be a surrogate marker for vascular age and has independent and incremental prognostic value over traditional risk factors, obstructive CAD and the Agatston score. Further studies are needed to understand how it can be incorporated into clinical practice and how it might direct preventative measures.

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Figure 1. Coronary artery tree, 17 segment model (reproduced and adapted with permission from the SCCT 2009 Guidelines). In a case of a 45 year old who has plaque in 3 of 17 segments (circled), SIS would be 3 and %SIS/age 0.39. Whilst previous published work would suggest SIS <5 portends lower risk than SIS ≥5 , applying %SIS/age restratifies this younger patient into the highest risk category, suggesting more extensive CAD for age.

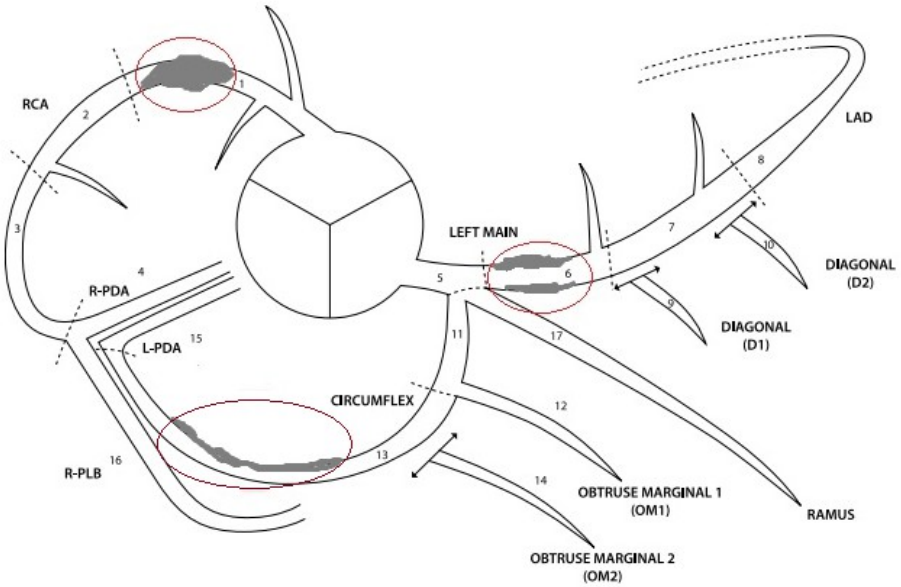


Table 1. Patient Characteristics

	All Patients N=22,211	%SIS/age = 0 N=8,763	%SIS/age 0.001 – 0.313 N=5,420	%SIS/age 0.314 – 0.699 N=5,009	%SIS/age ≥ 0.700 N=3,019	P value
Median Follow-up (months)	24.9 (17.8, 35.4)	28.0 (17.9, 37.8)	27.5 (18.0, 36.1)	26.5 (17.9, 33.3)	25.9 (17.5, 33.2)	<0.001
Age	58.5±12.7	51.9±12.4	61.8±11.2	63.4±10.9	63.0±10.6	<0.001
Male Gender	12,403(55.8%)	3,967(45.3%)	3,016(55.6%)	3,186(63.1%)	2,234(74.0%)	<0.001
Body Mass Index (kg/m^2) *	27.1±5.0	26.7±5.1	27.0±5.0	27.2±4.9	27.8±5.0	<0.001
Cardiac Risk Factors						
Smoker/Ex-smoker	6,471(29.1%)	2,247(25.6%)	1,445(26.7%)	1,569(31.3%)	1,210(40.1%)	<0.001
Hypertension	11,585(52.2%)	3,767(43.0%)	2,955(54.5%)	2,918(58.3%)	1,945(64.4%)	<0.001
Dyslipidemia	12,362(55.7%)	4,016(45.8%)	3,054(56.3%)	3,144(62.8%)	2,148(71.1%)	<0.001
Diabetes	3,876(17.5%)	1,057(12.1%)	949(17.5%)	1,119(22.3%)	751(24.9%)	<0.001
Family History of CAD	7,979(35.9%)	2,911(33.2%)	1,893(34.9%)	1,906(38.1%)	1,269(42.0%)	<0.001
Symptoms						
Chest Pain **	11,918(53.7%)	5,498(62.7%)	2,596(47.9%)	2,324(46.4%)	1,500(49.7%)	<0.001
Dyspnea †	5079(28.9%)	1990(27.5%)	1170(29.1%)	1174(31.3%)	745(28.7%)	0.001
NCEP ‡						
Low Risk (<10%)	6037(27.2%)	3609(41.2%)	1238(22.8%)	819(16.4%)	371(12.3%)	<0.001
Intermediate Risk (10-20%)	11610(52.3%)	3945(45.0%)	3132(57.8%)	2885(57.6%)	1648(54.6%)	<0.001
High Risk (>20%)	4564(20.5%)	1209(13.8%)	1050(19.4%)	1305(26.1%)	1000(33.1%)	<0.001
Medications						
Beta-Blocker	4,093(30.9%)	1,257(23.1%)	983(31.9%)	1006(37.3%)	847(42.3%)	<0.001
Aspirin	5,479(41.4%)	1,561(28.6%)	1,418(46.1%)	1,462(54.2%)	1,038(51.8%)	<0.001
ACE-inhibitor	2,073(15.7%)	561(10.3%)	477(15.5%)	506(18.7%)	529(26.4%)	<0.001
Statin	5,211(39.3%)	1,256(23.0%)	1,319(42.8 %)	1,430(52.9%)	1,206(60.1%)	<0.001
LV Parameters §						
LV Ejection Fraction (%)	62.0±12.5	60.9±12.3	62.2±12.1	62.9±12.5	62.2±13.4	0.001
Normal LVEF (≥50%)	10,623(85.1%)	4,158(87.3%)	2,432(85.4%)	2,437(83.9%)	1,596(81.5%)	<0.001
Obstructive CAD	5,749(25.9%)	2(0.0%)	1,216(22.4%)	2,358(47.1%)	2,173(72.0%)	<0.001
SIS	1.00 (0.00, 4.00)	0.00 (0.00, 0.00)	1.00(1.00, 2.00)	4.00(3.00, 5.00)	7.00 (6.00, 9.00)	<0.001
%SIS/age	0.16 (0.00, 0.47)	0.00 (0.00, 0.00)	0.18 (0.13, 0.25)	0.47 (0.39, 0.58)	0.93 (0.80, 1.12)	<0.001

* n=17,730 ** n=18,754 † n=17,601 ‡ 10 year absolute risk of cardiovascular event § n=12,476

Table 2. Univariable Analysis for mortality

	All Cause Death n=368	No All Cause Death n=21843	Hazard Ratio (95% CI)	P value
Male Gender	218 (58.7%)	12,187 (55.8%)	1.12(0.91-1.38)	0.292
Body Mass Index (kg/m^2) *	26.0±5.5	27.1±5.0	0.98(0.95-1.00)	0.070
Cardiac Risk Factors				
Smoker/Ex-smoker	140 (38.0%)	6,331 (29.0%)	1.88(1.52-2.32)	<0.001
Hypertension	245 (66.6%)	11,340 (51.9%)	1.93(1.56-2.40)	<0.001
Dyslipidemia	178 (48.4%)	12,184 (55.8%)	0.72(0.59-0.88)	0.001
Diabetes	101 (27.4%)	3,775 (17.3%)	1.74(1.38-2.19)	<0.001
Family History of CAD	121 (32.9%)	7,858 (36.0%)	1.24(0.99-1.54)	0.057
NCEP			1.88(1.61,2.19)	p<0.001
Low risk	45(12.2%)	5991(23.3%)		
Intermediate risk	194(52.7%)	12317(56.4%)		
High risk	129(35.1%)	4435(20.3%)		
Chest Pain **	161 (44.6%)	11,754 (53.8%)	0.64(0.51-0.81)	<0.001
Dyspnea †	112 (30.4%)	4,967 (22.7%)	2.19(1.72-2.79)	<0.001
Obstructive CAD (≥50%)	182 (49.5%)	5,567 (25.5%)	3.11(2.54-3.82)	<0.001
SIS	4.3±3.4	2.3±2.8	1.22(1.18-1.25)	<0.001
Age	69.0±12.7	58.3±12.3	1.09(1.08,1.10)	<0.001
%SIS	34.0±27.3	17.9±22.1	1.03(1.02,1.03)	<0.001
%SIS/Age	0.489±0.400	0.287±0.349	3.68(2.97-4.56)	<0.001
%SIS/Age category	2.7±1.0	2.1±1.1	1.75(1.59-1.92)	<0.001
Abnormal LVEF (≤50%) ‡	72 (19.6%)	1,781 (8.2%)	2.35(1.78-3.11)	<0.001

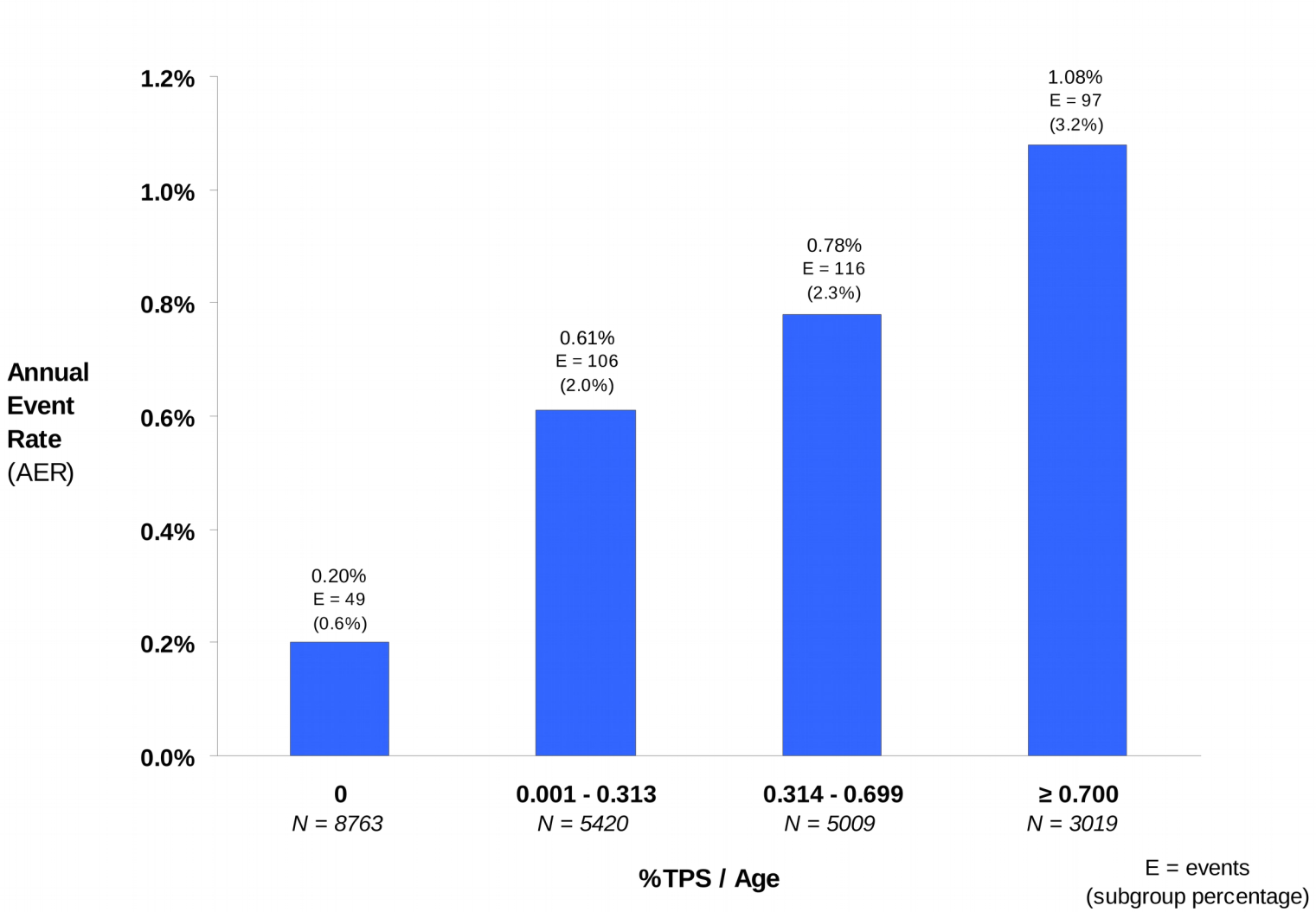
* n=17,730 ****** n=18,754 † n=17,601 ‡ n=12,476

Table 3. Cox Models for mortality. Only variables with a univariate p<0.05 were included in the cox regression model.

	Hazard Ratios (95% CI)	P value	Global Chi-Square	Harrell C-statistic (95% CI)
Clinical			98.71	0.679 (0.645-0.712)
Smoker/Ex-smoker	1.86(1.51-2.30)	<0.001		
Hypertension	1.92(1.54-2.39)	<0.001		
Dyslipidemia	0.64(0.52-0.78)	<0.001		
Diabetes	1.56(1.24-1.97)	<0.001		
Clinical + Obstructive CAD			184.63	0.710 (0.679-0.741)
Smoker/Ex-smoker	1.65(1.34-2.05)	<0.001		
Hypertension	1.77(1.42-2.21)	<0.001		
Dyslipidemia	0.60(0.49-0.74)	<0.001		
Diabetes	1.34(1.06-1.69)	0.016		
Obstructive CAD (≥50%)	2.76(2.24-3.40)	<0.001		
Clinical + Obstructive CAD + %SIS/Age*			220.24	0.723 (0.700-0.756)
Smoker/Ex-smoker	1.56(1.26-1.93)	<0.001		
Hypertension	1.72(1.37-2.14)	<0.001		
Dyslipidemia	0.55(0.45-0.68)	<0.001		
Diabetes	1.34(1.06-1.69)	0.015		
Obstructive CAD (≥50%)	1.85(1.45-2.38)	<0.001		
%SIS/Age*	2.40(1.83-3.16)	<0.001		

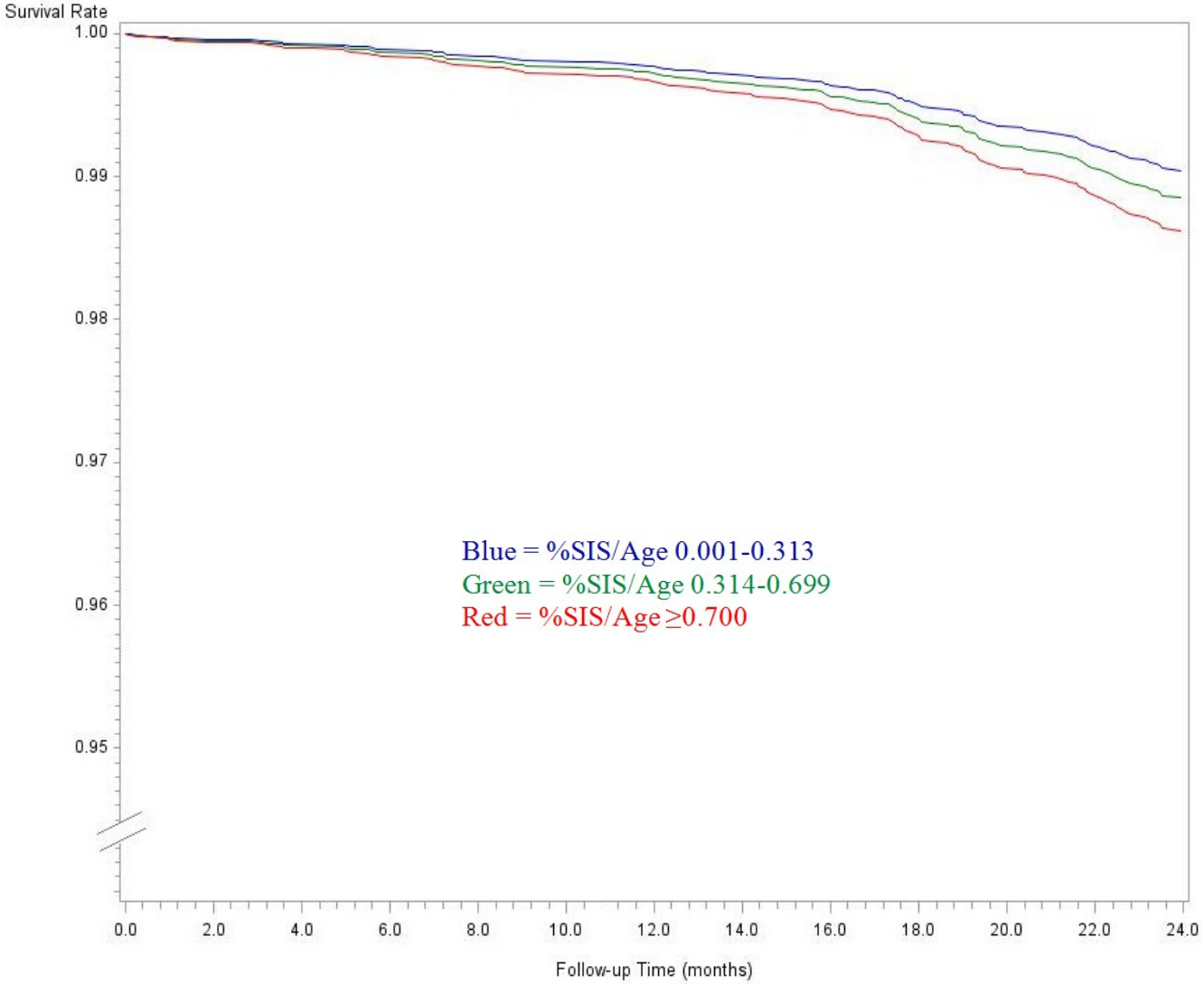
*Continuous variable

Figure 2: Annual event rates for mortality by %SIS/age category. Mortality comparison between %SIS/age categories had p <0.001 for all comparisons, except between 0.001-0.313 category and 0.314-0.699 category (p = 0.05).



SIS

Figure 3: Risk adjusted survival curves by %SIS/age category. %SIS/age= 0 category, whilst included in the continuous variable analysis, was not included in the curve constructions of this figure as it was used as a reference for outcomes for the other %SIS/age categories.



Supplementary Table 1. Subanalysis cohort of patients with available calcium score: patient characteristics

	All Patients N=15,186	%SIS/age = 0 N=6,411	%SIS/age 0.001 – 0.313 N=3,555	%SIS/age 0.314 – 0.699 N=3,185	%SIS/age ≥ 0.700 N=2,035	P value
Median Follow-up (months)	26.0 (17.7, 39.2)	27.0 (18.4, 41.1)	26.2 (17.8, 39.4)	25.5 (17.4, 37.1)	24.2 (17.0, 34.5)	<0.001
Age	58.4±12.5	52.3±11.9	61.7±11.1	63.8±10.8	63.3±10.8	<0.001
Male Gender	8655(57.0%)	2985(46.6%)	2060(57.9%)	2086(65.5%)	1524 (79.4%)	<0.001
Body Mass Index (kg/m^2)	27.2±5.1	26.8±5.1	27.2±5.0	27.4±5.0	28.0±5.1	<0.001
Cardiac Risk Factors						
Smoker/Ex-smoker	3544(23.3%)	1425(22.2%)	722(20.3%)	711(22.3%)	686(33.7%)	<0.001
Hypertension	7734(50.9%)	2666(41.6%)	1868(52.5%)	1819(57.1%)	1381(67.9%)	<0.001
Dyslipidemia	8634(56.9%)	3062(47.8%)	2045(57.5%)	2034(63.9%)	1493(73.4%)	<0.001
Diabetes	2208(14.5%)	572(8.9%)	522(14.7%)	620(19.5%)	494(24.3%)	<0.001
Family History of premature CAD	5058(33.3%)	1853(28.9%)	1195(33.6%)	1176(36.9%)	834(41.0%)	<0.001
Symptoms						
Chest Pain*	8431(67.9%)	4234(73.1%)	1684(66.2%)	1453(63.1%)	1060(59.3%)	<0.001
Dyspnea**	2255(20.1%)	990(19.4%)	464(19.8%)	446(20.9%)	355(21.4%)	0.230
NCEP †						
Low Risk (<10%)	4641(30.5%)	2940(45.9%)	884(24.9%)	579(18.2%)	238(11.7%)	<0.001
Intermediate Risk (10-20%)	7740(51.0%)	2759(43.0%)	2063(58.0%)	1830(57.5%)	1088(53.5%)	<0.001
High Risk (>20%)	2805(18.5%)	712(11.1%)	608(17.1%)	776(24.4%)	709(34.8%)	<0.001
Medications						
Beta-Blocker ¥	2986(29.6%)	1025(22.5%)	656(30.5%)	682(35.9%)	623(41.5%)	<0.001
Aspirin §	4169(41.3%)	1262(27.8%)	1007(46.8%)	1081(56.9%)	819(54.5%)	<0.001<
ACE-inhibitor ‡	1493(14.8%)	463(10.2%)	314(14.6%)	347(18.3%)	369(24.6%)	0.001
Statin ₭	3862(38.2%)	989(21.8%)	891(41.4 %)	1026(54.0%)	956(63.6%)	<0.001
LV Parameters						
LV Ejection Fraction (%) ǂ	61.7±12.5	60.7±12.3	62.0±12.1	62.7±12.5	61.8±13.4	0.001
Normal LVEF (≥50%) ‖	7234(87.4%)	2862(89.3%)	1627(87.3%)	1587(87.2%)	1158(83.2%)	<0.001
Calcium Score	237.3±604.8	54.9±319.8	167.6±488.7	363.8±706.2	735.7±907.4	<0.001
Obstructive CAD	5,749(25.9%)	2(0.0%)	1,216(22.4%)	2,358(47.1%)	2,173(72.0%)	<0.001
SIS	1.00 (0.00, 4.00)	0.00 (0.00, 0.00)	1.00 (1.00, 2.00)	4.00 (3.00, 5.00)	8.00 (6.00, 9.00)	<0.001
%SIS/age	0.13 (0.00, 0.45)	0.00 (0.00, 0.00)	0.17 (0.13, 0.24)	0.47 (0.39, 0.58)	0.94 (0.81, 1.14)	<0.001

* n=12,424 ** n=11,240 † 10 year absolute risk of cardiovascular event ¥ n=10,104 § n=10,096 ‡ n=10,096 ₭ n=10,099 ǂ n=4,338 ‖ n=8,280

Table 4. Subanalysis cohort of patients with available calcium score: univariable analysis for mortality

	All Cause Death n=273	No All Cause Death n=14,913	Hazard Ratio (95% CI)	P value
Male Gender	164 (60.1%)	8491 (56.9%)	1.18(0.93-1.51)	0.174
Body Mass Index (kg/m^2) *	27.2±5.1	26.2±5.6	0.99(0.96-1.01)	0.309
Cardiac Risk Factors				
Smoker/Ex-smoker	87 (31.9%)	3457 (23.2%)	1.88(1.46-2.42)	<0.001
Hypertension	186 (68.1%)	7548 (50.6%)	2.17(1.68-2.79)	<0.001
Dyslipidemia	137 (50.2%)	8497 (57.0%)	0.72(0.57-0.92)	0.007
Diabetes	72 (26.4%)	2136 (13.3%)	2.04(1.56-2.67)	<0.001
Family History of CAD	88 (32.2%)	4970 (33.3%)	1.33(1.03-1.72)	0.029
NCEP **			2.17(1.83-2.57)	<0.001
Low risk	37 (13.6%)	4604 (30.9%)		
Intermediate risk	140 (51.3%)	7600 (51.0%)		
High risk	96 (35.2%)	2709 (18.2%)		
Chest Pain†	115 (59.0%)	8316 (68.0%)	0.59(0.44-0.79)	<0.001
Dyspnea‡	58 (29.9%)	2197 (19.9%)	2.33(1.71-3.18)	<0.001
Obstructive CAD (≥50%)	122 (44.7%)	3185 (21.4%)	3.46(2.72-4.40)	<0.001
Calcium Score §	664.5 ± 1116.9	229.5 ± 588.5	1.06(1.05,1.07)	<0.001
SIS	4.3±3.5	2.2±2.8	1.23(1.19-1.27)	<0.001
Age	68.6±13.2	58.2±12.4	1.09(1.08,1.10)	<0.001
%SIS	34.3±28.4	17.3±22.3	1.03(1.02,1.03)	<0.001
%SIS/Age	0.487±0.420	0.276±0.352	4.20(3.28-5.37)	<0.001
%SIS/Age category	2.7±1.0	2.0±1.1	1.82(1.64-2.02)	<0.001
Abnormal LVEF (≤50%) ¥	50 (29.6%)	996 (12.3%)	2.79(2.00-3.88)	<0.001

* n=14665 ** 10 year absolute risk of cardiovascular event † n=12424 ‡ n=11240 § Hazard ratio is per 100 unit increase in calcium score ¥ n=8280

Table 5. Subanalysis cohort of patients with available calcium score: Cox models for mortality. Only variables with a univariate p<0.05 were added in the cox regression model.

Models	Hazard Ratios (95% CI)	P value	Global Chi-Square	Harrell C-Statistic (95% CI)
Clinical			93.76	0.693 (0.657-0.730)
Smoker/Ex-smoker	1.82(1.41-2.35)	<0.001		
Hypertension	2.12(1.64-2.75)	<0.001		
Dyslipidemia	0.60(0.48-0.77)	<0.001		
Diabetes	1.89(1.44-2.49)	<0.001		
Family History CAD	1.30(1.00,1.68)	0.048		
Clinical + Obstructive CAD (≥50%)			166.79	0.729 (0.696-0.762)
Clinical				
Smoker/Ex-smoker	1.66(1.28-2.15)	<0.001		
Hypertension	1.98(1.52-2.57)	<0.001		
Dyslipidemia	0.55(0.43-0.70)	<0.001		
Diabetes	1.62(1.23-2.13)	<0.001		
Family History CAD	1.14(0.88,1.48)	0.322		
CCTA Results				
Obstructive CAD (≥50%)	3.07(2.40-3.93)	<0.001		
Clinical + CAC			179.57	0.731 (0.697-0.765)
Clinical				
Smoker/Ex-smoker	1.89(1.46-2.44)	<0.001		
Hypertension	2.00(1.54-2.59)	<0.001		
Dyslipidemia	0.58(0.45-0.73)	<0.001		
Diabetes	1.62(1.23-2.14)	<0.001		
Family History CAD	1.17(0.91,1.52)	0.223		
CCTA Results				
Calcium Score *	1.06 (1.05,1.07)	<0.001		
Clinical + Obstructive CAD (≥50%) + CAC			219.19	0.746 (0.713-0.778)
Clinical				
Smoker/Ex-smoker	1.73(1.34-2.24)	<0.001		
Hypertension	1.89(1.45-2.45)	<0.001		
Dyslipidemia	0.54(0.43-0.69)	<0.001		
Diabetes	1.48(1.12-1.96)	0.005		
Family History CAD	1.10(0.85,1.43)	0.470		
CCTA Results				
Obstructive CAD (≥50%)	2.36(1.82-3.06)	<0.001		

Calcium Score *	1.05 (1.04,1.06)	<0.001		
Clinical + Obstructive CAD (≥50%)+ CAC + %SIS/Age †			230.59	0.758 (0.728-0.789)
Clinical Factors				
Smoker/Ex-smoker	1.63(1.26-2.12)	<0.001		
Hypertension	1.82(1.40-2.36)	<0.001		
Dyslipidemia	0.53(0.41-0.67)	<0.001		
Diabetes	1.47(1.11-1.93)	0.007		
Family History CAD	1.10(0.85,1.42)	0.476		
CCTA Results				
Obstructive CAD (≥50%)	1.77(1.30-2.41)	<0.001		
Calcium Score *	1.04 (1.03,1.05)	<0.001		
%SIS/Age †	1.82(1.30-2.55)	<0.001		

* Hazard ratio is per 100 unit increase in calcium score † Continuous variable

References

1. Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. J Cardiovasc Comput Tomogr 2010;4:407 e1-33.
2. Chow BJ, Wells GA, Chen L, et al. Prognostic value of 64-slice cardiac computed tomography severity of coronary artery disease, coronary atherosclerosis, and left ventricular ejection fraction. Journal of the American College of Cardiology 2010;55:1017-28.
3. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. Journal of the American College of Cardiology 2007;50:1161-70.
4. Lin FY, Shaw LJ, Dunning AM, et al. Mortality risk in symptomatic patients with nonobstructive coronary artery disease: a prospective 2-center study of 2,583 patients undergoing 64-detector row coronary computed tomographic angiography. Journal of the American College of Cardiology 2011;58:510-9.
5. Bittencourt MS, Hulten E, Ghoshhajra B, et al. Prognostic value of nonobstructive and obstructive coronary artery disease detected by coronary computed tomography angiography to identify cardiovascular events. Circulation. Cardiovascular imaging 2014;7:282-91.
6. Hadamitzky M, Distler R, Meyer T, et al. Prognostic value of coronary computed tomographic angiography in comparison with calcium scoring and clinical risk scores. Circulation. Cardiovascular imaging 2011;4:16-23.
7. Raggi P, Callister TQ, Shaw LJ. Progression of coronary artery calcium and risk of first myocardial infarction in patients receiving cholesterol-lowering therapy. Arterioscler Thromb Vasc Biol 2004;24:1272-7.
8. Waters D, Craven TE, Lesperance J. Prognostic significance of progression of coronary atherosclerosis. Circulation 1993;87:1067-75.
9. Nicholls SJ, Hsu A, Wolski K, et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. J Am Coll Cardiol 2010;55:2399-407.
10. Ayoub C, Yam Y, Chen L, et al. The Prognostic Value of Percentage Total Plaque Score Adjusted to Age: A Potential Marker of Coronary Vascular Age. Angiology 2016.
11. Min JK, Dunning A, Lin FY, et al. Rationale and design of the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) Registry. J Cardiovasc Comput Tomogr 2011;5:84-92.
12. National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults Adult Treatment Panel III. Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Washington, DC: National Institutes of Health, 2009
13. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med 1979;300:1350-8.

14. Chaitman BR, Bourassa MG, Davis K, et al. Angiographic prevalence of high-risk coronary artery disease in patient subsets (CASS). Circulation 1981;64:360-7.
15. Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina). J Am Coll Cardiol 1999;33:2092-197.
16. Raff GL, Abidov A, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. J Cardiovasc Comput Tomogr 2009;3:122-36.
17. Abbara S, Arbab-Zadeh A, Callister TQ, et al. SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr 2009;3:190-204.
18. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827-32.
19. Chow BJ, Wells GA, Chen L, et al. Prognostic value of 64-slice cardiac computed tomography severity of coronary artery disease, coronary atherosclerosis, and left ventricular ejection fraction. J Am Coll Cardiol 2010;55:1017-28.
20. Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. Stat Med 2004;23:2109-23.
21. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157-72; discussion 207-12.
22. Pencina MJ, D'Agostino RB, Sr., Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 2011;30:11-21.
23. Pen A, Yam Y, Chen L, Dennie C, McPherson R, Chow BJ. Discordance between Framingham Risk Score and atherosclerotic plaque burden. European Heart Journal 2013;34:1075-82.
24. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226-35.
25. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988;12:56-62.
26. Burke AP, Kolodgie FD, Farb A, et al. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. Circulation 2001;103:934-40.
27. Emond M, Mock MB, Davis KB, et al. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. Circulation 1994;90:2645-57.
28. Proudfit WL, Bruschke VG, Sones FM, Jr. Clinical course of patients with normal or slightly or moderately abnormal coronary arteriograms: 10-year follow-up of 521 patients. Circulation 1980;62:712-7.
29. Choi TY, Li D, Nasir K, et al. Differences in Coronary Atherosclerotic Plaque Burden and Composition According to Increasing Age on Computed Tomography Angiography. Academic Radiology 2013;20:202-208.

30. Maffei E, Seitun S, Romano M, et al. Computed tomography coronary angiography plaque burden in patients with suspected coronary artery disease. Journal of Cardiovascular Medicine 2009;10:913-920.
31. Tota-Maharaj R, Blaha MJ, Rivera JJ, et al. Differences in coronary plaque composition with aging measured by coronary computed tomography angiography. International Journal of Cardiology 2012;158:240-5.
32. Enos WF, Holmes RH, Beyer J. Landmark article, July 18, 1953: Coronary disease among United States soldiers killed in action in Korea. Preliminary report. By William F. Enos, Robert H. Holmes and James Beyer. JAMA 1986;256:2859-62.
33. McNamara JJ, Molot MA, Stremple JF, Cutting RT. Coronary artery disease in combat casualties in Vietnam. JAMA 1971;216:1185-7.
34. Kaski JC, Chester MR, Chen L, Katritsis D. Rapid angiographic progression of coronary artery disease in patients with angina pectoris. The role of complex stenosis morphology. Circulation 1995;92:2058-65.
35. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336-45.
36. Erbel R, Budoff M. Improvement of cardiovascular risk prediction using coronary imaging: subclinical atherosclerosis: the memory of lifetime risk factor exposure. Eur Heart J 2012;33:1201-13.
37. Polonsky TS, McClelland RL, Jorgensen NW, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. JAMA 2010;303:1610-6.
38. Hadamitzky M, Freißmuth B, Meyer T, et al. Prognostic Value of Coronary Computed Tomographic Angiography for Prediction of Cardiac Events in Patients With Suspected Coronary Artery Disease. JACC: Cardiovascular Imaging 2009;2:404-411.
39. Ostrom MP, Gopal A, Ahmadi N, et al. Mortality incidence and the severity of coronary atherosclerosis assessed by computed tomography angiography. Journal of the American College of Cardiology 2008;52:1335-1343.
40. Rubinshtein R, Halon DA, Gaspar T, Peled N, Lewis BS. Cardiac computed tomographic angiography for risk stratification and prediction of late cardiovascular outcome events in patients with a chest pain syndrome. International Journal of Cardiology 2009;137:108-115.
41. van Werkhoven JM, Schuijf JD, Gaemperli O, et al. Incremental prognostic value of multi-slice computed tomography coronary angiography over coronary artery calcium scoring in patients with suspected coronary artery disease. European Heart Journal 2009;30:2622-9.
42. Wexler L, Brundage B, Crouse J, et al. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association. Writing Group. Circulation 1996;94:1175-92.
43. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation 1995;92:1355-74.
44. Choi EK, Choi SI, Rivera JJ, et al. Coronary computed tomography angiography as a screening tool for the detection of occult coronary artery disease in asymptomatic individuals. Journal of the American College of Cardiology 2008;52:357-65.
45. Hausleiter J, Meyer T, Hadamitzky M, Kastrati A, Martinoff S, Schomig A. Prevalence of noncalcified coronary plaques by 64-slice computed tomography in patients with an intermediate risk for significant coronary artery disease. Journal of the American College of Cardiology 2006;48:312-8.

46. Sandfort V, Lima JAC, Bluemke DA. Noninvasive imaging of atherosclerotic plaque progression: Status of coronary computed tomography angiography. Circulation: Cardiovascular Imaging 2015;8:e003316.
47. Al-Mallah MH, Qureshi W, Lin FY, et al. Does coronary CT angiography improve risk stratification over coronary calcium scoring in symptomatic patients with suspected coronary artery disease? Results from the prospective multicenter international CONFIRM registry. European heart journal cardiovascular Imaging 2014;15:267-74.
48. Cheezum MK, Hulten EA, Smith RM, et al. Changes in Preventive Medical Therapies and CV Risk Factors After CT Angiography. Jacc-Cardiovascular Imaging 2013;6:574-581.
49. Uretsky S, Rozanski A, Supariwala A, et al. Clinical outcomes following a strategy of optimized medical management and selective "downstream" procedures following coronary computed tomography angiography. Int J Cardiol 2013;165:468-73.
50. LaBounty TM, Devereux RB, Lin FY, Weinsaft JW, Min JK. Impact of Coronary Computed Tomographic Angiography Findings on the Medical Treatment and Control of Coronary Artery Disease and Its Risk Factors. American Journal of Cardiology 2009;104:873-877.
51. Chow BJ, Small G, Yam Y, et al. Prognostic and therapeutic implications of statin and aspirin therapy in individuals with nonobstructive coronary artery disease: results from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter registry) registry. Arterioscler Thromb Vasc Biol 2015;35:981-9.
52. Martin SS, Blaha MJ, Blankstein R, et al. Dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the multi-ethnic study of atherosclerosis. Circulation 2014;129:77-86.
53. Hwang IC, Jeon JY, Kim Y, et al. Statin therapy is associated with lower all-cause mortality in patients with non-obstructive coronary artery disease. Atherosclerosis 2015;239:335-42.