



## Visually estimated coronary artery calcium score improves SPECT-MPI risk stratification



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### ABSTRACT

**Aims:** Computed tomographic attenuation correction (CTAC) scans for single photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) may reveal coronary artery calcification. The independent prognostic value of a visually estimated coronary artery calcium score (VECACS) from these low-dose, non-gated scans is not established.

**Methods & Results:** VECACS was evaluated in 4,720 patients undergoing SPECT-MPI with CTAC using a 4-point scale. Major adverse cardiac events (MACE) were defined as all-cause mortality, acute coronary syndrome, or revascularization > 90 days after SPECT-MPI. Independent associations with MACE were determined with multivariable Cox proportional hazards analyses adjusted for age, sex, past medical history, perfusion findings, and left ventricular ejection fraction. During a median follow up of 2.9 years (interquartile range 1.8 – 4.2), 494 (10.5%) patients experienced MACE. Compared to absent VECACS, patients with increased VECACS were more likely to experience MACE (all log-rank  $p < 0.001$ ), and findings were similar when stratified by normal or abnormal perfusion. Multivariable analysis showed an increased MACE risk associated with VECACS categories of equivocal (adjusted hazard ratio [HR] 2.54, 95% CI 1.45–4.45,  $p = 0.001$ ), present (adjusted HR 2.44, 95% CI 1.74–3.42,  $p < 0.001$ ) and extensive (adjusted HR 3.47, 95% CI 2.41–5.00,  $p < 0.001$ ) compared to absent. Addition of VECACS to the multivariable model improved risk classification (continuous net reclassification index 0.207, 95% CI 0.131 – 0.310).

**Conclusion:** VECACS was an independent predictor of MACE in this large SPECT-MPI patient cohort. VECACS from CTAC can be used to improve risk stratification with SPECT-MPI without additional radiation.

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## 1. Introduction

Single photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) is a well-established and widely utilized non-invasive imaging modality for the diagnosis and prognostication of coronary artery disease (CAD) [1–4]. SPECT-MPI provides a functional assessment of CAD through evaluation of stress-induced perfusion abnormalities [1,5]. Traditional prognostic findings on SPECT-MPI include the extent and severity of ischemia, scar burden, left ventricular systolic function and volume [6–8]. Contemporary SPECT-MPI systems incorporate non-gated low-dose computed tomography imaging for attenuation correction. This innovation allows for correction of soft tissue attenuation

artifacts inherent to myocardial nuclear imaging and has become the standard of care. Computed tomography attenuation correction (CTAC) improves diagnostic accuracy [9], and can decrease the number of patients who require rest imaging after a stress-first protocol [10].

CTAC imaging with SPECT-MPI also allows for visualization of coronary artery calcium (CAC) [11], but this is not routinely evaluated or reported. In contrast, the quantitative Agatston coronary artery calcium score (CACS) is a well-established prognostic marker for CAD [2,3,12–15]. Agatston CACS imaging requires a dedicated, ECG-gated non-contrast CT-scan. CTAC imaging contains thicker slices, which is known to influence CACS [16], and is not ECG-gated. SPECT-MPI and Agatston CACS provide complementary functional and anatomic information and yield independent risk stratification [2,13]. Since CTAC is embedded within the SPECT-MPI workflow, with no additional cost or radiation, it may be beneficial to extract similar anatomic information. Visual CAC estimates derived from CTAC imaging correlate well with the Agatston

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CACS [17,18]. However, it is unclear whether a visually estimated coronary artery calcium score (VECACS) from CTAC imaging can provide incremental prognostic value. The aim of this study was to determine if a VECACS derived from CTAC has independent prognostic value in SPECT-MPI.

## 2. Methods

### 2.1. Study population

This was a retrospective study of consecutive patients who underwent SPECT-MPI with CTAC between September 1, 2014 to December 31, 2018 at a single tertiary academic hospital system. SPECT-MPI was performed in two affiliated nuclear testing laboratories and the population included both outpatients and inpatients with suspected or known CAD. Patients who underwent early revascularization (revascularization within 90 days of SPECT MPI) were excluded (n = 304) because SPECT MPI results may influence the decision to pursue revascularization [1], which may alter long-term outcomes [19,20]. The study was approved by University of Calgary Research Ethics Board (REB-ID ASD-7564), including waiver of consent. Data will be shared upon receipt of reasonable written request.

Past medical history and family history were prospectively collected in the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) database [21]. History of CAD was classified as history of previous myocardial infarction or revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)[22]. Information about resting ECG and stress induced ECG changes were also recorded prospectively.

### 2.2. Myocardial perfusion imaging protocol/scoring

Patients underwent a  $^{99m}\text{Tc}$ -Sestamibi rest-stress acquisition protocol with CTAC [23]. All studies were reported by experienced cardiologists with at least 5 years of experience in CACS and SPECT-MPI. Stress testing was conducted with symptom-limited exercise stress (n = 2,954) or pharmacological stress using dipyridamole (n = 1,534), adenosine (n = 17) or dobutamine (n = 91).

Weight-adjusted stress and rest dosages of  $^{99m}\text{Tc}$ -Sestamibi were used. The resting dosages were: standard-one day, 259 MBq (7 mCi); 350 MBq (9.5 mCi) for patients > 100 kg; and two-day each at 777 MBq (21 mCi) > for patients > 136 kg. The stress dosages corresponded to: standard-one day, 777 MBq (21 mCi); 1050 MBq (28.4 mCi) for patients > 100 kg. For pharmacological stress testing, both stress and rest SPECT images were obtained at least 45 min after tracer injection. For patients who underwent treadmill stress testing the SPECT images was acquired 15–30 min after stress. In total, 2,951 (61.9%) patients were scanned using the GE Discovery 570 CZT scanner (GE, Boston, USA). The remaining patients (n = 1,817, 38.1%) were imaged with a Ventri camera system (GE, Boston, USA).

The interpretation of SPECT-MPI was performed unblinded to clinical history and VECACS, using a 17-segment model [24]. Summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) were calculated for each patient as previously described [24]. Normal myocardial perfusion was defined as SSS < 4 [25]. Left ventricular ejection fraction was calculated from gated images.

### 2.3. CTAC image acquisition and interpretation

CTAC was performed using a built in CT scanner (Lightspeed VCT 64, GE, Boston, USA). CTAC study was performed after the rest

acquisition during end-expiratory breath hold with no ECG-gating, in helical mode with a slice thickness of 5-mm, tube voltage of 120 kVp and 30 mA, using a 512x512 matrix. CTAC images were reviewed at the time of SPECT-MPI reporting and graded as: absent, equivocal, present or extensive. Extensive calcification was defined as estimated Agatston CACS>400 [26,27]. Fig. 1 shows a representative case from each group. We did not assess interobserver agreement, but previous studies have demonstrated excellent interobserver agreement for similar estimates (kappa 0.89 to 0.94) [17,18].

### 2.4. Clinical outcomes

Follow up for major adverse cardiovascular events was obtained through the Discharge Abstracts/National Ambulatory Care Reporting system and Alberta Vital Statistics. MACE was defined as late revascularization (PCI or CABG, >90 days after SPECT-MPI), non-fatal acute coronary syndrome (non-fatal myocardial infarction or admission for unstable angina), or all-cause mortality. Follow-up was established up until December 31, 2019. However, these databases do not capture emigration and it's possible that some patients were lost to follow-up on this basis. Patients undergoing early revascularization were excluded. Event rates for VECACS score categories (absent, equivocal, present, and extensive) were determined. SPECT-MPI and VECACS findings were combined to assess whether VECACS yielded incremental prognostic information and resulted in risk re-classification beyond SPECT-MPI findings alone.

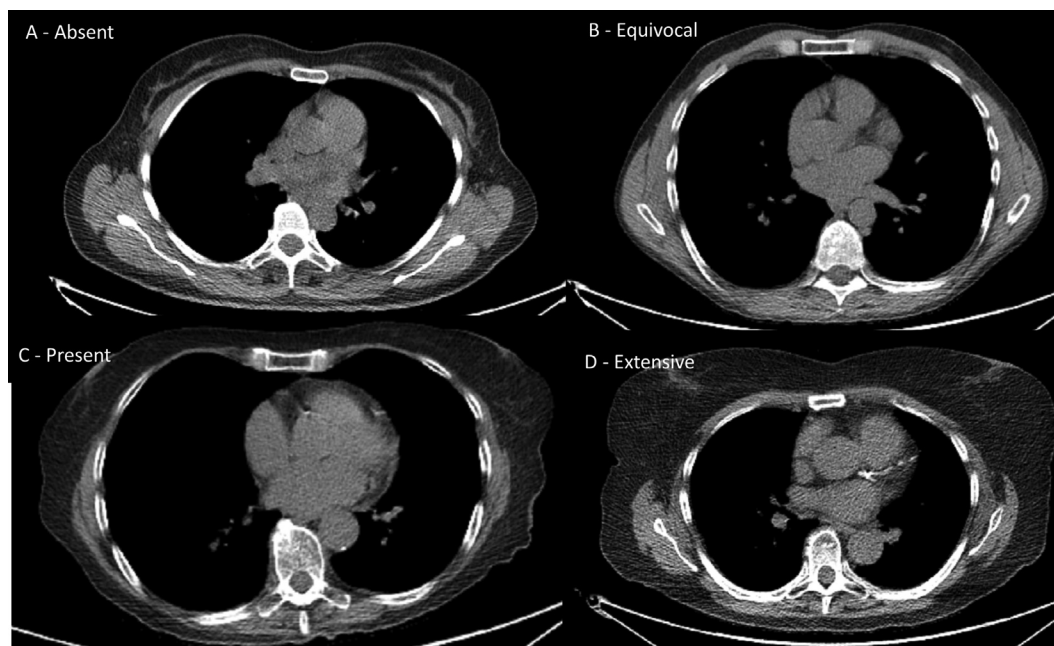
### 2.5. Statistical analysis

Continuous variables were summarized as mean (standard deviation [SD]) if normally distributed and compared using a Student's *t*-test or analysis of variance. Continuous variables that were not normally distributed were summarized as median (interquartile range [IQR]) and compared using a Mann-Whitney *U* test or Kruskal-Wallis test. Associations with MACE were assessed for categories of perfusion abnormality and VECACS in bivariable and multivariable Cox proportional hazards analyses. There was minimal missing data (0.04%). Missing variables were imputed with the population mean value for continuous variables and a distinct missing category for categorical variables.

The multivariable model included VECACS in addition to age, sex, past medical history (hypertension, diabetes, dyslipidemia, smoker, CHF, stroke, CKD, or prior CAD), mode of stress, inpatient status, SRS, SDS and LVEF similar to previous studies [2,8,28,29]. We assessed for interactions between perfusion and VECACS with all other variables included in the multivariable model.

The analysis was repeated to assess associations with each of the components of the composite outcome. The proportional hazards assumption was assessed for all models using Schoenfeld residuals and was found to be valid in all analyses. Lastly, we assessed the net reclassification index of adding VECACS to the full multivariable model. Net reclassification index (NRI) was used to assess the additive prognostic utility of VECACS when added to the other components of the multivariable model.[30]. Bootstrapping was used to calculate 95% confidence intervals (CI) for event, non-event, and continuous NRI.[31] Categorical NRI was also assessed. Model goodness-of-fit was compared with a likelihood ratio test and calibration was assessed using Brier scores.

All statistical tests were two-sided and a *p*-value < 0.05 was considered statistically significant. All analyses were performed using Stata/IC version 13.1 (StataCorp, College Station, Texas, USA).



**Fig. 1.** Examples of visually estimated coronary artery calcium groups. A) absent, no coronary artery calcification B) equivocal, possible calcification in proximal right coronary artery C) present, calcification in the left anterior descending and right coronary artery ostium D) extensive, calcification in the left main, left anterior descending, and left circumflex arteries.

### 3. Results

#### 3.1. Patient characteristics

A total of 4,720 patients who underwent SPECT MPI between September 1, 2014 and December 31, 2018 were included. Population characteristics are shown in [Table 1](#). The patients who experienced MACE were older ( $69.9 \pm 11.1$  vs  $64.9 \pm 11.7$ ,  $p < 0.001$ ) and more likely to be male (64.0% vs 52.4%,  $p < 0.001$ ) or have a history of diabetes (35.8% vs 23.8%,  $p < 0.001$ ). Patients experiencing MACE were more likely to have extensive VECACS (42.7% vs 18.8%,  $p < 0.001$ ). Patients without MACE were more likely to have absent VECACS at baseline (32.7% vs 8.9%,  $p < 0.001$ ). Characteristics of patients with and without MACE are shown in [Table S1](#).

#### 3.2. Associations with MACE

During median follow-up of 2.9 years (IQR 1.8 – 4.2), at least one MACE occurred in 494 (10.5%) patients including a total of 322 (6.8%) deaths, 155 (3.3%) acute coronary syndromes, and 111 (2.4%) late revascularizations. Kaplan-Meier survival estimate curves stratified by VECACS in the overall population are demonstrated in [Fig. 2](#). Patients with equivocal, present, or extensive VECACS were more likely to experience MACE during follow-up compared to patients without VECACS (all log-rank  $p < 0.001$ ). Patients with extensive VECACS were more likely to experience MACE than patients with equivocal or present VECACS (log rank  $p < 0.001$ ). Annualized MACE rates across categories of perfusion and VECACS are shown in [Fig. 3](#).

Kaplan-Meier survival curves stratified by VECACS in patients with normal ( $SSS < 4$ ) and abnormal ( $SSS \geq 4$ ) stress perfusion are shown in [Fig. 4a and 4b](#) respectively. Differences between groups of VECACS were similar to the overall results in patients with normal SPECT perfusion. However, in patients with abnormal perfusion, only extensive VECACS was associated with increased MACE compared to patients with absent VECACS (log-rank  $p < 0.001$ ) or compared to patients with equivocal or present

VECACS (both log-rank  $p < 0.03$ ). We also assessed results in patients without a history of CAD ([Fig. 4c](#)) and with known CAD ([Fig. 4d](#)). In patients without CAD, patients with equivocal, present, or extensive VECACS were more likely to experience MACE during follow-up compared to patients with absent VECACS (all log-rank  $p < 0.001$ ). There were no significant differences in patients with a history of CAD (all log-rank  $p > 0.05$ ).

Results of univariable and multivariable Cox proportional hazard analysis for the primary outcome are shown in [Table 2](#). VECACS categories of equivocal (adjusted HR 2.54, 95% CI 1.45–4.45,  $p = 0.001$ ), present (adjusted HR 2.44, 95% CI 1.74–3.42,  $p < 0.001$ ) and extensive (adjusted HR 3.47, 95% CI 2.41–5.00,  $p < 0.001$ ) were all independently associated with increased MACE events compared to absent. Additionally, increasing SDS was independently associated with increased risk of MACE (adjusted HR 1.05 per point, 95% CI 1.02–1.07,  $p < 0.001$ ).

The multivariable analysis was repeated for each of the components of the MACE outcome with results in [Table 3](#). Associations with non-fatal outcomes were assessed using a Fine Gray competing risk analysis and death as the competing risk. There was an independent association with increased all-cause mortality associated with VECACS categories of equivocal (adjusted HR 2.39,  $p = 0.007$ ), present (adjusted HR 1.75,  $p = 0.004$ ) and extensive (adjusted HR 2.44,  $p < 0.001$ ) compared to a VECACS category of absent. For the non-fatal outcomes there was a more stepwise increase in risk associated with increasing VECACS categories. Associations with VECACS in patients with and without history of CAD are shown in [Table S2](#).

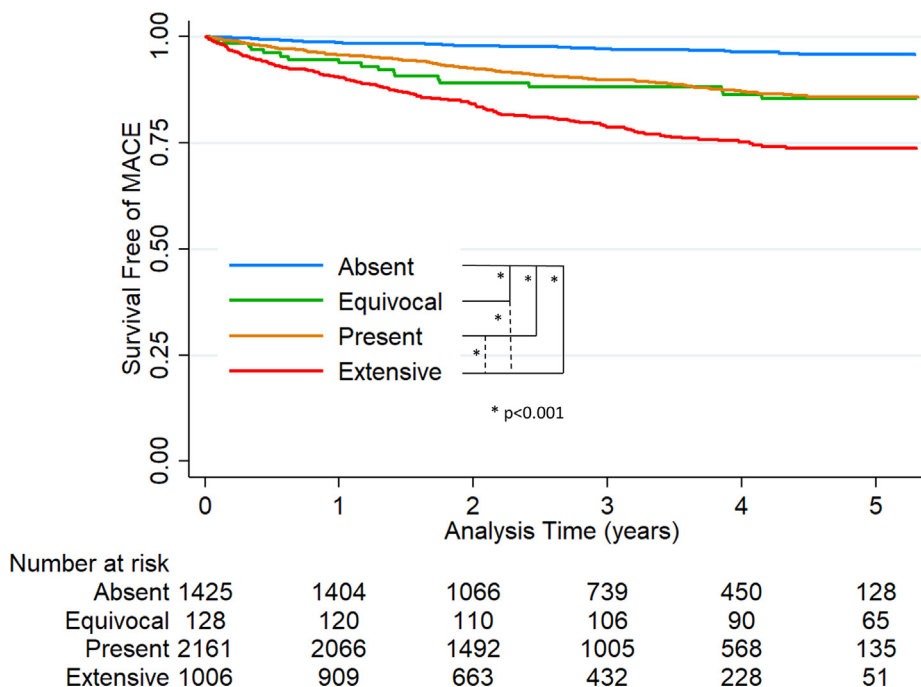
#### 3.3. Net reclassification

We assessed the net risk reclassification when VECACS was added to the remainder of the multivariable model (as shown in [Table 2](#)). Addition of VECACS using the four-group system improved overall reclassification (continuous NRI 0.207, 95% CI 0.131– 0.310), with improvement in model fit (increase LR  $\chi^2$  44.9,  $p < 0.001$ ). This was driven by improved reclassification of

**Table 1**  
Baseline Population Characteristics that stratified by VECACS score.

	Absent (n = 1,427)	Equivocal (n = 128)	Present (n = 2,181)	Present-extensive (n = 1,032)	P-Value
Age, mean ± SD	68.5 ± 11.3	63.4 ± 12.6	66.9 ± 10.6	72.1 ± 9.2	<0.001
Male, n(%)	571 (40.0)	66 (51.6)	1,254 (57.5)	673 (65.2)	<0.001
Past Medical History					
Hypertension, n(%)	646 (45.3)	54 (42.2)	1,332 (61.1)	712 (69.0)	<0.001
Diabetes, n(%)	229 (16.1)	28 (21.9)	597 (27.4)	344 (33.3)	<0.001
Dyslipidemia, n(%)	446 (31.3)	43 (33.6)	1,093 (50.1)	621 (60.2)	<0.001
Current Smoker, n(%)	143 (10.0)	11 (8.6)	224 (10.3)	133 (12.9)	0.077
History of CAD, n(%)	41 (2.9)	22 (17.2)	258 (11.8)	272 (26.4)	<0.001
CHF, n(%)	28 (2.0)	6 (4.7)	98 (4.5)	81 (7.9)	<0.001
Stroke, n(%)	9 (0.6)	4 (3.1)	19 (0.9)	11 (1.1)	0.035
CKD, n(%)	6 (0.4)	2 (1.6)	32 (1.5)	19 (1.8)	0.008
Family History, n(%)	613 (43.0)	24 (18.8)	963 (44.2)	422 (40.9)	<0.001
Exercise Stress, n(%)	1,017 (71.3)	82 (64.1)	1364 (62.5)	525 (50.9)	<0.001
Inpatient, n(%)	470 (32.9)	54 (42.2)	829 (38.0)	418 (40.5)	0.001
SSS	0 (0 - 0)	0 (0 - 2)	0 (0 - 2)	2 (0 - 6)	<0.001
SRS	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 3)	<0.001
SDS	0 (0 - 0)	0 (0 - 1)	0 (0 - 1)	0 (0 - 2)	<0.001
LVEF	69 (61 - 74)	69 (60 - 75)	66 (57 - 73)	63 (49 - 71)	<0.001

Categorical variables presented as n (%), continuous variables presented as mean ± SD or median (interquartile range). MACE - major adverse cardiac event, CAD-coronary artery disease, CKD-chronic kidney disease, SSS-summed stress score, SRS-summed rest score, SDS- summed difference score, LVEF-left ventricular ejection fraction, LVESV-left ventricular end systolic volume, VECACS- Visually estimated coronary artery calcium score



**Fig. 2.** MACE-free survival based on visually estimated coronary artery calcium score in the overall patient population. Significance assessed using log-rank p-values.

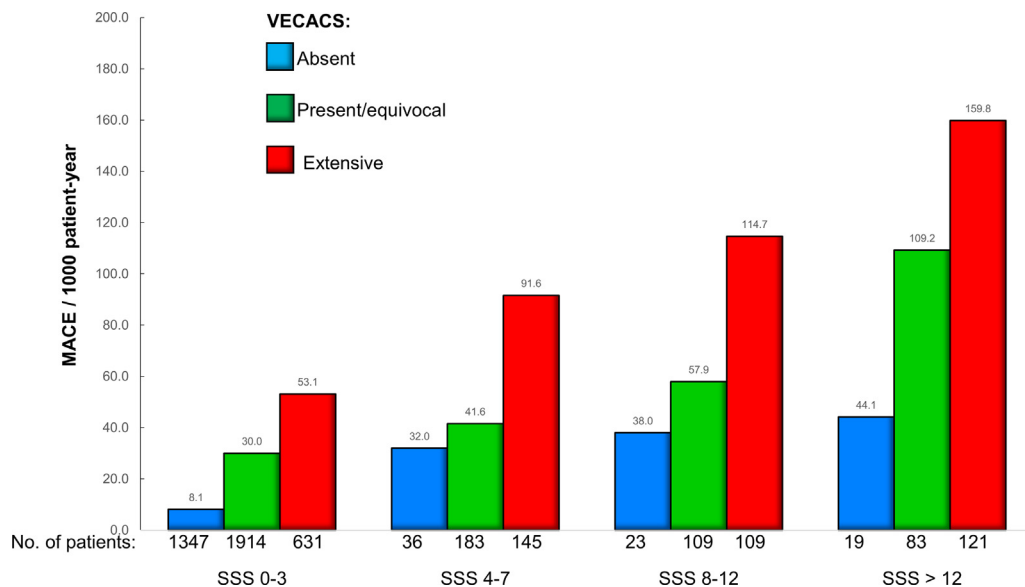
the proportion of patients with events to higher predicted risks (event NRI 0.219, 95% CI 0.165– 0.297) but not patients without events to lower predicted risks (non-event NRI –0.012, 95% CI –0.052 to 0.038). Model calibration was similar with (Brier score 0.102) and without VECACS (Brier score 0.108). VECACS with 4 groups resulted in better model fit compared to the presence/absence of coronary calcification alone (increase LR  $\chi^2$  11.4, likelihood ratio test p-value = 0.003). Results of the categorical NRI analysis are shown in **Table S3**.

**4. Discussion**

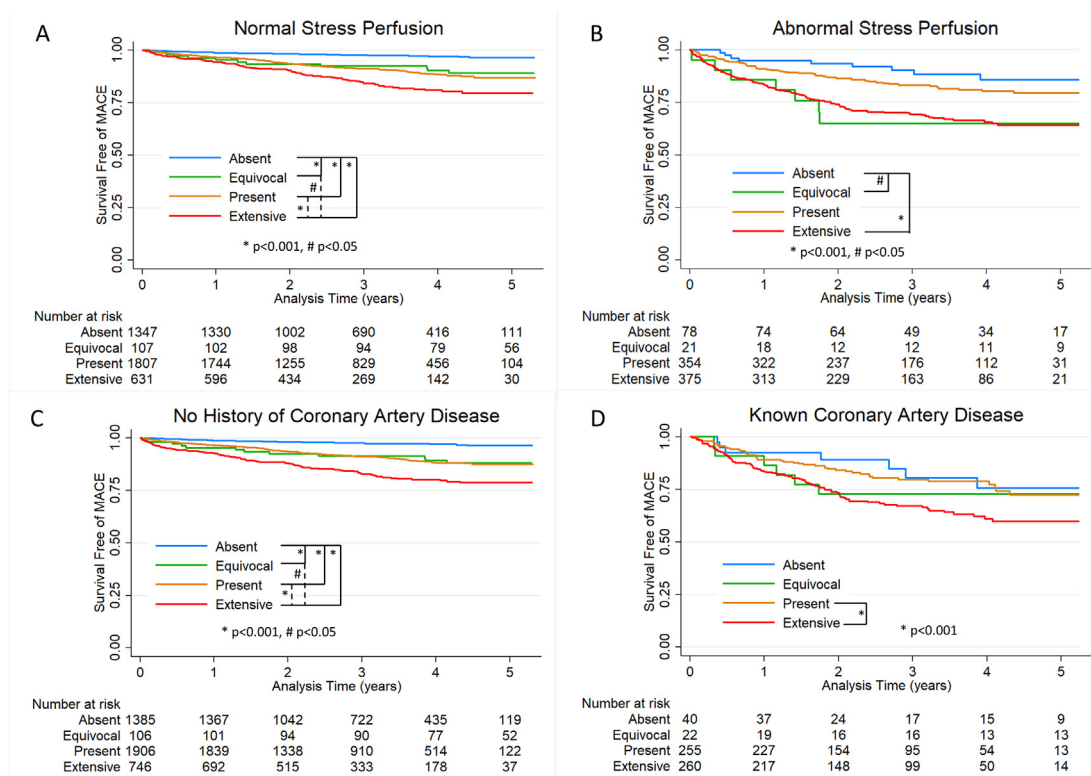
In patients who underwent SPECT-MPI, VECACS was a significant and independent predictor of MACE, which persisted after

adjusting for traditional SPECT-MPI results. We found an independent increase in death, ACS, and late revascularization that occurred in a stepwise fashion with progressively increased VECACS category. VECACS stratified risk of MACE in patients with normal and abnormal regional perfusion. Additionally, reporting of extensive VECACS significantly improved risk estimation when added to other SPECT MPI variables. Our findings suggest that a VECACS should be reported on SPECT-MPI studies using CTAC.

There is growing evidence that physicians should incorporate both anatomical and functional information when assessing patients with known or suspected CAD. Although a sensitive marker for coronary atherosclerosis, the Agatston CACS has modest predictive value for obstructive CAD on cardiac catheterization [32]. In contrast, SPECT-MPI identifies flow limiting CAD but is



**Fig. 3.** Incidence of major adverse cardiovascular events (MACE), stratified by stress perfusion and visually estimated coronary artery calcium (VECACS). SSS – summed stress score.



**Fig. 4.** MACE-free survival based on visually estimated coronary artery calcium score in patients with a) normal SPECT-MPI b) abnormal SPECT-MPI c) no history of coronary artery disease (CAD) d) known CAD. Significance assessed using log-rank p-values.

insensitive to subclinical atherosclerosis [33]. When combined, SPECT-MPI and quantitative CACS provide both anatomical and functional assessment of CAD, which may improve sensitivity and specificity compared with each test alone [3]. Chang et al. (2009) demonstrated that quantitative CACS combined with SPECT-MPI findings provided independent and complementary information among a cohort of 1,126 patients without prior CAD [13]. The prevalence of abnormal perfusion increased with increasing CACS, and CACS score predicted cardiovascular risk among

patients with both normal and abnormal perfusion. Engbers et al. evaluated combined Agatston CACS and SPECT-MPI in 4,897 symptomatic patients without prior CAD[2], demonstrating a stepwise increase in MACE with increasing CACS among patients with both normal and abnormal perfusion. Our study is in line with these findings and confirms that anatomical data from the VECACS has an added prognostic value when combined with SPECT-MPI.

The strong prognostic value of VECACS on CTAC has implications for reporting of CAC detected through other non-dedicated

**Table 2**  
Results of Cox proportional hazard analysis for primary outcome.

Variable	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age (per 10 years)	1.46(1.35–1.58)	<0.001	1.16 (1.05 – 1.27)	0.002
Male	1.60 (1.33–1.92)	<0.001	1.15 (0.94 – 1.40)	0.179
Hypertension	1.24(1.03–1.48)	0.020	0.95 (0.77 – 1.16)	0.587
Diabetes	1.82 (1.51–2.19)	<0.001	1.43 (1.17 – 1.74)	<0.001
Dyslipidemia	1.11(0.93–1.33)	0.247	0.78 (0.64 – 0.95)	0.012
Current Smoker	1.01(0.76–1.33)	0.953	1.00 (0.75 – 1.33)	0.982
History of CAD	3.52 (2.91–4.27)	<0.001	2.06 (1.67 – 2.53)	<0.001
CHF	2.72 (2.04, 3.64)	<0.001	1.33 (0.62 – 2.86)	0.461
Stroke	2.14 (1.15 – 4.01)	0.017	1.42 (0.75 – 2.68)	0.282
CKD	1.94 (1.07 – 3.53)	0.029	1.12 (0.61 – 2.06)	0.707
Exercise Stress	0.41 (0.34 – 0.49)	<0.001	0.56 (0.47 – 0.68)	<0.001
Inpatient	1.69 (1.41 – 2.01)	<0.001	1.34 (1.11 – 1.60)	0.002
SSS	1.07 (1.06 – 1.08)	<0.001	–	–
SRS	1.07 (1.06 – 1.08)	<0.001	1.02 (1.00 – 1.03)	0.049
SDS	1.10 (1.08 – 1.13)	<0.001	1.05 (1.02 – 1.07)	<0.001
LVEF	0.97 (0.96–0.97)	<0.001	0.99 (0.98 – 1.00)	0.003
<b>VECACS</b>				
Absent	Reference	Reference	Reference	Reference
Equivocal	3.81 (2.20 – 6.59)	<0.001	2.54 (1.45 – 4.45)	0.001
Present	3.51 (2.54 – 4.85)	<0.001	2.44 (1.74 – 3.42)	<0.001
Extensive	7.61 (5.50 – 10.5)	<0.001	3.47 (2.41 – 5.00)	<0.001

CAD: coronary artery disease, CHF: congestive heart failure, CKD: chronic kidney disease, SSS: summed stress score, SRS: summed rest score, SDS: summed difference score, LVEF: left ventricular ejection fraction, VECACS: visually estimated coronary artery calcium score.

**Table 3**  
Results of multivariable Cox proportional hazard analysis MACE components.

	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
All-cause mortality				
Absent	Reference	Reference	Reference	Reference
Equivocal	3.50 (1.89 – 6.50)	<0.001	2.39 (1.26 – 4.54)	0.007
Present	2.65 (1.84 – 3.83)	<0.001	1.75 (1.19 – 2.56)	0.004
Extensive	5.57 (3.85 – 8.05)	<0.001	2.44 (1.61 – 3.69)	<0.001
Acute coronary Syndrome				
Absent	Reference	Reference	Reference	Reference
Equivocal	3.84	0.054	2.51 (0.62 – 10.2)	0.196
Present	6.18 (2.83 – 13.5)	<0.001	4.90 (2.12 – 11.3)	<0.001
Extensive	13.2 (6.04 – 28.8)	<0.001	7.37 (2.95 – 18.4)	<0.001
Late revascularization				
Absent	Reference	Reference	Reference	Reference
Equivocal	6.88(1.52 – 31.2)	0.012	4.13 (0.86 – 19.8)	0.076
Present	8.56 (3.09–23.7)	<0.001	6.80 (2.27 – 20.4)	<0.001
Extensive	18.8 (6.82 – 52.1)	<0.001	11.6 (3.50 – 38.5)	<0.001

Results of univariable and multivariable Cox proportional hazard analysis for each of the components of MACE. Association with non-fatal outcomes modeled with a competing hazard of death and values representing sub-hazard ratio estimates. CI – confidence interval, HR- hazard ratio.

CT scans. Coronary calcification has significant prognostic value on lung cancer screening CT scans [34]. Recent Society of Cardiovascular CT guidelines recommend the routine reporting of incidental CAC detected on non-cardiac chest CT [35]. The suggested visually estimated Coronary Artery Calcium Data and Reporting System (CAC-DRS) parallels the VECACS score used in our study [36]. Our study highlights the significance of incidental CAC detected during clinical practice and supports recommendations for reporting VECACS.

VECACS from low-dose CTAC scans have shown good correlation with the quantitative Agatston CACS [17,18]. Einstein et al. compared these values in 492 patients who underwent both SPECT-MPI and quantitative CACS imaging [18]. Experienced readers scored VECACS using a six-level scale (0, 1–9, 10–99, 100–399, 400–999 and > 1,000). The CACS score was within the visually estimated range in 63% of cases and within one category in 93% of cases (weighted kappa 0.89,  $p < 0.0001$ ). Mylonas et al. assessed VECACS and CACS in 91 patients who underwent positron emission tomography MPI and CACS within 6 months [17]. VECACS from CTAC images had good intraclass correlation with CACS (0.844),

and demonstrated excellent interobserver agreement using a 4-point scale (kappa 0.941) [17]. Therefore, while VECACS is inherently subjective there seems to be reasonable accuracy and interobserver agreement. The radiation exposure from CTAC (<1mSv) is lower compared to dedicated CAC scanning which average ~ 1 mSv [37,38]. However, both are associated with relatively low radiation exposure compared to a 1-day myocardial rest stress study using Tc-99 m sestamibi (~9 mSv) [39].

In addition to improving risk estimation, reporting VECACS may influence patient management decisions. Current guidelines recommended use of CACS to identify intermediate risk patients who may benefit from lipid lowering therapy [40]. In a randomized trial use of the Agatston CACS to guide therapy improved vascular risk profile versus conventional management alone [41]. It is likely that patient knowledge of CACS improved compliance with medications and lifestyle changes. CACS also identifies patients most likely to benefit from statin therapy, with an NNT of 12 to prevent 10-year MACE with CACS > 100 [42]. Detecting coronary calcium may facilitate preventative interventions, facilitating appropriate therapy intensification but also enabling de-escalation of low-

yield strategies. In our study, patients with absent VECACS had a low risk of MACE independent of SPECT-MPI findings. Additionally, even equivocal VECACS, which represents patients with a small burden of coronary calcification, was associated with increased risk. Reporting VECACS could help physicians target medical therapies, but also be used to engage patients in their care.

Our study has a few important limitations in addition to its retrospective design. Readers were not blinded to VECACS and this likely influenced interpretation of perfusion findings. In spite of this, VECACS was an independent predictor of MACE. Some patients may have been lost to follow-up due to emigration; however, this is less common in the older age groups represented in our study [43]. VECACS was reported by individual readers experienced in MPI and quantitative CACS imaging. While there was inherent interobserver variability, previous studies of VECACS have shown this variability is low. The simple visual VECACS classification scale utilized in this study was readily integrated into a clinical workflow and provided meaningful risk stratification. However, the development of automated methods to quantify CAC, for example using artificial intelligence techniques [34,44], may provide more precise estimates of CACS and remove the need for visual estimation. Future studies could investigate novel risk scores incorporating VECACS, with dedicated derivation and validation cohorts. Finally, VECACS was reported clinically which could have influenced patient management and decisions to pursue revascularization. However, increasing VECACS was also associated with increased risk for all-cause mortality and ACS.

## 5. Conclusion

The VECACS is an independent predictor of MACE, complementary to traditional clinical and SPECT-MPI risk-markers. SPECT-MPI readers should consider routinely evaluating and reporting VECACS based on CTAC. Future SPECT-MPI reporting guidelines may consider recommendations for VECACS assessment as well as standardized reporting criteria.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2021.100827>.

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