American Journal of Preventive Cardiology 12 (2022) 100423

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/american-journal-of-preventive-cardiology

Original Research

Association between plaque localization in proximal coronary segments and MACE outcomes in patients with mild CAC: Results from the EISNER study

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ARTICLE INFO

Keywords:
Coronary artery calcium
Coronary artery disease
Plaque location
Prognosis
Computed tomography

ABSTRACT

Objective: Coronary artery calcium score (CAC) is a validated tool to predict and reclassify cardiovascular risk. Additional metrics such as regional distribution and extent of CAC over Agatston CAC score may allow further risk stratification. In this study, we evaluate the prognostic significance of proximal CAC involvement in asymptomatic population from the prospective EISNER (Early-Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) registry, focusing on patients with mild CAC (score 1-99).

Methods: This study included a total of 2,047 adult asymptomatic subject who underwent baseline CAC scan and 14-year follow-up for MACE, defined as myocardial infarction, late revascularization, or cardiac death. Proximal involvement was defined as presence of CAC in the LM, proximal LAD, LCX or RCA. CAC was categorized as 0, 1-99, and ≥100.

Results: 1,090 (53.2%) subjects had no CAC, 576 (28.1%) had CAC 1-99, and 381 (18.7%) had CAC ≥100. Proximal involvement was seen in 67.2% of subjects with CAC 1-99 and 97.3% of subjects with CAC ≥100. In the CAC 1-99 category, the presence of proximal CAC was associated with increased MACE risk after adjustment for CAC score, CAC extent and conventional risk factors compared to those without proximal CAC (HR: 2.84 95% CI: 1.29-6.25, p=0.009).

Conclusion: In asymptomatic subjects with CAC scores of 1-99, the presence and extent of proximal CAC plaques provides strong independent prognostic information in predicting MACE

1. Introduction

Coronary artery calcium (CAC) is a marker of atherosclerosis and a powerful predictor of future adverse cardiovascular disease (CVD) events [1]. The Agatston CAC score is the most widely used method to quantify the burden of CAC [2]. Consistent evidence from a large number of registry and population-based studies has shown that presence and extent of CAC improves prediction of CVD events over traditional risk factors [1,3]. In 2018, the American College of Cardiology/American Heart Association guideline on the management of blood cholesterol made a class IIa recommendation for use of CAC in intermediate risk asymptomatic patients in whom a risk-based treatment decision is uncertain [4]. The guideline recommends the use of statin for CAC ≥ 100 unless contraindicated. For patients with CAC 1-99, the recommendations favor use of statin, but there is no specific direction given regarding its use in these patients.

Recent studies have suggested incorporating additional metrics such as CAC density, number of CAC lesions, regional distribution, or extent

Abbreviations: CAC, Coronary artery calcium; CVD, cardiovascular disease; CAD , coronary artery disease; MACE, major adverse cardiac events; EISNER, Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ASCVD, 10-year risk atherosclerotic cardiovascular disease score; HR, hazard ratio; NRI, net classification index; LM, left main; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

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https://doi.org/10.1016/j.ajpc.2022.100423
Received 27 July 2022; Received in revised form 20 September 2022; Accepted 26 September 2022
Available online 27 September 2022

of CAC can improve the predictive utility of the CAC score[5–7]. Previous studies have shown that coronary artery disease (CAD) involvement of the proximal portions of the coronary arteries is associated with a poorer prognosis compared to non-proximal disease [8–11]. Although the location and distribution of CAC can be assessed by non-contrast CAC scan, information about distribution of CAC in each coronary artery is not utilized in routine clinical practice. We hypothesized that incorporating proximal CAC location will improve the identification of asymptomatic patients at a high risk of future CVD events. To test this hypothesis, we evaluated the significance of proximal CAC involvement as a predictor of major adverse cardiac events (MACE) in a cohort of patients with CAC scores 1-99 within the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) registry.

2. Methods

2.1. Study population

Our study population included asymptomatic subjects enrolled in the EISNER registry who completed long-term 14-year prognostic follow up [12,13]. The EISNER registry included adult asymptomatic subjects age between 45-80 years with an intermediate risk of CAD based on presence of at least one CAD risk factor in younger individuals (age 45-54 years in men or 55- 64 years in women) or age (> 55 years in men, >65 years in women), who underwent CAC scanning between September 1998 and May 2005. Subjects with a history of CVD (stroke or myocardial infarction) or chest pain, prior CAC scanning or invasive coronary angiography, or significant medical co-morbidity were excluded. The current analysis included 1,061 (51.8%) subjects from the CAC scan group from the randomized EISNER trial [14] and 986 (48.2%) subjects with available cardiac CT scans and long-term follow-up from the EISNER 4 sub-trial with no randomization [15]. This study was approved by Cedars-Sinai Medical Center Institutional Review Board and all participants provided written informed consent.

2.2. Data collection and outcome assessment

CVD risk factors and clinical information were collected from all participants through a detailed questionnaire. Information obtained was co-morbidities, smoking history, alcohol consumption and medications. Measurements like body mass index (BMI), blood pressure, fasting total, high density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol, triglycerides, and serum glucose were also collected. 10-year risk atherosclerotic cardiovascular disease (ASCVD) score was calculated using the Pooled Cohort Equation [16]. Participants were followed up for a mean of 14 ± 3 years for MACE. MACE was defined as a composite endpoint, consisting of myocardial infraction, late revascularization (> 180 days after CT), or cardiac death. Prospective outcomes data was gathered in 2047 (77%) individuals. The study chart is highlighted in Fig. 1. Subjects were followed up through clinical visits, phone calls and mail. Any adverse events were verified by comprehensive medical, hospital and death records by two independent cardiologists [17].

2.3. Image acquisition and analysis

All subjects underwent baseline non-contrast CAC scanning CT on an Electron Beam CT scanner (e-Speed, GE Healthcare, Milwaukee, WI, USA) or 4-slice CT scanner (Somatom Volumezoom, Siemens Medical Solutions, Erlangen, Germany). The electrocardiogram gated slices were obtained during single breath hold; tube voltage was 120 kVp and with 2.0, 2.5 or 3 reconstructed slice thickness.

CAC was measured using semi-automated CAC scoring software (ScImage Inc., Los Altos, CA, USA). CAC was categorized as no (0), low (1–99), intermediate (100–399) and high (≥400). For localization of CAC, we used the coronary segment model of the Society of Cardiovascular Computed Tomography [18]. The three coronary arteries were identified, and the proximal location of CAC in each coronary artery was determined based on the branches (left anterior descending artery (LAD) based on the first diagonal branch, left circumflex (LCX) based on the first obtuse marginal branches) or distance from the ostium to the origin of first acute marginal artery for right coronary artery (RCA) with two imaging cardiologists (RT and DH), including arbitrations of ambiguous

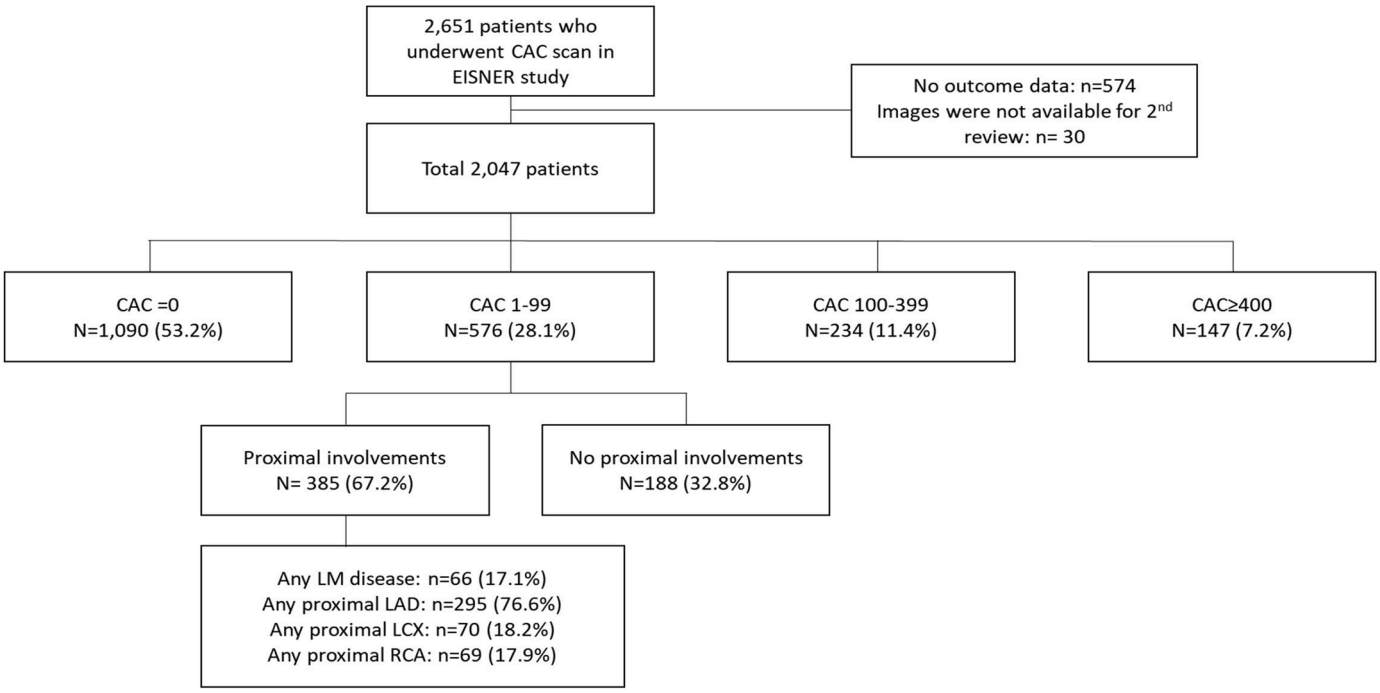

Fig. 1. Study flow. Abbreviations: CAC, coronary artery calcium; N, number of subjects; LM, left main; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery

cases.

2.4. Statistical analysis

Continuous variables are reported as mean ± standard deviation. Group comparisons were done using independent student t-test or the one-way analysis of variance (ANOVA) for the continuous variables and chi-square test for categorical variables. Cumulative MACE incidence was assessed using the Kaplan–Meier method and compared with log-rank test, or log-rank test for trend as appropriate. Cox proportional hazards regression models were used to calculate hazard ratios (HR) with 95% confidence intervals (CI). Multivariable model included age, sex, BMI, hypertension, dyslipidemia, diabetes, smoking, family history of premature CAD, log transformed CAC score, CAC extent, and proximal CAC involvement. CAC extent was assessed using the number of vessels with CAC [19]. The incremental discriminative value of proximal CAC involvement over CAC score and CAC extent for MACE was assessed using global χ^2 and net classification index (NRI) analyses [20]. All analyses were performed by STATA (version 16; StataCorp, College Station, TX, USA), and a P-value <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Among the population, 1,090 (53.2%) subjects had no CAC, 576 (28.1%) had CAC 1-99, and 234 (11.4%) and 147 (7.1%) subjects with CAC 101-399 and ≥400, respectively. Baseline characteristics of subjects according to CAC categories are summarized in Table 1. Subjects with increased CAC were older and had a higher proportion of men and patients with hypertension, diabetes, and dyslipidemia. The frequency of smoking and family history of premature CAD did not differ between the CAC groups. The frequency of statin and aspirin use was higher in subjects with increased CAC.

The prevalence of proximal CAC increased with higher CAC categories (Table 1). Among the subjects with high CAC (CAC ≥400), 76% had left main coronary artery (LM) or three vessel proximal involvement, compared to 37.6% of those with CAC 100-399 and 12.5% of those with CAC 1-99. In subjects with CAC ≥100, 97.4% had proximal segment involvement, while 67% of subjects with CAC 1-99 had proximal involvement.

3.2. Proximal CAC in subjects with CAC 1-99

Baseline characteristics of 576 subjects with CAC 1-99 according to proximal involvement are outlined in Table 2. Overall, 385 (67.2%) subjects had proximal CAC involvement and 188 (32.8%) did not. Age, the proportion of males, and frequency of conventional CVD risk factors and statin/aspirin use did not differ significantly between the groups. The CAC score was higher in the proximal involvement group compared to no proximal involvement group (38.0±29.0 vs. 20.1±21.0, p<0.001)

3.3. MACE risk according to the presence and extent of proximal CAC

During the follow up period of 14 ± 3 years, 218 (10.7%) MACE were occurred. There was a progressive increment in MACE with increasing CAC. Proximal CAC involvement was associated with higher MACE in comparison to non-proximal CAC in subjects with CAC 1-99 (annualized MACE rate 0.95 vs 0.36, p=0.004). By Kaplan-Meier survival curve analysis, the presence of proximal involvement was associated with higher rates of MACE when compared to subjects without proximal involvement (P = 0.014, Fig. 2). Subjects with CAC 1-99 and no proximal involvement had comparable risk of MACE to CAC 0 group (p=0.966).

Univariate and multivariate Cox regression analysis in subjects with CAC 1-99 for MACE are summarized in Table 3. In multivariate Cox analysis, the presence of proximal CAC was associated with near three times higher MACE risk compared to those without proximal CAC after adjustment for CAC score, CAC extent, statin/aspirin use, and conventional CVD risk factors (HR: 2.84 95% CI: 1.29-6.25, p=0.009).

MACE incidence according to the location and extent of proximal involvement in individual coronary arteries in subjects with CAC 1-99 is shown in Table 4. The presence of CAC in any proximal segment, LM or the other three major epicardial coronary arteries (proximal LAD, LCX and RCA) was associated with higher MACE risk compared to subjects with no proximal CAC (all p<0.05). There was a significant association between MACE risk and the number of vessels with proximal CAC.

Table 1
Baseline characteristics according to CAC

	CAC=0 (n=1,090)	CAC 1-99 (n=576)	CAC 100-400 (n=234)	CAC>400 (n=147)	P value
Age	52.7±8.6	57.3±8.3	59.9±7.8	63.2±8.1	<0.001
Men	586 (53.6)	363 (63.4)	149 (63.7)	110 (74.8)	<0.001
BMI	26.2±4.9	26.7±4.6	27.3±4.8	27.3±5.1	0.113
Hypertension	358 (32.8)	256 (44.7)	122 (52.1)	89 (60.5)	<0.001
Dyslipidemia	693 (63.4)	437 (76.3)	171 (73.1)	121 (82.3)	<0.001
Diabetes	36 (3.3)	48 (8.4)	14 (6.0)	18 (12.2)	<0.001
Current smoker	56 (5.1)	46 (8.0)	16 (6.8)	10 (6.8)	0.129
Family history of CAD	328 (30.0)	163 (28.5)	83 (35.5)	45 (30.6)	0.267
ASCVD score	5.4±5.5	8.5±7.6	10.1±8.9	14.2±12.1	<0.001
Statin use	165 (15.2)	140 (24.5)	80 (34.2)	54 (37.0)	<0.001
Aspirin use	180 (16.5)	107 (18.7)	55 (23.5)	53 (36.1)	<0.001
Lab					
Total cholesterol	210.0 ± 38.3	212.5 ± 42.6	210.8 ± 39.8	210.3 ± 44.7	0.696
LDL cholesterol	129.3 ±34.7	134.6 ±41.2	131.7 ±37.2	131.2 ±39.1	0.053
HDL cholesterol	56.7±17.5	53.8 ±17.3	52.9 ±15.9	52.3±15.2	<0.001
Triglycerides	120.1 ±75.0	125.5 ±73.4	129.6 ±68.4	135.2 ±91.9	0.055
Proximal involvement					
Any Proximal	0 (0)	386 (67.0)	224 (95.7)	147 (100)	<0.001
LM	0 (0)	66 (11.5)	64 (27.4)	57 (38.8)	<0.001
Proximal LAD	0 (0)	296 (51.5)	204 (87.2)	144 (98.0)	<0.001
Proximal LCX	0 (0)	70 (12.2)	111 (47.4)	113 (76.9)	<0.001
Proximal RCA	0 (0)	69 (12.0)	94 (40.2)	110 (74.8)	<0.001
Number of vessels with proximal					<0.001
No	0 (0)	190 (33.0)	10 (4.3)	0 (0)	
1 VD	0 (0)	249 (43.3)	59 (25.2)	11 (3.5)	
2 VD	0 (0)	64 (11.1)	77 (32.9)	25 (17.0)	
3 VD or LM	0 (0)	72 (12.5)	88 (37.6)	111 (75.5)	
MACE					
MACE event, %	45 (4.1)	60 (10.4)	50 (21.4)	64 (41.9)	<0.001
Annualized rate	0.28 (0.21-0.38)	0.75 (0.58-0.97)	1.66 (1.25-2.18)	3.72 (2.90-4.76)	<0.001

Abbreviations: BMI, body mass index; CAD, coronary artery disease; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; HDL, high density lipoprotein; LDL, low-density lipoprotein; LM, left main; LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex; VD, vessel disease; MACE, major adverse cardiovascular events

Table 2
Baseline characteristics in CAC 1-99 subjects by proximal CAC involvement

	With proximal (n=385, 67.2%)	Without proximal (n=188, 32.8%)	P-value
Age	57.7±8.2	56.5±8.3	0.123
Men	244 (63.4)	119 (63.3)	0.985
BMI	26.8±4.6	26.5±4.4	0.830
Hypertension	174 (45.2)	82 (43.6)	0.721
Dyslipidemia	295 (76.6)	142 (75.5)	0.773
Diabetes	35 (9.1)	13 (6.9)	0.377
Current smoker	32 (8.3)	14 (7.5)	0.721
Family history of CAD	111 (28.8)	52 (27.7)	0.770
ASCVD risk score	8.8±7.8	7.7±7.0	0.112
Statin use	94 (24.4)	46 (24.7)	0.935
Aspirin use	70 (18.2)	37 (19.7)	0.666
Lab			
Total cholesterol	214.7±43.8	207.9±39.6	0.077
LDL cholesterol	136.3±42.8	131.2±37.6	0.165
HDL cholesterol	53.9±17.3	53.7±17.2	0.916
Triglycerides	128.8±77.6	118.7±63.9	0.121
CAC score	38.0±29.0	20.1±21.0	<0.001
Proximal involvement			
LM	66 (17.1)	0 (0)	N/A
Proximal LAD	295 (76.6)	0 (0)	N/A
Proximal LCX	70 (18.2)	0 (0)	N/A
Proximal RCA	69 (17.9)	0 (0)	N/A
MACE			
MACE event, %	50 (13.0)	10 (5.2)	0.004
Annualized rate	0.95 (0.72-1.26)	0.36 (0.20-0.68)	0.004

Abbreviations: BMI, body mass index; CAD, coronary artery disease; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; HDL, high density lipoprotein; LDL, low-density lipoprotein; LM, left main; LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex; VD, vessel disease; MACE, major adverse cardiovascular events; NA, non-applicable

Increased number of vessels with proximal CAC was associated with increased annualized MACE rate (no proximal CAC: 2.94, 1-2 VD with proximal CAC: 8.97, and 3VD with proximal CAC: 10.40, Table 4.

The addition of proximal CAC involvement improved discrimination beyond CAC score and extent (χ^2 for CAC score + CAC extent: 11.82 vs. proximal CAC + CAC score + CAC extent: 18.56, p for difference=0.010, Table 5). In the NRI analysis, proximal CAC involvement resulted in a net increase of 67.9% in cases and a net decrease of 29.1% in controls correctly reclassified, with overall NRI of 35.8% for MACE outcomes when added to the model with CAC score and CAC extent in patients with CAC 1-99 (p=0.010 for difference, Table 5.

4. Discussion

In this prospective observational study involving an asymptomatic population with no prior history of CAD, we explored the prognostic significance of proximal plaque location assessed by non-contrast CAC scanning. Concordant with prior studies, there was an increasing event rate across categories of CAC>0. Our principal findings include the following. In individuals with CAC≥100, nearly all had proximal plaque. We focused on subjects with CAC 1-99, as current guidelines provide no strong recommendation for preventive management including the use of

Table 3
Cox regression analysis in subjects with CAC 1-99

	Univariable			Multivariable		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	0.99	0.96-1.02	0.537	0.97	0.94-1.00	0.086
Male	1.08	0.62-1.88	0.791	0.92	0.52-1.65	0.788
BMI	1.02	0.97-1.08	0.455	1.00	0.94-1.07	0.964
Hypertension	1.88	1.10-3.21	0.022	1.86	1.05-3.28	0.032
Dyslipidemia	1.14	0.60-2.16	0.694	0.86	0.43-1.74	0.684
Diabetes	0.89	0.32-2.48	0.830	0.64	0.22-1.87	0.414
Current smoker	0.42	0.11-1.72	0.226	0.40	0.10-1.64	0.202
Family history of CAD	0.89	0.32-2.48	0.830	1.25	0.70-2.24	0.450
Statin use	1.19	0.66-2.16	0.556	1.25	0.65-2.41	0.510
Aspirin use	0.95	0.48-1.88	0.878	1.15	0.56-2.36	0.702
Log CAC	1.21	0.93-1.56	0.141	0.91	0.68-1.23	0.544
Number of vessels with CAC	1.78	1.30-2.42	<0.001	1.62	1.11-2.36	0.012
Proximal CAC involvement	3.03	1.43-6.41	0.004	2.84	1.29-6.25	0.009

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CAC, coronary artery calcium

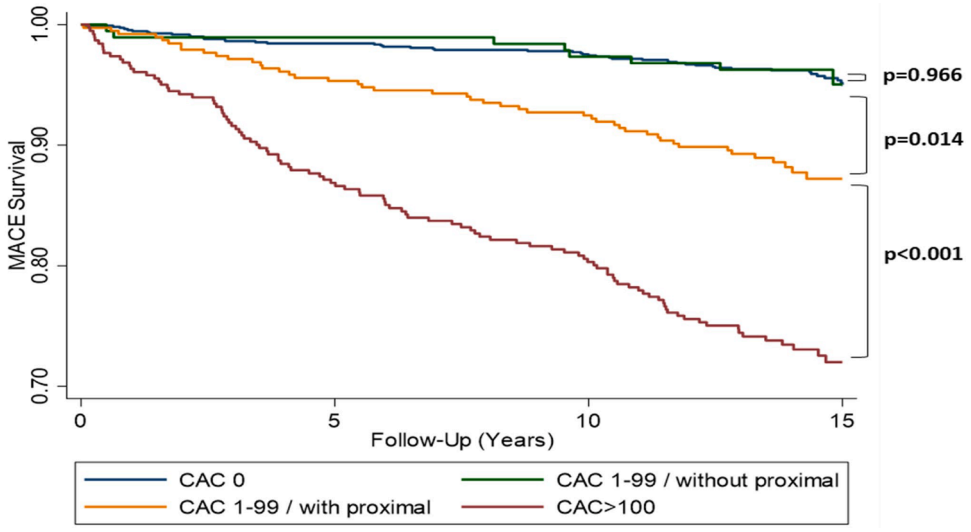

Fig. 2. (Central illustration), Kaplan–Meier curve for MACE according to CAC score and proximal involvement. Abbreviations: MACE, major adverse cardiac events; CAC, coronary artery calcium

Table 4
MACE incidence according to location and extent of proximal involvement in subjects with CAC 1-99

	N (%)	Event rate (1,000-person year)	95% CI	p-value (compared to no proximal CAC)
Any proximal	386 (67.0)	9.02	6.78-12.00	0.002
LM	66 (11.5)	10.18	5.30-19.58	0.005
Proximal LAD	296 (51.4)	9.58	6.97-13.17	<0.001
Proximal LCX	70 (12.2)	11.26	6.24-20.34	0.002
Proximal RCA	69 (12.0)	8.58	4.29-17.15	0.022
Extent of proximal CAD				
3 VD or LM	72 (12.5)	10.40	5.59-19.32	0.007
1 or 2 VD	316 (54.7)	8.97	6.53-12.33	0.004
No proximal CAC	188 (32.8)	2.94	1.47-0.59	N/A

Abbreviations: CAC, coronary artery calcium; LM, left main; LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex; VD, vessel disease; MACE, major adverse cardiovascular events

statin in this group. One third of subjects with CAC 1-99 had only non-proximal plaques. In adjusted analyses, we observed that the presence and extent of proximal CAC increases the MACE risk by near three times compared to subjects without proximal CAC in the CAC category 1-99. This finding was independent of the CAC score, CAC extent and conventional CVD risk factors.

For the last 3 decades there has been increase in use of the CAC for predicting CVD risk and in shared clinical decision making [21]. Importantly, CAC scoring helps reclassify risk in asymptomatic patients with intermediate risk [1,3,22]. However, consideration of just the CAC score ignores important information that may be obtained by further assessing the nature of CAC distribution within the coronary vessels. Various studies suggest that assessing the regional distribution of CAC and the number of plaques involved improves CVD risk prediction in addition to the traditional assessment of the CAC score. Specifically, Blaha et al has identified that presence of diffuse multivessel CAC pattern adds significant value to traditional CAC in predicting CVD mortality [19]. Studies have shown that the number of calcified plaques also add to the CAC score in risk prediction. For instance, Williams et al reported a proportional increment in CVD mortality rate with increase in number of calcific lesions [8] and Arnson et al reported that the number of calcified plaques using CAC scans demonstrated the stepwise increase in mortality with increase in plaque number in subjects with CAC scores of 1-399. In the group CAC 1-99, six or more plaques were associated with increased mortality [23].

In other work, Lahti et al have shown that presence of LM CAC increased the risk of all cause and cardiovascular mortality by 20-30% in asymptomatic adults [24]. There was proportionate increase in risk of death with LM CAC percentage. A study from Framingham Heart Study also assessed the distribution of CAC in coronary arteries [9]. The presence of proximal CAC in the dominant coronary artery had independent prognostic significance after adjusting to Framingham risk score and traditional CAC score. This study, however, did not separately evaluate the CAC categories, especially in patients with CAC 1-99 who might have benefit from the proximal CAC assessment. Finally, a study by Maharaj et al emphasized the importance of CAC localization in LM and LAD had significantly worse prognosis independent of CAC and increasing vessels with CAC [25].

Our current study findings are consistent with these previous studies, but we uniquely focused on patients with a CAC score of 1-99, since CAC scores in this range are common and are classically considered as representing intermediate clinical risk. Within this category, we found that proximal involvement of any major epicardial coronary arteries was associated with higher risk of MACE. Importantly, among ancillary variables that can be assessed along with the global CAC score, the assessment of proximal coronary artery involvement can be easily incorporated into routine CAC analysis and reporting. Given the need for further definition of risk in subjects with CAC 1-99 for management purposes, confirmation of our findings with larger numbers of subjects are needed to assess how the various possible additional analyses of CAC beyond the CAC score can best be combined into comprehensive risk assessment. Potentially, these analyses could include proximal coronary involvement, diffusivity, number of lesions, lesion size and CAC density each of which has been shown to have supplementary benefit in risk stratifying the asymptomatic intermediate risk population with CAC 1-99 [19].

Of note, prior studies involving CCTA provide further indirect support for our findings by demonstrating that the addition of coronary atherosclerosis distribution on CCTA improves the prediction of future CVD risk. For instance, Han et al have recently shown that proximal coronary involvement had higher MACE risk CCTA patients with non-obstructive CAD [10]. In a study by Mushtaq et al, presence of coronary plaques in LM, proximal LAD and LCx were shown to be independently associated with elevated CVD risk in CCTA [26]. Bax et al also reported that proximal plaques had higher volume and progressed faster than distal plaques making them more prone for future plaque rupture [27].

5. Limitations

Our study has limitations. The data regarding downstream pharmacological and/or interventional treatment plans following the scans were not available in the entire study population; thus, we cannot examine the impact of changes in the use of statin therapy and risk factor control. In addition, although this is a prospective study, we cannot eliminate that unmeasured confounding factors might have played a role in influencing our clinical endpoints.

6. Conclusion

In asymptomatic subjects with CAC scores of 1-99, the presence and extent of proximal CAC plaques provides strong independent prognostic information in predicting MACE, potentially providing additional considerations in the guiding the use of and intensity of statin therapy.

Author contributions

RT, DH and DB conceived the study design and wrote the initial draft of the manuscript. DH and HG performed the statistical analysis. JF. SH, LT, PS, AR, DD and DB contributed to the data collection and provided

Table 5
Global $\chi 2$ values and net reclassification index for the addition of proximal CAC assessment in patients with CAC 1-99

Baseline model	χ^2 for Baseline	χ^2 for Proximal CAC + Baseline model	χ^2 improvement	p-value	NRI (95% CI)	Net cases	Net control	P-value
CAC score	2.27	11.05	8.8	0.003	41.7% (14.4-69.1%)	71.9%	-30.2%	0.003
CAC score and extent	11.82	18.56	6.7	0.010	35.8% (8.5-63.2%)	67.9%	-29.1%	0.010

Abbreviations: CAC, coronary artery calcification; NRI, net reclassification index

critical review of the manuscript.

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

Funding Sources

The work was supported in part by the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

Acknowledgements

None

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