

*Research Article*

## Coronary Artery Calcium Score: Refining Risk stratification and Predicting Number Needed to Screen in Outpatients with Intermediate Risk Chest Pain

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### Abstract

**Objectives:** Several studies have shown that coronary artery calcium scoring (CACs) is significantly associated with the occurrence of major cardiovascular events. We aimed to look at the feasibility of combining the Framingham risk Score (FRS) and CACs to refine risk stratification in outpatients with intermediate risk chest pain and adding the value of using this combination to predict the number need to screen (NNS) in those patients. **Methods:** We retrospectively reviewed 266 patients who underwent CCTA and CAC score and their FRS. The yield of screening for CAC was assessed by determining the NNS. Patients in this study were grouped based on FRS into very low risk (0-5), low risk (5.1-10), intermediate risk (10.1-20) and high risk (> 20) groups. **Results:** The mean age of our patients was 51±10.56 years; 148 (55.76 %) were men. Of 266 study patients, 52.08% had a CACs of 0. Patients with CACs >100 were significantly older and were men. Also, the prevalence of a positive CACs for men was higher than that for women (P <0.013). Also, there was a significantly higher CACs values with body mass index >27, smoking, diabetes mellitus and hypertension according to Chi square nonparametric test. The CAC scores were significantly rising as the FRS increased. Using CCTA, the number of CAD increased as the CAC score rose and the NNS decreased significantly as the CAC score rose. Our study revealed that 93.1% of patients with zero CAC score had no significant CAD and only 6.9 % had significant CAD (i.e. ≥70% stenosis on CCTA). **Conclusion:** The strategy of combining FRS and CAC is feasible in clinical practice to refine risk stratification in outpatients with intermediate risk chest pain. However, there is substantial heterogeneity between traditional risk and actual atherosclerosis burden. Also, our study can concluded that knowledge regarding the NNS can lead to a more precise estimation of risk and may provide additional information of such patients. NNS was much higher in participants with an FRS of 0 compared with those with an FRS >10%

**Keywords:** CAC score, coronary artery calcium, chest pain, cardiovascular risk screening.

### Introduction

Cardiovascular disease is considered the leading cause of death and disability worldwide but cardiovascular risk prediction remains an imprecise science. Much work has been carried out to determine patients' risk of adverse cardiovascular events<sup>(1)</sup>. The Framingham risk score (FRS) is one of the most widely used scores to predict 10-year cardiovascular risk. However, it failed to identify many persons who were destined to have coronary events<sup>(2)</sup>. The total risk scores are very useful and should be used as the initial method of stratification, although they are able to predict only 65–80% of future cardiovascular events<sup>(3)</sup>.

The idea of using a noninvasive imaging test to detect early coronary atherosclerosis before it causes serious consequences is great. The Coronary CT angiography (CCTA) is nearly as good as an ICA in detecting coronary atherosclerosis but it has also the associated risks of contrast material and radiation exposure<sup>(4)</sup>.

Coronary artery calcium (CAC) is a part of the development of atherosclerosis and occurs almost exclusively in atherosclerotic arteries. The degree of calcification is proportional to the severity of atherosclerosis and can be quantified by the CAC score (CACs) as a separate study or part of CCTA<sup>(5)</sup>. Several studies have shown

that the CACs is significantly associated with the occurrence of major cardiovascular events in the medium- and long-term follow-up<sup>(6)</sup>.

The strategy of combining FRS and CACs is feasible in clinical practice to refine risk stratification in outpatients with intermediate risk chest pain. CACs does not require contrast, an inexpensive, reproducible technique and it uses lower doses of radiation<sup>(7)</sup>. Currently, guidelines from around the world endorse the measurement of CAC to improve clinical risk prediction in appropriately selected individuals<sup>(1,8)</sup>.

### Aim of the Work

We aimed to look at the feasibility of combining FRS and CACs to refine risk stratification in outpatients with intermediate risk chest pain and adding the value of using this combination to predict the number need to screen in those patients.

### Materials and Methods

In the present single-center study; we retrospectively reviewed patients who underwent CCTA and had a CAC test as well; between December 2018 and November 2019. A total of 283 patients aged  $51 \pm 10.56$  years were enrolled in the study. The informed consent requirement was waived due to the study's retrospective nature. We excluded patients with incomplete charts and those with past history of coronary heart disease. Also, CCTA scans with non-diagnostic image quality were excluded from our study. After applying the criteria, 266 patients were included (Fig. 1). Population study's clinical characteristics, including age, sex, body mass index, and cardiovascular risk factors; were obtained from patients records. The 10 years FRS of each participant was calculated on the basis of age, sex, blood pressure, blood glucose level, cholesterol profile levels, body weight and any smoking in the past years. The participants were classified according to FRS as very low risk (0%- 5% risk of an event within 10 years), low risk (5.1%-10%), intermediate risk (10.1%-20%), and high risk ( $> 20\%$ )<sup>(3)</sup>

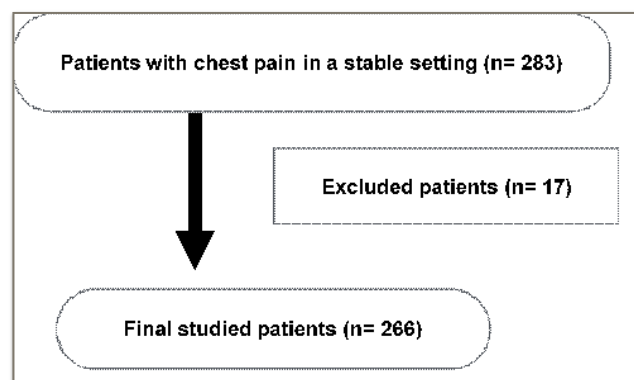


Figure (1): Study flow chart. n: Number.

### Scan Protocol and Image Reconstruction:

CAC scan and/or CCTA was performed with a 64-slice scanner VCT XT (General Electric, Milwaukee, WI, USA). First, an ECG gated CAC scan without contrast was performed, followed by CCTA. Before imaging, patients with a heart rate over 65 bpm were given beta-blocking agents and 2 minutes before imaging; patients were given a sublingual nitroglycerine

tab (5 mg) for coronary artery vasodilatation. The dosage of contrast medium was tailored to ensure aortic enhancement using the test-bolus technique provided by the manufacturer. The test boluses were conducted with 20 ml of contrast media, followed by 20 ml of saline. The following scanning parameters were employed: a contrast bolus of 60–90 mL non-ionic contrast medium (Ultravist 370 mg/ml, Berlex) was

injected with an 18 gauge intravenous catheter placed in the antecubital vein using a dual-head power injector. The default injection rate was 5-6 ml/sec, followed by a saline flush of 50 mL. Automated detection of peak enhancement in the aortic root was used to time the scan. A retrospective ECG-triggered scan was performed at tube voltages between 100 and 135kV, adapted to BMI and thoracic anatomy, with an effective tube current of 100—580 mA, 0.5 mm slice thickness reconstruction and a gantry rotation time of 350ms. Three-dimensional images were reconstructed and viewed on a dedicated workstation (Advantage Workstation; General Electric, Milwaukee, WI, USA) using cardiac post-processing software.

### Image Interpretation:

All CCTA images were interpreted by a radiologist who is specialized in this area. CAC score was reported using the Agatston scoring system, calculated as the product of the calcium density factor, stratified by Hounsfield unit (HU), multiplied by the area of the calcification to define the quantity of coronary calcium. The sum of the calcium score of each calcification within all of the tomographic slices was then summed up to give the total CAC score (4, 9). The study patients were classified into four groups: “zero” (no coronary calcification), “ $0 < \text{CACs} \leq 100$ ” mild coronary calcification, “ $100 < \text{CACs} \leq 400$ ” moderate coronary calcification, and “ $> 400$ ” severe coronary calcification (9, 10). Coronary calcium was defined as an area of at least three “face-connected” voxels of peak density  $\geq 130\text{HU}$  within a coronary artery, corresponding to a minimum lesion area  $> 1 \text{ sq mm}$ , which was used as the reference value for the calcium scores. Patients with a high CACs ( $\geq 1000$ ) did

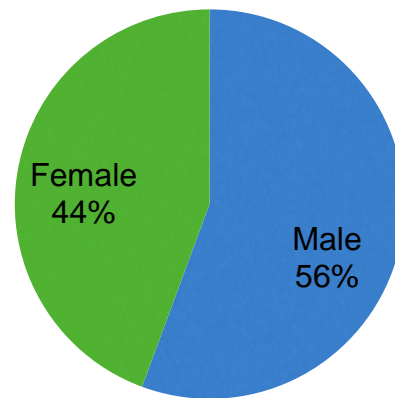
not undergo contrast CCTA and were referred for ICA. For all coronary artery segments, axial and multiplayer reformatted reconstruction images were created. Coronary anatomy was assessed in a standardized manner and a significant lesion was defined as stenosis of  $\geq 50\%$  in the luminal diameter of the left main coronary artery or of  $\geq 70\%$  in the major epicardial coronary artery in the presence or absence of coronary calcium<sup>(11, 12)</sup>.

### Statistical Analysis

All statistical analysis was performed using Statistics Package for Social Sciences (SPSS) software, version 19 (Armonk, NY, USA). All statistical tests were 2-tailed, and a  $P$  value  $< 0.05$  was statistically significant. Continuous variables were presented as means and standard deviations while categorical variables were presented as percentages. Baseline characteristics were compared according to FRS 10- year risk categories and by CAC classification using McNemar's test for categorical variables. The correlation between FRS parameters and CAC parameters were evaluated by Pearson correlation coefficients. The yield of screening for CAC was assessed by determining the number needed to screen (NNS), which was calculated by dividing the total number of participants in each FRS stratum by the number of people with CAC within that FRS stratum. The NNS defines the number of people who need to be screened to identify one individual with coronary artery calcification in each FRS stratum.

### Results

The study population consisted of 266 patients who underwent CCTA and CAC score. The mean age of the study cohort was  $51 \pm 10.56$  years; 148 (55.76 %) were men (Fig. 2).



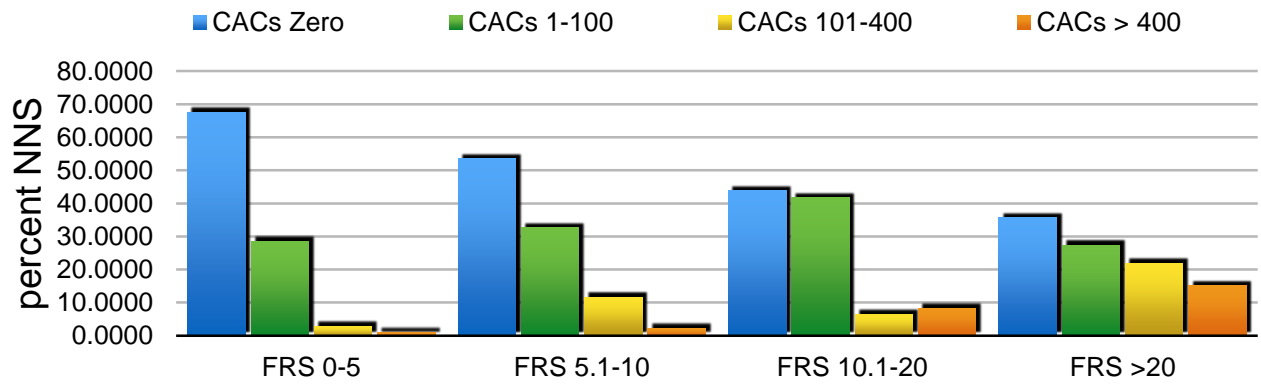
**Figure (2): percent men and women included in the study population.**

139 out of 266 patients (52.08%) had a CACs of 0. Patients with CACs >100 were significantly older and were men. Also, the prevalence of a positive CACs for men was higher ( $P < 0.013$ ) than that for women. Our study revealed that an excessive CACs (> 400), when compared with a moderate CACs (101–400), was best associated with male gender (31 {20.9% } and 22 {14.9%};

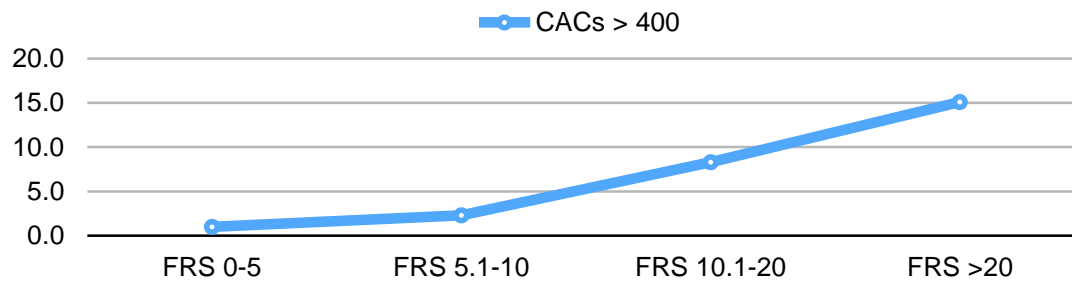
respectively). It was also noted that, there was a significantly higher CACs values with body mass index >27, smoking, diabetes mellitus and hypertension. On the other hand, we found no significant differences between these groups concerning dyslipidemia ( $P > 0.05$ ) (Table 1) (Fig 3a,b).

**Table (1): Baseline characteristics of the whole study population with and without coronary artery calcification (CAC) - SD: Standard Deviation - BMI: Body mass index.**

Risk	Variables	All	CACs 0	CACs 1-100	CACs 101-	CACs >400	P Value
Age	Year	51.01±10.67	47.39 ± 10.12	51.89 ± 9.62	61.3 ± 7.52	59.76 ± 7.72	<0.0001
Gender	Male	148	67 (45.3)	28 (18.9)	22 (14.9)	31 (20.9)	0.013
	Female	118	72 (61)	12 (10.2)	21 (17.8)	13 (11)	
BMI	(<27)	79	54 (68.4)	19 (24.1)	4 (5.1)	2 (2.5)	0.001
	(≥27)	187	85 (45.5)	64 (34.2)	23 (12.3)	15 (8.0)	
Smoking	No	179	101 (56.4)	51 (28.5)	18 (10.1)	9 (5.0)	0.001
	EX	25	10 (40)	9 (36)	3 (12)	3 (12)	
	Yes	62	28 (45.2)	23 (37.1)	6 (9.7)	5 (8.1)	
Diabetes	No	197	113 (57.4)	58 (29.4)	18 (13.7)	8 (13.2)	0.003
	Yes	69	26 (38.5)	25 (15.4)	9 (23.1)	9 (24.6)	
Dyslipidemia	No	131	73 (55.7)	43 (32.8)	8 (6.1)	7 (5.3)	0.03
	Yes	135	66 (56.4)	40 (34.2)	10 (8.5)	1 (0.9)	
Hypertension	No	143	65 (52.8)	45 (36.6)	8 (6.5)	5 (4.1)	0.001
	Yes	123	54 (43.9)	38 (130.9)	19 (15.4)	12 (9.8)	



**Figure (3a):** Distribute and prevalence of the CAC score categories in the various FRS groups. The CAC scores rose significantly as the FRS increased.



**Figure (3b):** Distributions and prevalence of the CAC score > 400 categories in the various FRS groups.

Table 2 showed study patient groups based on FRS where the CAC scores were significantly rising as the FRS increased. We evaluated the number need to screen to identify one individu-

al with calcification of the coronary artery; within each specified FRS strata. The NNS to detect one participant with CACs decreased as the FRS rose as shown in Fig 4a,b and table 3.

**Table (2):** Distributions and prevalence of the CAC score categories in the various FRS groups. FRS: Framingham risk score - CAC: coronary artery calcification.

	(%)	All N = 266	CACs 0 N= 139	CACs 1-100 N = 83	CACs 101-400 N = 27	CACs >400 N = 17
FRS	0-5	102	69 (67.6)	29 (28.4)	3 (2.9)	1 (1.0)
	5.1-10	43	23 (53.5)	14 (32.6)	5 (11.6)	1 (2.3)
	10.1-20	48	21 (43.8)	20 (41.7)	3 (6.3)	4 (8.3)
	>20	73	26 (35.6)	20 (27.4)	16 (21.9)	11 (15.1)

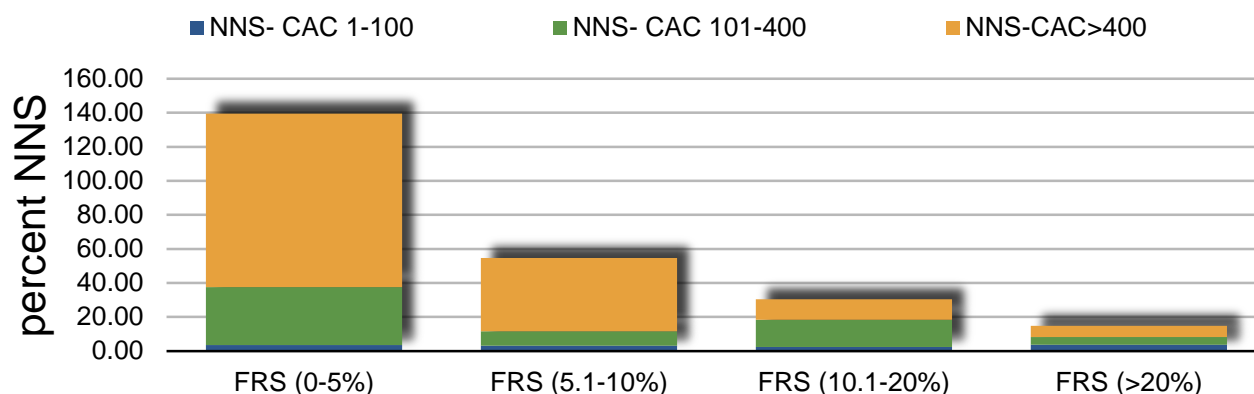


Figure (4a): Number need to screen (NNS) in the various FRS strata to identify one individual with CACs above a specified cutoff point.

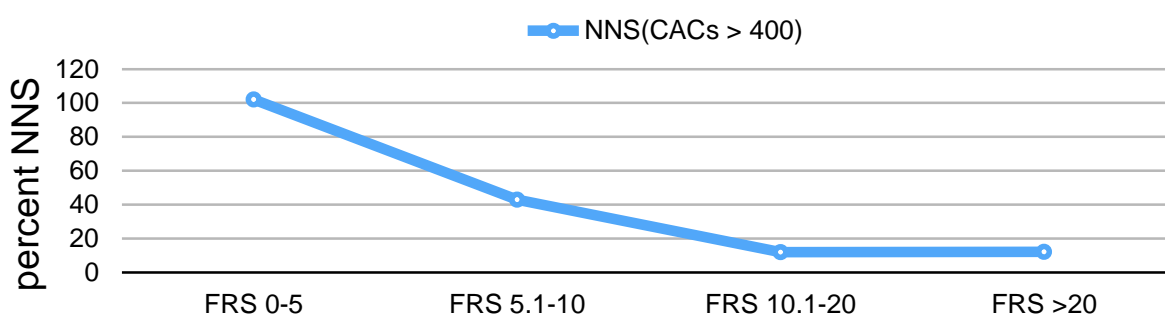


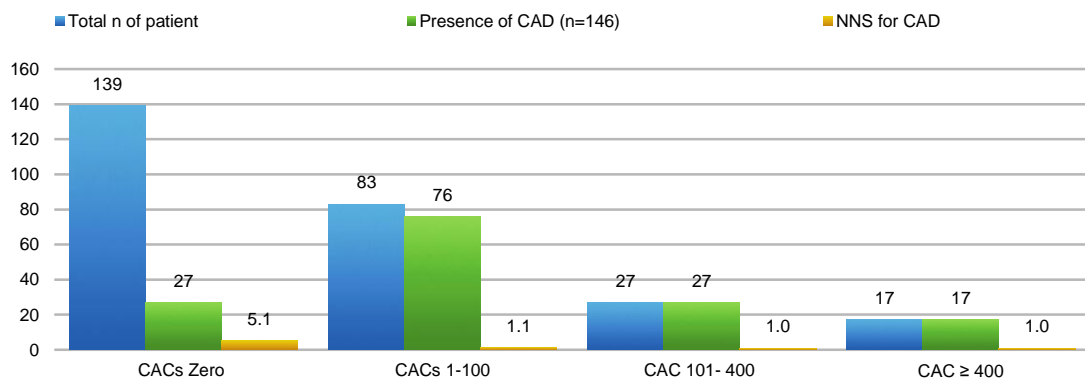
Figure (4b): Number need to screen (NNS) in the various FRS strata to identify one individual with CACs more than 400.

Table (3): Number need to screen (NNS) in the various FRS strata to identify one individual with CACs above a specified cutoff point.

Calcium score strata	Framingham risk score strata (n=266)				P value
	0-5% (n=102)	5.1-10% (n=43)	10.1-20% (n=48)	> 20% (n=73)	
CACs Zero	69 (67.6%)	23 (53.5%)	21 (43.8%)	26 (35.6%)	0.001
CACs 1-100	29 (28.4%)	14 (32.6%)	20 (41.7%)	20 (27.4%)	
CACs 101-400	3 (2.9%)	5 (11.6%)	3 (6.3%)	16 (21.9%)	0.001
CACs > 400	1 (1%)	1 (2.3%)	4 (8.3%)	1 (15.1%)	
CAC Zero (n= 139)	69 (67.6%)	23 (53.5%)	21 (43.8%)	26 (35.6%)	
CAC 1-100 (n= 83 )	29 (28.4%)	14 (32.6%)	20 (41.7%)	20 (27.4%)	0.001
NNS (CAC 1-100)	3.52	3.07	2.40	3.65	
CAC 101- 400 (n=27)	3 (2.9%)	5 (11.6%)	3 (6.3%)	16 (21.9%)	0.001
NNS (CAC 101-400)	34.00	8.60	16.00	4.56	
CAC ≥ 400 (n=17)	1 (1%)	1 (2.3%)	4 (8.3%)	11 (15.1%)	0.006
NNS (CAC ≥ 400 )	102.00	43.00	12.00	6.64	

Comparing CCTA to CACs; our study revealed that, 93.1% of patients with zero CAC score had no significant CAD and only 6.9 % had significant CAD (i.e.  $\geq 70\%$  stenosis on CCTA).

We studied how the presence of CAD within each specified CAC score strata and we found that; the number of CAD increased as the CAC score rose (Fig 5)



**Figure (5): Distributions of the presence of CAD within the CAC score categories and the NNS in various strata. CAD: Coronary Artery Disease - CAC: Coronary Artery Calcium.**

## Discussion

Initially, in this study, we classified our patients based on FRS for future cardiovascular events and the nature of chest pain. Consistent with our study, the vast majority of research trials involving CAC have used FRS as the default risk prediction tool<sup>(13-15)</sup>.

In the present study, patients with excessive CACs were significantly older and were men. This is concordant with Anne B, et al., 2011, who stated that the extent of coronary artery calcification was strongly associated with age. Anne B, et al., added that CAC scanning detected a broad range of disease in older adults, and many with higher levels of calcification would not have been distinguished by traditional risk factors<sup>(16)</sup>. Increase age of the patients can be explained by that Atherosclerosis is a chronic inflammatory disease process<sup>(17)</sup>. Nakanishi R, et al., 2016 stated that; even in the older patients, those with absent or low CAC had a significantly lower risk of mortality compared with the general population<sup>(18)</sup>.

A complex relationship between obesity and vascular calcification has been described in the literature. In our study, there was a significant association between increase BMI and higher CACs values which was not concordant with Takx et al., 2015<sup>(19)</sup>.

Cigarette smoking is a potent risk factor for atherosclerosis. In the present study, there was a significant association between smoking and higher CACs values which was concordant with Rasmussen, et al., 2013<sup>(20)</sup>.

Historically hypertension was considered a risk factor promoting atherosclerosis and associated intimal calcification. In our study, there was a significantly higher prevalence of hypertension in patients with higher CACs values. In 2013 Grossman, et al., detected that the presence of CAC is associated with the development of hypertension<sup>(21)</sup>. Such an association between hypertension and CAC was described by Peralta et al., 2010 in the Multi-Ethnic Study of Atherosclerosis (MESA)<sup>(22)</sup>.

Diabetes is associated with an increased prevalence of atherosclerotic vascular disease. In Concordant with Lee et al., 2017 who stated that; diabetes is an independent risk factor associated with CACS  $\geq 300$  and plays an important role in coronary artery calcification<sup>(23)</sup>. Our study demonstrated a significantly higher prevalence of DM in patients with higher CACs values. After adjusting for other risk factors, patients with DM had twice the overall risk of CAD, as well as a higher risk of cardiac death and non-fatal myocardial infarction<sup>(24)</sup>.



### Zero Calcium Score in Symptomatic Patients:

Our study population included 139 patients out of 266 (52.08%) had a CACs of 0. Only 6.9 % of those with Zero CACs had significant CAD (i.e.  $\geq 70\%$  stenosis on CCTA). Our results correlated with Villines et al., 2011, their published study was on 10,037 symptomatic patients without CAD who underwent concomitant CCTA and CAC scoring revealed that 84% of patients with zero CAC score had no CAD, 13% had non-obstructive stenosis and 3.5% had  $\geq 50\%$  stenosis and only 1.4% had  $\geq 70\%$  stenosis<sup>(25)</sup>. This shows that even among symptomatic persons, CAC rules out obstructive CAD with 98.6% sensitivity. Nabi et al., 2010 studied 1031 patients with CAC and nuclear testing. Only two events occurred in 625 patients with a CACs of zero (0.3 %). These results suggest that patients with a CACs of zero can be discharged home, without further cardiac testing, strongly supporting the NICE guidelines<sup>(26)</sup>.

Other studies have shown that the absence of a CACs does not exclude obstructive CAD. In 2005 Haberl R, et al., studied 133 symptomatic high-risk patients, the median CAC was 66 and 19% of patients had a negative CAC scan. Of symptomatic patients with CAC zero, 32% of patients showed significant stenosis on invasive angiography<sup>(27)</sup>. In this scenario, other factors come into play like a much higher pre-test probability and the pathophysiological issues of plaque rupture, non-calcified plaque, and thrombotic occlusions, none of which are detected by the calcium score. Therefore they stated that a negative CAC scan cannot be used to rule out a relevant obstruction in the setting of symptomatic patients.

### The Number Need to Screen (NNS):

Although our study aimed to look at the feasibility of combining FRS and CACs to refine risk stratification in outpatients with intermediate risk chest pain but the distribution of CAC within FRS groups was heterogeneous. This result consistent with Okwuosa TM, et al., 2011 who stated that, although there is a direct relationship between predicted FRS and the presence and severity of CAC, the distribution of CAC within FRS groups remains heterogeneous<sup>(28)</sup>. The National Heart, Lung, and Blood Institute (NHLBI)- funded population-based

Multi-Ethnic Study of Atherosclerosis (MESA) is an optimal study to observe this heterogeneity. In this study, the NNS to detect a CAC score of zero among older individuals aged 75 to 84 is  $\approx 5$ . Similarly, among individuals with  $\geq 3$  risk factors, the NNS to detect a CAC score zero is just  $\approx 3$ . Nearly identical trends can be observed for smoking status and diabetes mellitus status. Among those traditionally classified as intermediate to high risk based on age, conventional risk factor burden, or calculated risk score, the NNS to detect a CAC score zero remains  $< 6$ . Among individuals with no modifiable risk factors, the NNS to identify 1 individual with CAC  $> 100$  is 9<sup>(29)</sup>.

Our results demonstrated that among population with FRS of 0-5%, 5.1-10%, 10.1-20%, and more than 20%, the prevalence of CAC of 1 to 100 was 28%, 33%, 42% and 27%, respectively, translating into a NNS of 3.5, 3.1, 2.4 and 3.7 to detect a CAC of 1 to 100. Also from our results, a CAC of 101 to 400 among population with FRS of 0-5%, 5.1-10%, 10.1-20% and more than 20%, the prevalence of CAC of 101 to 400 was 3%, 12 %, 6% and 22%, respectively, translating into a NNS of 34, 8.6, 16 and 34.6.

Comparing our results with Okwuosa et al., and MESA, they have demonstrated that among individuals with 10-year FRS estimates of 5% to 7.5%, 7.5% to 10%, 10% to 15%, and 15% to 20%, the prevalence of CAC  $\geq 100$  was 18%, 25%, 33%, and 41%, respectively, translating into a NNS of 5.5, 4, 3, and 2.5 to detect a CAC score  $\geq 100$ . At the same time, individuals with a 10-year FRS estimate of 10% to 15%, 15% to 20%, and  $> 20\%$  had a prevalence of CAC zero of 36%, 27%, and 17%, translating into a respective NNS of 2.8, 3.7, and 5.6 to detect a CAC score zero (28, 29).

### CAD in Various CAC Score Strata:

Finally, we evaluated the presence of CAD within each specified CAC score strata and we found that the number of CAD increased as the CAC score rose. The Mayo Clinic guidelines were consistent with our results in that, the probability of the presence of hemodynamically significant stenosis greater in patients with a CACs  $> 400$  (4). Regarding the individuals with CAD in the present study, the NNS decreased



significantly as the CAC score became more excessive.

Although the presence and extent of arterial calcium are predictive of coronary artery stenosis in general, it is a better indicator of the extent of coronary atherosclerosis than of stenosis severity. Therefore, testing for CAC can help emergency departments quickly identify those patients with chest pain at risk for a future cardiac event.

#### Study Limitations:

Our population was not large enough to determine whether patients with intermediate risk chest pain with for non-calcified plaque evaluation a CACs of zero should undergo CCTA. We did not follow up every participant without significant coronary stenosis, and the incidences of adverse events are not fully known.

#### Conclusion

The strategy of combining FRS and CAC is feasible in clinical practice to refine risk stratification in outpatients with intermediate risk chest pain. However, there is substantial heterogeneity between traditional risk and actual atherosclerosis burden. Also, our study can concluded that knowledge regarding the the NNS can lead to a more precise estimation of risk and may provide additional information of such patients. NNS was much higher in participants with an FRS of 0 compared with those with an FRS >10%

#### Recommendations and Clinical Implications:

Our findings lay the groundwork for future studies to identify those who might benefit from further diagnostic workup. Future randomized multicenter studies are needed to determine the safety and outcomes of using zero CAC as a gatekeeper in patients with chest pain.

#### Additional Informations:

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Critical review and revision: all authors

Final approval of the article: all authors

Accountability for all aspects of the work:

all authors

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