Impact of high Calcium Score in patients with negative Myocardial Perfusion Imaging

Mahmoud Abdelaziz Abdelrashid, Montaser Mostafa Alcekelly, Ghada Ibrahim Mohammed, Adel Hassan Allam, Abanoub Ezzat Faheem

Cardiology Department, Faculty of Medicine, Zagazig University, Egyp

Corresponding author: Abanoub E.Faheem,

Email: dr.abanoub.ezzat@gmail.com

ABSTRACT

Background: Coronary artery disease (CAD) is a disease has been proved to be the major cause of death in both the developed and developing countries. Lifestyle, environmental and genetic factors pose as risk factors for the development of cardiovascular disease. This study aimed to diminish the generalization of doing Calcium score for all coronary cardiac patients with negative myocardial perfusion imaging.

Patients and methods: A retrospective study involved 1168 participants with negative myocardial perfusion imaging not known to have history of CAD, and age ranged between 20 to 80 years from both sexes who conducted on Alfa scan radiology center, Cairo and cardiology department, faculty of medicine, Zagazig university, Egypt. All patients are subjected for scoring of coronary artery calcium (CAC**)** scans for estimating overall coronary plaque burden using noncontrast-enhanced calcium scoring CT (CSCT) (following the negative SPECT-MPI) and documentation of the data.

Results: The mean exercise EF is 70.5 ± 8.4 %, the mean exercise EDV is 84.6 ± 23.3 ml and the mean exercise ESV is 26.2 ± 12.7 ml. The mean rest EF is 67.6 ± 8.5 %, the mean rest EDV is 98.4 ± 25 ml and the mean rest ESV is 33.3± 17.1 ml. Age distribution regarding to CAC score. Among CAC > zero there are 14.1% aged from 20 to 39 years, 37.8% aged from 40 to 59 years and 74.3% aged from 60 to 80 years. There were 122 females and 470 males among low risk DTS group, there were 265 females and 300 males among moderate risk DTS and there were 11 females and no males among high risk DTS group. The increase in CAC score is exponential with old age. Regression model for (CAC > 100) showed age, gender and Statin are the predictors of significant Coronary Artery Calcification (CAC > 100) in patients with negative Myocardial Perfusion Imaging.

Conclusion: This study concluded that age, male gender, DTS and statin therapy were strong independent predictors of high CAC score in the setting of negative MPI study.

Keywords: CAC Score; Myocardial Perfusion; CAD; DTS

INTRODUCTION

Coronary artery disease (CAD), also called coronary heart disease (CHD), ischemic heart disease (IHD), or simply heart disease, involves the reduction of blood flow to the heart muscle due to build-up of plaque (atherosclerosis) in the arteries of the heart. It is the most common of the cardiovascular diseases. Types include stable angina, unstable angina, myocardial infarction, and sudden cardiac death. A common

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

symptom is chest pain or discomfort which may travel into the shoulder, arm, back, neck, or jaw **(1).**

Atherosclerosis is a disease in which the wall of the artery develops abnormalities, called lesions, and considered the most popular cause of CAD. These lesions may lead to narrowing due to the build-up of atheromatous plaque. Initially, there are generally no symptoms. When severe, it can result in coronary artery disease, stroke, peripheral artery disease, or kidney problems, depending on which arteries are affected. Symptoms, if they occur, generally do not begin until middle age **(2).**

Risk factors include high blood pressure, smoking, diabetes, lack of exercise, obesity, high blood cholesterol, poor diet, depression, and excessive alcohol. A number of tests may help with diagnoses including electrocardiogram, cardiac stress testing, coronary computed tomographic angiography, and coronary angiogram, among others (**3).** There is limited evidence for screening people who are at low risk and do not have symptoms. Procedures such as percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) may be used in severe disease. In those with stable CAD it is unclear if PCI or CABG in addition to the other treatments improves life expectancy or decreases heart attack risk **(4)**.

Single-photon emission computed tomography (SPECT) is a widely available modality with well-established clinical and prognostic validation. The tracers currently used include the potassium analog thallium-201 (201Tl) and technetium-99m (99mTc) –labeled compounds **(5)**.

Myocardial uptake of 201Tl is dependent on regional flow and sarcolemma membrane integrity. Several protocols can be used with 201Tl that require injection of a tracer either after stress or at rest with subsequent late imaging following the redistribution of the tracer. The initial acquisition soon after 201Tl injection primarily reflects delivery of the tracer through blood flow. The images acquired 4 to 24 hours after tracer injection are a markers of sarcolemma integrity, which in turn reflects tissue viability **(6).** This study aimed to diminish the generalization of doing Calcium score for all coronary cardiac patients with negative myocardial perfusion imaging.

PATIENTS AND METHODS

A retrospective study involved 1168 participants with negative myocardial perfusion imaging not known to have history of CAD, and age ranged between 20 to 80 years from both sexes who conducted on Alfa scan radiology center, Cairo and cardiology department, faculty of medicine, Zagazig university, Egypt.

Inclusion and exclusion criteria:

Patients with negative SPECT myocardial perfusion imaging and not known to have history of CAD, patients with higher category of hypertension were selected for the purposes of classification. While, patients with positive SPECT myocardial perfusion imaging who known to have history of CAD and patients who refuse to do calcium score test or unavailability of CT were excluded from this study.

Assessment procedures:

Patients were conducted on full history taking, clinical and laboratory. The collected samples used to estimate of plasma glucose, glycohemoglobin (HbA1c), lipid profiles and urinary albumin/creatinine ratio. CT scanning was performed on a Philips ICT 256 (Alfa scan, Cairo, Egypt).

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

Echocardiography evaluation:

Using standard echocardiographic views, EDD, ESD, PWD, IVSD, FS, LVEF, LA dimension and RV function by TAPSE were estimated for detection of wall motion abnormalities and assessment of LV systolic function. Using [Philips Epic 7 machine (California, USA) in National heart institute and Vivid 9, General Electric Healthcare (GE Vingmed, Norway) in Zagazig university]. all measures were taken blindly according to ASE recommendations by two independent echo experts**.**

Electrocardiogram Estimation:

Using Standard 12-lead ECG recordings from all patients at resting and stress ECG to document sinus rhythm.

Electrocardiograms were recorded using 12-channel equipment, at paper speed of 25mm/s and with 10mm/ mV standardization.

All patients were subjected for single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) after the intravenous injection of Tc-99m-sestamibi (99mTc-sestamibi) and documentation of the data.

Coronary artery calcium (CAC) scans:

Using noncontrast-enhanced calcium scoring CT (CSCT) (following the [negative] SPECT-MPI) and documentation of the data for estimation of overall coronary plaque burden. CAC was quantified by the Agatston scoring method and was confirmed when needed in OsiriX, Version 3.9 (Pixmeo, Switzerland) 64-bit image processing software.

Treadmill exercise:

The equation for calculating the Duke treadmill score (DTS): Duke treadmill score = maximum exercise time in minutes – 5×ST segment deviation in mm – 4×angina index. Angina index is expressed as 0 = no angina, 1 = non-limiting angina, 2 = exercise limiting angina. Values +5 or > corresponds to low-risk DTS. Moderate-risk DTS corresponds to values between +4 and -10. High-risk DTS is defined as a score of < -10. For the exercise portion of the test, the patient was asked to walk or run on a treadmill in order to elevate the heart to its peak rate. Patients who were unable to exercise are given a drug that elevates the heart rate (called a pharmacologically induced stress test). The patient's heart rate and blood pressure were monitored during this phase of the test.

The patient then received an intravenous injection of a radiotracer called thallium, which accumulates in the heart muscle. Next, the patient was moved to an imaging suite, where images of the heart are taken with a SPECT camera or PET scanner. Several hours later, the patient was imaged again. The interpretation was as the follow:

* Myocardial perfusion defects. [No]
* SestaMIBI scintigraphy for myocardial ischemia. [Negative]
* Normal MPI indicates the absence of coronary obstruction but does not exclude non-obstructive coronary disease.

The currently available noninvasive techniques, such as exercise treadmill testing (ETT) and myocardial single photon emission computed tomography (SPECT), can identify only patients with advanced CAD who manifest myocardial ischemia.

CAC was quantified using the Agatston scoring method and was confirmed when needed in OsiriX, Version 3.9 (Pixmeo, Switzerland) 64-bit image processing

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

software. CT scanning was performed on a Philips ICT 256 (Alfa scan, Cairo, Egypt). The interpretation was as the follow:

* Account on calcium density, location of calcium and spatial distribution of calcium.
* Correlated the data of CAC with burden of coronary atherosclerosis.

Coronary artery calcium score (CACS) identifies a high-risk group of asymptomatic subjects who have clinically important silent myocardial ischemia.

Statistical analysis

Data was analyzed using SPSS program (Statistical Package for Social Science) version 17.Qualitative data was represented as frequencies and relative percentages. Chi square test ($\chi 2$) was used to calculate difference between qualitative variables as indicated. Quantitative data was expressed as mean± SD and range. Student t test and ANOVA was used to calculate difference between quantitative variables in two groups and more than two groups. All statistical comparisons were significant when Level of P-value ≤ 0.05, p <0.001 indicates highly significant difference while, P> 0.05 indicates non-significant difference.

RESULTS

The present study included 1168 participants with a the mean age is 48 ± 9 years and the median is 49 years. They were 770 males (66%) and 398 females (34%) **(Figure 1).** Regarding signs among the participants, there are 66.4% have chest pain **(Figure 2)**. The mean exercise EF is 70.5 ± 8.4 %, the mean exercise EDV is 84.6 ± 23.3 ml and the mean exercise ESV is 26.2 ± 12.7 ml. The mean rest EF is 67.6 ± 8.5 %, the mean rest EDV is 98.4 ± 25 ml and the mean rest ESV is 33.3± 17.1 ml **(Table 1)**. Age distribution regarding to CAC score. Among CAC > zero there are 14.1% aged from 20 to 39 years, 37.8% aged from 40 to 59 years and 74.3% aged from 60 to 80 years **(Figure 3)**.There were 122 females and 470 males among low risk DTS group, there were 265 females and 300 males among moderate risk DTS and there were 11 females and no males among high risk DTS group **(Figure 4)**. The increase in CAC score is exponential with old age **(Figure 5)**.

Regression model for (CAC > 100) showed age, gender and Statin are the predictors of significant Coronary Artery Calcification (CAC > 100) in patients with negative Myocardial Perfusion Imaging **(Table 2)**.

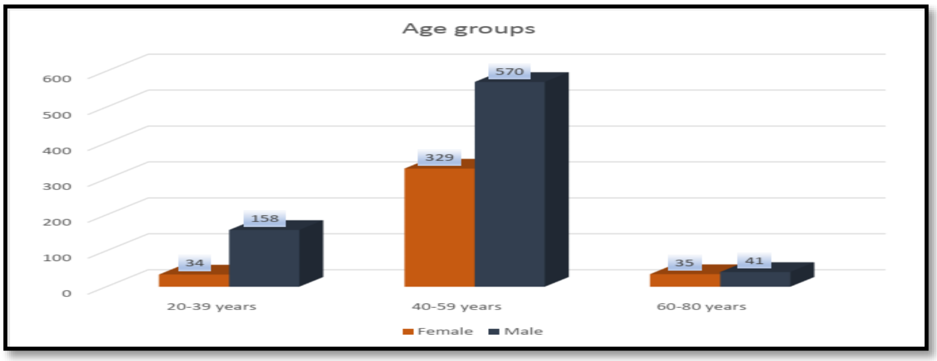

Figure (1): Gender distribution among age groups

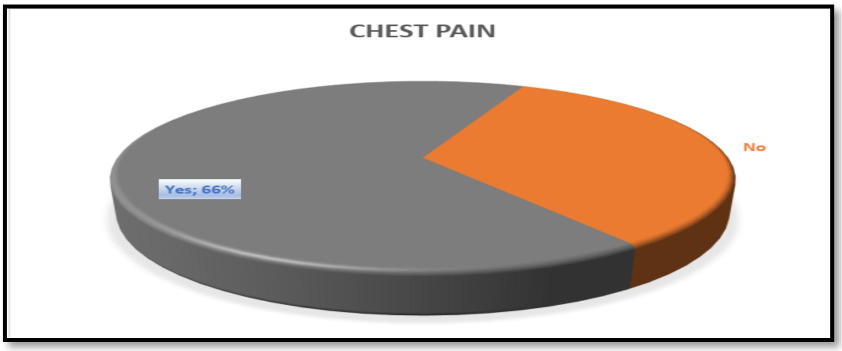

Figure (2): Chest pain among the participants.

Table 1. Left ventricular functional parameters among the participants in rest and exercise

Variables	Mean± SD
Exercise EF	71 ± 8 %
Exercise EDV	85 ± 23 ml
Exercise ESV	26 ± 13 ml
Rest EF	68 ± 9 %
Rest EDV	98 ± 25 ml
Rest ESV	33± 17 ml

EF: ejection fraction , EDV: end-diastolic volume, ESV: end-systolic volume

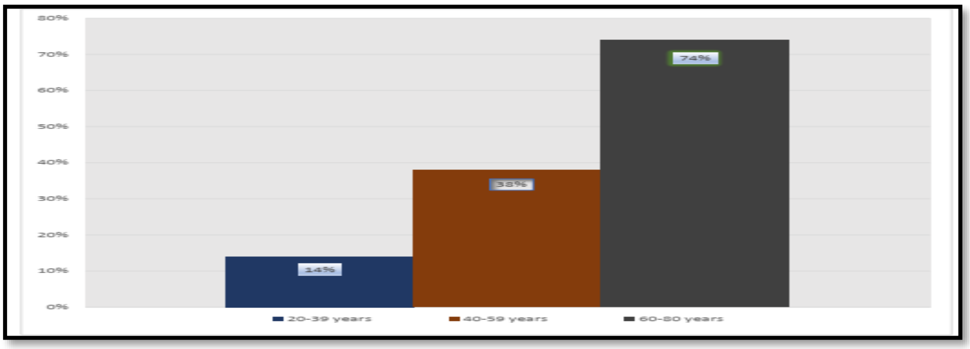

Figure (3): Age distribution among CAC more than zero

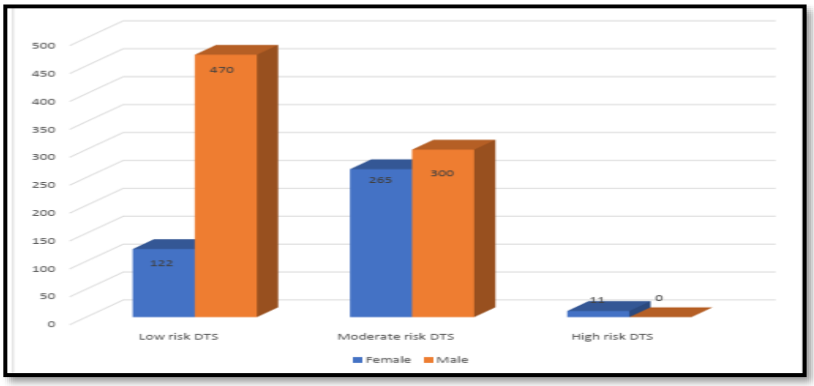

Figure (4): Gender distribution regarding DTS

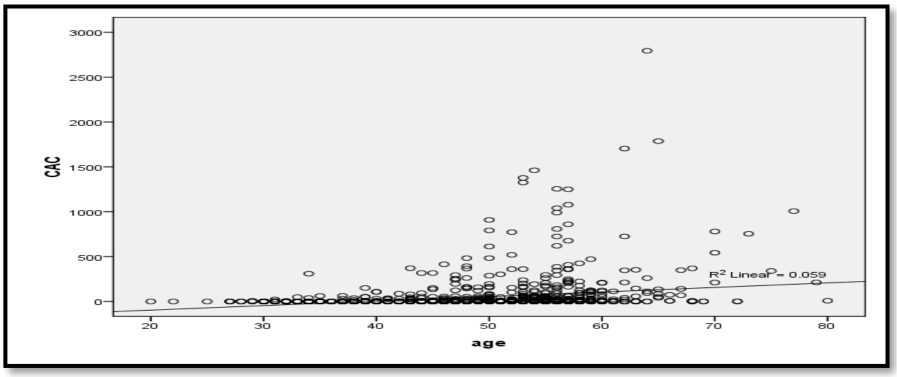

Figure (5): Association between age and CAC score

Table 2. Regression model for significant Coronary Artery Calcification (CAC > 100) adding Statin as a variable in the model

Variable	Wald test	p value	95% C.I.for EXP(B)	
			Lower	Upper
Age	57.633	**<0.001***	1.096	1.169
Gender	15.146	**<0.001***	1.776	5.696
Hypertension	1.275	.259	0.821	2.086
Diabetes mellitus	.243	.622	0.550	1.430
Smoking	1.624	.203	0.586	1.120
DTS	2.205	.138	0.922	1.011
Exercise EF	.730	.393	0.959	1.016
Statin	5.019	**.025***	1.068	2.685

DISCUSSION

Cardiovascular diseases CVD is a major cause of disability and premature death throughout the world and despite advances in diagnosis and treatment, Coronary artery disease (CAD) remains the number 1 cardiovascular (CV) cause of mortality and morbidity making it as a major health concern **(7)**.

There are many risk factors for CAD, and some can be controlled but not others. The risk factors that can be controlled (modifiable) are: High Blood Pressure BP; high blood cholesterol levels; smoking; diabetes; overweight or obesity; lack of physical activity; unhealthy diet and stress. Those that cannot be controlled (conventional) are Age (simply getting older increases risk); sex (men are generally at greater risk of coronary artery disease); family history; and race **(8)**.

Cardiac imaging specially noninvasive cardiac imaging modalities has become an essential component in the diagnosis and management of heart disease and with the increased prevalence of heart disease **(9)**.

A complete assessment of CAD requires both anatomical and functional information **(10)**. Multiple noninvasive cardiac imaging modalities can also anatomically delineate or functionally assess for significant coronary artery stenosis, as well as detect the presence of myocardial infarction (MI) **(11)**.

In patients with known or suspected CAD, stress single-photon emission computed tomography myocardial perfusion imaging (MPI) accounts for the vast majority of tests currently performed for ischemia detection. stress MPI is best suited for patients with intermediate likelihood of CAD. However, over the past two decades, the

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

prevalence of ischemia in patients without established CAD has dramatically declined. Therefore, as patients with lower probability of CAD are being tested, the prognostic and diagnostic utility of stress MPI is expected to be diminished **(12)**.

SPECT MPI may detect obstructive CAD but fail to discover subclinical atherosclerosis. CAC score has been reported as a surrogate for coronary atherosclerosis that correlates with outcome in large patients cohorts **(13)**. Coronary CT angiography can help assess the degree of anatomic stenosis, its inability to assess the physiologic significance of lesions limits its specificity. Physiologic significance of coronary artery stenosis can be determined by SPECT MPI, and combined with stress echocardiography **(11)**.

Our study involved 1168 participants with negative myocardial perfusion imaging not known to have history of CAD, and age ranged between 20 to 80 years from both sexes. patients conducted on cardiology department, faculty of medicine, Zagazig university for diminishing the generalization of doing Calcium score for all coronary cardiac studied patients with negative myocardial perfusion imaging.

Our study revealed A greater percentage of the patients involved in the study were males (n= 770, 66%) and 66.4% of patients complained chest pain during routine activity. Several studies done in calcium score recorded a similar ratio, suggestive of a likely higher prevalence in males compared to females **(14)**.

In our study, The age distribution regarding to CAC score showed that the majority of patients who had a CAC > zero were within the age group of 60–80 years (74.3%), followed by patients within the age group of 40-59 years (37.8%) and (14.1%) of patients aged from 20 to 39 years, further reinforcing the opinion that coronary artery calcification steadily increases with increasing age (**14)** showed comparable study and suggests further that a rising CS may be associated with an increase in age as noted by other studies.

On a multiethnic study on the incidence and progression of CAC, **McClelland et al. (15)** reported that the incidence of CAC increased steadily across age. The annual amount of CAC progression also increased exponentially across age, with a similar trend for men and women **(16)**.

Our results revealed that about 25% of patients aged above 60 had no CAC. The fact that a significant fraction of the elderly population had no CAC and that those patients could potentially be reclassified as lower risk is of immediate clinical impact with regard to downstream healthcare utilization **(17)**. Overall, our results suggest that the broader use of CAC scoring in elderly patients may be clinically useful.

Younger patients have a lower burden of CAC, leading to the suggestion that a CAC score would be of lesser value in this population. Indeed, in our study, 14% of patients in the <40-year-old age group were noted to have CAC > 0. These results were in line with **Tota-Maharaj et al. (17)** and **Loria et al. (18)** showed 9.6% of adults below 45 had any CAC , with a greater prevalence among men. Other studies by **Kang et al. (19)** have determined similar associations in young adults, as a large study (n=33 637) of South Korean adults younger than 40 years found a graded increase in CAC prevalence with increases in systolic blood pressure.

Although age is a dominant factor associated with atherogenesis, multiple traditional risk factors and lifestyle behaviors have been associated with the development of premature CAC. In addition to age, **Javaid et al. (20)** found strong independent associations of male sex, hypertension, hyperlipidemia, and tobacco use with any CAC and severe CAC.

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

There is statistically significant difference between two groups regarding age, male gender, weight, chest pain, hypertension, dyslipidemia, diabetes, family history of CAD, in addition to medical treatment with (beta blockers, aspirin), furthermore with resting DBP, rest ECG abnormalities and exercise duration.

In the MESA cohort, many traditional cardiovascular risk factors were associated with both the risk of developing incident coronary calcium and an increase in severity of calcification. These included older age, male gender, hypertension, higher body mass index, DM, and family history of cardiovascular events. In diabetic patients without obstructive coronary disease, myocardial perfusion study can be predictor of cardiac events. A negative study can be an indicator of a better cardiovascular prognosis **(21)**

The DTS score is well recognized noninvasive simple prognostic score in patients with suspected CAD **(22)**. A meta-analysis of 24,047 patients in 147 studies found Treadmill exercise score to have sensitivity of 50% to 68% and specificity of 77% to 90% for detection of coronary artery disease. Confounders such as resting ST-segment depression, digoxin usage, and left ventricular hypertrophy with repolarization changes decrease specificity, whereas mild single-vessel disease decreases sensitivity **(23)**.

According to DTS score regarding gender, our study revealed that the majority of patients (592) were classified as low risk DTS group with 122 females and 470 males, followed by 565 of patients were classified as moderate risk DTS, and only 11 females with no males among high risk DTS group. These results indicate the high prevalence of male in both low and moderate risk DTS compared to women, with high prevalence of elder women in high risk DTS.

The diagnostic and prognostic accuracy of exercise testing in women can be improved by incorporating parameters such as exercise capacity, chronotropic response, heart rate recovery, blood pressure response, and the DTS, in addition to ST-segment depression with exercise **(24)**.

Cremer et al. (25) reported in their large cohort study of patients who underwent treadmill testing, concluded a differential effect of exercise variables and clinical risk factors on overall mortality according to sex. Also, risk stratification is improved with sex-specific risk scores, and in particular, patients at the highest risk are more readily identified. For years we've used Duke Treadmill Score for both men and women, but as most physicians know, Duke Treadmill Score was developed in men a long time ago, validated in men, and not well-validated in women.

Any CAC score appeared to corelate with the demographic date from age and gender, in addition to the correlation with traditional cardiovascular risks as diabetes mellitus and dyslipidemia and considered as predictors for any Coronary Artery Calcification in patients with negative Myocardial Perfusion Imaging. Certain factors also appeared to be related only to the risk of incident CAC but not to the progression of existing calcification. So after the adjustment of the model with significant calcification (progression phase), our results still confirmed the correlation with age, gender and for the first time DTS whereas the model power cannot detect the traditional cardiovascular risk factors neither DM, nor dyslipidemia. These results disagree with **Park et al. (26)** demonstrate that DM contributes to CAC, both in incident CAC and the progression of CAC. Given the association between CAC score and traditional cardiovascular risks, including laboratory and demographic data, the prediction of CAC score based on these variables is a reasonably conceivable approach.

Our study could not detect the correlation of DTS for any calcification, but the power detected the relationship for only the significant calcification CAC>100 regardless the

ISSN:0975-3583,0976-2833 VOL13,ISSUE 01,2022

other traditional risk factors. The model was adjusted to remove dyslipidemia and was replaced by Statin medication as a therapy for lowering LDL cholesterol for dyslipidemic patients and the associations that persisted after adjustment for baseline CAC>100 was gender, age and interestingly the use of statins was linked to increasing CAC>100 in patients with negative myocardial perfusion. Similar results were identified by **Mortensen et al. (27)** showed that CAC might identify those expected to derive both the most and the least net benefit from statin therapy have been performed for patients meeting criteria for any one of the statin clinical trials. Thus, CAC scoring may help to match intensified risk factor modification to atherosclerotic plaque burden as well as actual risk, while avoiding statin therapy in patients with low CAC scores and low 10-year event rates **(28)**.

Several studies have now shown that treating a patient who has atherosclerosis with statins can increase the cardiac calcium score. Evidence supports the idea that statin therapy not only reduces cholesterol levels but also changes existing plaques to make them less dangerous. As part of this process, the plaques may become more calcified and thus, calcium score goes up. An increasing calcium score with statin therapy, therefore, may indicate treatment success, and should not be a cause for alarm. While this theory is not settled science, at this point it best fits the available evidence **(29)**.

A key mechanism underlying this phenomenon is that statins increase plaque density thereby paradoxically raising the Agatston CAC score as density is upweighted. The population of statin users with high CAC scores therefore encompasses very high-risk individuals and individuals with highly stable plaques at relatively lower risk of events. an alternative approach to overcome the density paradox could be to expand the use of alternative CAC scoring methods that focus on volume alone or better distinguish the protective role of densely calcified plaque **(30)**.

CONCLUSION

This study concluded that age, male gender, DTS and statin therapy were strong independent predictors of high CAC score in the setting of negative MPI study.

No Conflict of interest.

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