Review

Importance of coronary artery calcium score in clinical practice

Sirous Darabian[1], Panteha Rezaeian[1], Muhammad Aamir Latif[1], Ramin Hormoz Diaran[1] & Matthew Budoff*[1]

Practice points

- Appropriate patient selection, limited scan length and lowering tube voltage are approaches for further lowering the radiation dose.
- A zero coronary artery calcium (CAC) score especially in asymptomatic patients largely rules out presence of significant coronary artery disease and identifies a very-low-risk patient.
- Numerous studies show that CAC score increases the predictive power of the Framingham Risk Score for future cardiovascular events.
- A zero CAC score rules out significant coronary artery disease in both symptomatic and asymptomatic patients.
- Higher CAC score is associated with lower effective glomerular filtration rate and longer duration of hemodialysis.
- CAC score may be used as a predictor of worse outcome among the renal failure, hemodialysis and renal transplant recipient populations.
- High CAC score may positively affect patient behavior, patient lifestyle and physician.

SUMMARY Similar to mammography in screening of breast cancer, coronary artery calcium (CAC) scanning could be used for the screening of at-risk patients for coronary artery disease (CAD). Strong correlations between CAC score and CAD have been established. CAC allows for early identification of atherosclerosis to permit early targeting of lifestyle and pharmacologic intervention for heart disease. The predictive value of CAC score differs in population with different pretest probability for CAD. In addition, combination of CAC score with other risk factors may produce a model with higher predictive value for presence, severity and future events of cardiovascular disease. We reviewed all correlated published studies indexed in PubMed during the last 5 years to combine with older, generally accepted concepts to establish the most valid current role for CAC testing.

[1]St. John Cardiovascular Research Center, Los Angeles Biomedical Research Institute, Torrance, CA, USA
*Author for correspondence: Tel.: +1 310 222 4107; Fax: +1 310 782 9652; mbudoff@labiomed.org

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Office-based risk assessment tools, such as the Framingham Risk Score (FRS), are currently used to estimate the probability of coronary artery disease (CAD) and the risk of future cardiovascular disease (CVD) events. The Framingham model creates three categories of 10-year risk for a future cardiovascular event: <10% (low risk), 10–20% (intermediate risk) and >20% (high risk). Since FRS was only able to predict 60–65% of cardiovascular risk, many clinical trials studied other markers and risk factors to establish a predictive model with higher predictive value by combination of various risk factors and markers. There are a lot of autopsy, radiologic and histopathologic reports that support a significant correlation between CAD and coronary artery calcium (CAC). It has been established that CAC detected by computed tomography (CT) is strongly correlated with presence of CAD. It has been suggested that, similar to mammogram in breast cancer screening, CAC may be used as a screening tool to accurately predict CVD presence, severity and future CVD events. In order to summarize an update regarding to CAC and its recent role in clinical practice, we reviewed all correlated published studies in PubMed to combine with older established concepts to establish the most valid current role for CAC testing. We systematically reviewed all published papers indexed in PubMed over the last 5 years. The majority of papers utilized electron beam CT and several utilized 64 slice CT. The methodology of CAC testing has been validated and results for both multidetector CT and electron beam tomography are similar.

Technical aspects

The clinical benefit of CAC scanning needs to be balanced against the risk of CT ionizing radiation. National and international guidelines should be used for patient selection. Monitoring of radiation exposure (dose-length product and effective radiation dose (E) in all patients is highly recommended). The dose-length product should be <200 mGy × cm; E should average 1.0–1.5 mSv and should always be <3.0 mSv. CAC imaging in an axial mode with prospective electrocardiographic triggering and similar with all scanner platforms, most commonly uses a tube voltage of 120 kV. Chest lateral width measured on the topogram as a marker of patient size should be used for appropriate tube current selection. To keep a lower radiation dose we may consider both slice thickness of 2.5 mm and scanning of the heart with limited length coverage. Appropriate selection of these parameters in CAC scanning can decrease radiation dose level and may decrease the risk of ionizing radiation-related side effects [1]. Radiation doses are very similar to mammography, another test used widely for screening asymptomatic persons.

Predictors of CAC presence & severity

It is important to know which patients will benefit more from CAC scan. For this reason at first we need to know about the factors that affect presence and severity of CAC (see **Box 1**). In a group of asymptomatic participants with low risk (<10%) 10 year-FRS, traditional risk factors such as age, gender, lipid profile, blood pressure, smoking, diabetes and family history of premature CAD were the foremost important factors associated with presence of any CAC and advanced CAC [2]. Similarly, a study done on 9341 asymptomatic participants showed age, sex and classical CAD risk factors were strong predictors for the presence of CAC and its severity [3]. Another study done on 1825 cases, showed that male gender (odds ratio [OR]: 3.2; 95% CI: 2.5–4.2; $p < 0.0001$) and an age of 60s versus 50s (OR: 2.2; 95% CI: 1.7–2.8; $p < 0.0001$) have the greatest association with the presence of CAC. Diabetes and smoking were also independently associated with the presence of CAC, with ORs of 2.0 (95% CI: 1.1–3.5; $p = 0.03$) and 1.9 (95% CI: 1.4–2.5; $p < 0.0001$), respectively [4]. Similarly, studies on 677 patients revealed that very high CAC (≥1000), when compared with a relatively high CAC (400–999), was best associated with two factors: male gender (OR: 3.10; $p < 0.001$) and older age (OR: 1.42 per 10-year increase; $p < 0.001$) [5]. Based on the result of a study done on 2620 low-risk FRS individuals who were followed up for 2.5 years, CAC progression occurred in 574 participants and they concluded that even in individuals at low predicted risk according to FRS, traditional risk factors predicted CAC progression in the short term [6].

Race is another important predictor. A study on 861 subjects showed that white race was a strong predictor of CAC whereas the African-American race was associated with lower CAC scores in age-adjusted models in males (Tobit ratio for African–Americans vs whites: 0.14 [95% CI:

0.08–0.24; p < 0.001]) and females (Tobit ratio 0.26 [95% CI: 0.09–0.77; p = 0.015]) [7]. In another study carried out on 200 male participants, ethnic differences in the rates of CAC progression over 4 years were evaluated. Significant CAC progression (increase equal or more than 15% per year) was observed in 43.5% of all participants. Prevalence and extent of CAC were significantly lower in African-American participants but the incidence of CAC progression was similar to whites [8].

Physical activity (PA) was not a strong predictor but showed that it does affect CAC severity to some extent. In a study on patients with two or more metabolic risk factors, it was shown that long-duration PA had an independent inverse association with advanced CAC [9]. However, in another study on 443 participants no relation between PA and CAC scores was shown to exist [10].

In addition, some other factors such as education level, discrimination experiences and uric acid (UA) levels seem to independently predict presence and severity of CAC. A study on 571 cases older than 45 years without history of CAD revealed that the odds of having CAC were approximately three-times higher for those experiencing discrimination (OR: 2.95; 95% CI: 1.19–7.32) after adjusting for age, gender, race/ethnicity, education, BMI, hyperlipidemia, smoking status, hypertension, diabetes and a first degree relative with heart disease. Again, this study seemed to confirm that participants with CAC had the following traits: were older, male, white, had higher BMI, smoked, were diabetic, hypertensive, had hyperlipidemia and had a first degree relative with heart disease (p < 0.05 for all variables), compared with participants without calcification [11].

To examine the association of education with CAC, a population-based, prospective, observational study (Coronary Artery Risk Development in Young Adults) on 2913 participants with an overall CAC prevalence of 9.3% revealed that after adjusting for age, race and gender, the ORs for having CAC were lower among participants with higher level of education. Even after adjustment for baseline systolic blood pressure, smoking, waist circumference, PA and total cholesterol, ORs still remained strong and significant [12].

A study on 371 asymptomatic men showed that after controlling for age, PA, smoking and metabolic syndrome, a high UA level was independently associated with the presence of CAC (p = 0.043) and with higher levels of CAC (p = 0.028). Also, in patients with metabolic syndrome, independent from age, smoking, PA and white blood cell count, high levels of UA were strongly associated with the presence and the higher level of CAC (OR: 3.47; 95% CI: 1.26–9.53; p = 0.01 and OR: 2.74; 95% CI: 1.15–6.50; p = 0.02, respectively). Conversely, there were no significant associations of high UA levels in patients without the metabolic

Box 1. Risk factors that correlate with presence and severity of coronary artery calcium.

Factors that correlate with presence of CAC

- Clinical
  - Older age
  - Male gender
  - White race
  - High blood pressure
  - Smoking
  - Higher BMI
  - Discrimination experience
  - Lower education level
- Laboratory
  - Diabetes
  - Dyslipidemia
  - Renal failure
  - Higher uric acid
  - Insulin resistance
  - Vitamin D deficiency
  - Low serum fetuin A in renal failure
  - Epicardial fat volume

Factors that correlate with more severe CAC

- Clinical
  - Male gender
  - Older age
  - White race
  - Higher blood pressure
  - Positive family history for CAD
  - Abdominal obesity
  - Lower physical activity in the presence of at least two metabolic risk factors
- Laboratory
  - Dyslipidemia
  - Diabetes
  - Higher uric acid level
  - Level of IL-6, IL-8 and IL-13
  - Abdominal visceral fat

CAC: Coronary artery calcium; CAD: Coronary artery disease.

syndrome [13]. Another study on 1107 participants revealed that UA was associated with CAC presence and quantity (after adjustment for age and gender) [14]. In another study carried out on 2498 participants, prevalence of CAC increased with an increase in UA level, each unit increase in UA was associated with a 22% increase in Agatston score (p = 0.008) after adjusting for the above covariates [15].

According to a systematic review in 2008, most studies evaluating inflammatory markers and CAC demonstrated either a weak or no relationship [16]. Those that reported a weak relationship found that this association was lost after correction for obesity and BMI, and did not show any predictive benefits for future CAD for inflammatory markers such as C-reactive protein once the CAC score was known. However, based on some recent studies, vitamin D and cytokines IL-6, IL-8 and IL-13 correlate significantly with prevalence and severity of CAC by multivariate analysis [17,18].

CAC score is correlated with presence & severity of CAD

There is a difference between absolute predictive value and additive predictive value of a test. In multiple population studies, it has been established that even small changes in CAC score affect the possibility of CAD presence, its severity and related events, incrementally and independently to FRS.

■ Zero CAC versus non-zero

It has been shown that zero CAC versus non-zero CAC is associated with less CAD. A recently published study on 10,037 symptomatic patients without CAD who underwent concomitant CT coronary angiography (CTCA) and CAC scoring revealed that 84% of patients with zero CAC score had no CAD, 13% had nonobstructive stenosis and 3.5% had ≥50% stenosis and only 1.4% had ≥70% stenosis on CTCA [19] This shows that even among symptomatic persons, CAC rules out obstructive CAD with 98.6% sensitivity. A zero CAC score in asymptomatic patients largely rule outs presence of significant CAD and predicts lower events and mortality. In a study carried out on 44,052 asymptomatic participants, 19,898 patients (45%) had no CAC. After adjustment for traditional risk factors the hazard ratio (HR) for all-cause mortality among a CAC score of 1–10 versus a zero CAC score was 1.99 (95% CI: 1.44–2.75). They also found that the absence of CAC predicts excellent survival with 10-year event rates of approximately 1% [20]. Even a minimal increase in CAC score significantly changes the risk of future cardiovascular events. In another study done on 3923 patients, with zero and <10 CAC scores, it has been revealed that during the 4-year follow-up period, patients with CAC scores of 1–10 had over a threefold increase in cardiovascular events compared with patients with a zero CAC score. (HR: 3.66; 95% CI: 1.71–7.85) [21].

■ Combination of CAC & Framingham Risk Scores

Patients, who are on the extremes of the FRS scale, having very low or very high pretest probabilities for CAD, may benefit less from a CAC scan. However, CAD in intermediate FRS group is less predictable and adding CAC score as an independent factor makes a very powerful model. A study on 5933 asymptomatic participants revealed that adding CAC scores to the FRS (age, sex, systolic blood pressure, treatment of hypertension, total and high-density lipoprotein cholesterol levels, smoking and diabetes) improved the accuracy of risk predictions for CAD (c-statistic increase: 0.05 [95% CI: 0.02–0.06]; net reclassification index: 19.3% overall [39.3% in those at intermediate risk, by FRS]) [22]. Based on another study conducted on 1461 asymptomatic participants, HR for coronary death and nonfatal myocardial infarction differs for the same CAC scores among a population with different FRS, and also changes for the same FRS with different CAC scores. Among patients with zero CAC score, HR increased from 1 to 3.4 and 7.8 for patients with <10, 16–20 and >20 FRS, respectively. Similarly, among the patients with FRS <10, patients with zero CAC score (HR: 1) have a lower HR compared with patients with CAC score >300 (HR: 4.6). Among patients with FRS of 10–15, 16–20 and >20, HR increased significantly from 1 to 4.6, 1 to 17.6, 3.4 to 8.9 and 7.2 to 19.1, respectively. Based on these data, adding CAC score to FRS has changed the HR in the 10–15 FRS group more than other groups and this may indicate that the predictive value of CAC score for future events in patients with low intermediate FRS (10–15) is more than for other subgroups [23].

CAC score in asymptomatic versus symptomatic patients

Although zero CAC score could be presented as a marker of no CAD, the sensitivity and specificity, positive predictive value (PPV) and negative predictive value (NPV) are significantly different in symptomatic versus asymptomatic patients. In one study carried out on 210 consecutive patients that were referred for CAC and CTA, none of the asymptomatic patients with zero CAC score had CAD. In this group of patients, sensitivity, specificity, PPV and NPV of CAC for detection of obstructive CAD were 1.00 (0.66–1.00), 0.32 (0.21–0.45), 0.18 (0.10–0.31) and 1.00 (0.80–1.00), respectively (p = 0.05). However, sensitivity, specificity, PPV and NPV of CAC in the symptomatic population for detection of obstructive CAD were 0.86 (0.66–0.95), 0.42 (0.33–0.52), 0.28 (0.19–0.39) and 0.92 (0.8–0.97), respectively (p = 0.007). This difference between symptomatic and asymptomatic groups was significant (p = 0.005) [24]. In another study, 2115 consecutive symptomatic patients were evaluated undergoing cardiac catheterization with no prior diagnosis of CAD. For any CAC present, the overall sensitivity was 99% for obstructive angiographic disease. With calcium scores >100, the sensitivity to predict significant stenoses on angiography decreased to 87% and the specificity increased to 79% [25]. Along the same lines, a multicenter study on 230 symptomatic patients showed that with CAC >0, >100 and >400, the sensitivities to predict stenosis were 98, 88 and 60%, whereas the specificities were 42, 71 and 88%, respectively [26]. A large, multicenter study on 1851 symptomatic patients who underwent coronary angiography for clinical indications, demonstrated that the overall sensitivity was 95%, and specificity was 66% for CAC score to predict obstructive disease on invasive angiography [27]. In a recently published study, it was shown that among 447 symptomatic patients approximately 10% of those with zero CAC score had noncalcified plaques and less than 1% had significant CAD. Patients with positive CT coronary angiography, compared with those with normal CT coronary angiography, had significantly higher mean age and higher pretest CAD probability (26 vs 34%; p < 0.0001) [28].

Based on these facts, a negative result in both asymptomatic and symptomatic patients strongly rules out CAD and predicts few future cardiovascular events. Furthermore, a high CAC score in a symptomatic patient is highly specific for CAD.

CAC score in acute coronary events

The role of CAC score in acute cardiovascular events is under debate. In 97 consecutive patients with new-onset chest pain suggestive of an acute coronary syndrome, coronary artery calcium was present in 81.8% of patients with and in 15.6% of patients without CAD (p < 0.0001). The presence of CAC had 82% sensitivity, 84% specificity, 73% PPV and 90% NPV for CAD diagnosis (OR: 24.3; 95% CI: 7.98–73.94) [29]. In another study, 263 patients with chest pain and low-to-moderate probability of CAD underwent both conventional emergency department (ED) chest pain evaluation and CAC assessment prospectively. In this double-blinded study it has been shown that 51% of patients had zero CAC score, and short-term and long-term cardiovascular events after discharge from ED and/or hospital, mostly happened among the patients with nonzero CAC score. In the same line, 97% of patients with cardiac chest pain had evidence of CAC on their cardiac CTs. Conversely, patients with zero CAC score had more noncardiac chest pain. Only 1% of them experienced cardiac chest pain. Moreover, in the follow-up period, none of them had cardiac events [30]. However, in another study on 136 Korean patients who presented to the ED with acute chest pain and nondiagnostic ECG, 92 patients out of 136 (68%) did not show detectable CAC, and 14 out of these 92 without CAC (15%) had ≥50% CAD on CTCA. Sensitivity, specificity, PPV and NPV of zero calcium score criteria for the detection of ≥50% CAD were 0.66 (95% CI: 0.50–0.80), 0.83 (0.74–0.90), 0.64 (0.48–0.77), 0.85 (0.75–0.91), respectively. A total of 45 patients (33%) were subsequently diagnosed as having acute coronary syndrome, and 38% of them had no CAC. They concluded that even in Asian patients older than 60 years old, zero CAC score did not necessarily guarantee the absence of significant CAD [31]. Further investigation is needed to assess whether CAC score differentiate between cardiac and noncardiac pain and lead to a meaningful change in clinical outcomes in different races.

CAC score in renal failure

Chronic kidney disease (CKD) is associated with a larger atherosclerosis risk factor and higher

CVD and mortality rates. In fact, CVD is the leading cause of death in patients with end-stage renal disease. In 1908 participants who underwent coronary calcium scanning as part of the multiethnic Chronic Renal Insufficiency Cohort Study, there was a strong and graded relationship between lower effective glomerular filtration rate and increasing CAC [32]. In another study on 85 consecutive asymptomatic outpatients with chronic renal failure (CRF) without previous history of myocardial infarction, coronary bypass surgery, angioplasty or diabetes and 55 controls, CAC was found in 40% of patients and 13% of controls; CAC was already present in the early phase of CRF. The prevalence was greater in patients with CRF than in controls, but less than that reported in dialysis patients [33]. In hemodialysis patients a cross-sectional study on 74 cases showed that duration of hemodialysis and hsCRP were two independent risk factors for CAC [34]. Another study of 46 dialysis patients showed that total CAC correlated with the number of diseased vessels ($p = 0.0001$), the severity of atherosclerosis in all of the vessels ($p = 0.0001$) and was the strongest predictor of CAD [35]. CAC was most strongly influenced by elevated serum phosphorus and calcium–phosphorus product in a dialysis population. Hypertension, lipid profile and calcium intake did not affect CAC initiation or progression [36]. In a cross-sectional study of 38 asymptomatic patients who were undergoing chronic hemodialysis, a logistic regression analysis revealed that elevated concentrations of troponins (both T and I) were independently associated with severe CAC after adjusting for age, duration of dialysis, diabetes and previous cardiovascular events [37]. In addition, CAC is prevalent in renal recipients and is predictive of cardiovascular events and mortality. In a study on 97 CKD patients with and without kidney transplantation it has been shown that 43.8% of transplant recipients versus 16.7% of CKD without transplant kidneys had CAC ($p < 0.001$) [38]. In a prospective cohort of 112 asymptomatic renal transplant recipients, recipients with cardiovascular events or death during the follow-up period compared with those without them had a higher mean and median CAC score. Cumulative survival rate was better among recipients with CAC score <100 [39].

Coronary calcification progression is common and predicts clinical outcomes in patients with CKD. A study showed that in hemodialysis patients, the median CAC increased by 1.27 ± 1.88 score/days ($p = 0.013$). All patients with zero CAC score remained the same at follow-up. The dialysis patients who died during 15 months follow-up had a significantly higher CAC score at baseline compared with the patients who remained alive. Similarly, hospitalized patients had greater baseline CAC score compare to those who were not hospitalized. In patients undergoing a renal transplant, CAC score was more stable over the follow-up time period [40]. A study on 31 kidney transplant (KTR) patients showed that duration of pretransplantation dialysis treatment and smoking were identified as independent predictors of post-transplantation CAC progression. Conversely, changes in calcium and phosphate levels were not associated with calcification [41]. Along the same lines, progression of CAC has been studied in 197 KTR patients after 4.40 ± 0.28 years. By multivariable linear regression, higher baseline CAC score, history of cardiovascular event, use of a statin, and lower 25-hydroxyvitamin D_3 level were independent determinants of CAC progression [42]. Another study carried out on 56 patients revealed that CAC had significantly progressed in hemodialysis patients during the 15-month observation period. Microinflammation was the only independent risk factor for CAC progression in hemodialysis patients [43]. A study of 83 KTR patients who were followed-up prospectively during 1 year revealed that CAC diminished in 14.5%, stabilized in 59.2% and progressed in 26.3% of patients. Post-transplant CAC progression was predicted by baseline CAC score [44].

Correlations between CAC with mineral metabolism and inflammatory markers are under investigation. A study of 53 patients on chronic hemodialysis revealed that the mean CAC score of patients with cardiac events (2568.5 ± 2575.1 mm^3) was significantly higher than that of patients without cardiac events (258.0 ± 409.2 mm^3). They did not find a significant correlation between CAC score and parameters of mineral metabolism, such as serum levels of calcium, phosphorus and parathyroid hormone [45]. However, some other studies suggested a correlation between progression of CAC in CKD and medication, level of phosphorus and some inflammatory markers. In a study on 40 hemodialysis patients, the time-integrated levels of C-reactive protein, phosphorus and calcium-x phosphorus product were positively

correlated with progression of the CAC score but did not correlate with the levels of fetuin-A or lipid parameters [46]. Progression of vascular and cardiac valve calcification was studied in 360 adult hemodialysis patients with secondary hyperparathyroidism treated with either cinacalcet plus low-dose vitamin D or flexible doses of vitamin D sterols alone. In this study, cinacalcet plus low-dose vitamin D sterols attenuated vascular and cardiac valve calcification [47]. In 49 peritoneal dialysis, the logistic regression revealed that the independent determinants of CAC were age (OR: 1.12; $p = 0.006$) and number of prescribed antihypertensive drugs (OR: 2.38; $p = 0.048$). When the population was stratified by calcium score quartile, soluble Fas levels were significantly higher in patients with severe calcification. In patients younger than 45 years of age, CAC correlated positively with phosphorus levels ($r = 0.52$; $p = 0.04$) [48].

Effect of CAC scan on patient behavior, lifestyle & physician prescriptions

Results of a CAC scan highly affects patients' behavior and also changes their physician recommendations. In one study conducted on 980 asymptomatic patients after initial CAC scan, patients were followed-up for an additional 2–3 years. Aspirin initiation, dietary changes and exercise were lowest (29, 33 and 44% in order) among those with CAC = 0, and gradually increased significantly with higher CAC scores [49]. In another study, 2137 patients divided on two scanned and nonscanned groups before CAD risk factors assessment were followed up for 4 years to observe changes in risk factors and FRS. Favorable changes in systolic blood pressure ($p = 0.02$), low-density lipoprotein cholesterol ($p = 0.04$) and waist circumference for those with increased abdominal girth ($p = 0.01$), and tendency towards weight loss among overweight participants ($p = 0.07$) were observed in the scan group compared with the no-scan group. In the no-scan group, mean FRS rose while FRS remained the same in the scan group (0.7 ± 5.1 vs 0.002 ± 4.9; $p = 0.003$). Patients with increased CAC score among the scan group, exhibit improvement in systolic and diastolic blood pressure ($p < 0.001$), total cholesterol ($p < 0.001$), low-density lipoprotein cholesterol ($p < 0.001$), triglycerides ($p < 0.001$), weight ($p < 0.001$) and FRS ($p = 0.003$). In the scan group, downstream medical testing and costs were comparable to those of the no-scan group, with lower resource utilization for subjects with normal CAC scans [50,51].

Current directions for CAC utilization

The most common utilization of CAC for a practitioner is in the setting of intermediate cardiovascular risk, or those patients with either borderline cholesterol values or family history of premature CAD. Too often, family history is dismissed based on environmental factors (i.e., "my father had a heart attack, but he smoked cigarettes"). The use of CAC testing is ideal to see if the patient at hand has atherosclerosis, and if so, may have inherited the 'gene'. Similarly, those patients with borderline cholesterol values are ideal candidates for atherosclerosis testing. Those with negative studies can continue on lifestyle management, while those with elevated scores can be given medical therapy. Even the National Cholesterol Education Panel guidelines support the use of CAC testing in this environment, stating that "measurement of coronary calcium is an option for advanced risk assessment in appropriately selected persons. In persons with multiple risk factors, high coronary calcium scores (e.g., >75th percentile for age and sex) denote advanced coronary atherosclerosis and provide a rationale for intensified low-density lipoprotein lowering therapy. Moreover, measurement of coronary calcium is promising for older persons in whom the traditional risk factors lose some of their predictive power" [52].

Conclusion

FRS as an office-based cardiovascular risk assessment tool only covers 65% of cardiovascular events. Based on many studies, CAC score in combination with FRS produces a higher predictive value. However, this additive value is highest among patients with intermediate FRS. The only prospective clinical trial using CAC testing in this capacity is the EISNER study, which demonstrated improvement in multiple biomarkers but was not powered for outcomes [50]. A zero CAC score predicts a better cardiovascular outcome among all groups, and strongly rules out presence and severity of CAD in asymptomatic patients. A small increase in CAC score is associated with higher risk of cardiovascular events in all cohorts studied, both asymptomatic and symptomatic, both stable and acute coronary syndrome. In

CKD, in addition to other risk factors, CAC is affected by change in mineral metabolism but still showed an important predictive role for future cardiovascular events. CAC scores have been shown to positively affect patients' lifestyle and physician recommendations. However, we still need more studies regarding the combination of CAC score with other predictive tools such as FRS, epicardial fat volume (which can be measured by the same CT scan applied for CAC score) and new biomarkers to find the best algorithms for clinical use for prediction of subclinical atherosclerosis, as well as the presence of high-risk plaques and future cardiovascular events.

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- ▪ of interest
- ▪▪ of considerable interest

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