

## Clinical Review

# Coronary Artery Calcium Scoring in Asymptomatic Patients

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### Abstract

#### Abstract

Coronary artery calcium (CAC) scoring is an important prognostic tool for personalized cardiovascular preventive care and has recently been incorporated into American College of Cardiology/American Heart Association guidelines. CAC provides direct visualization and quantification of CAC burden for risk stratification and primary prevention of cardiovascular events in an asymptomatic population. CAC scoring is recommended for individuals with intermediate 10-year atherosclerotic cardiovascular disease (ASCVD) risk and selective populations with borderline ASCVD risk. In this review, we outline the interpretation of CAC scores for predicting the risk of cardiovascular events, and we highlight the guidelines for starting statin and potentially starting aspirin therapy. A CAC score of 0 is the strongest negative predictive factor for cardiovascular disease (CVD), and a 0 score can successfully de-risk a patient. On the contrary, higher CAC scores correlate with worse cardiovascular prognostic outcomes. The CAC scan is a widely available and reproducible means for an early look at the atherosclerotic burden, and it can help strategize early interventions. The CAC interpretation and the decision to start treatment need to be personalized based on individual risk factors. We believe the emerging literature supports our contention that the CAC score can be used more broadly to improve the prophylaxis and treatment of a wider range of apparently healthy patients.

#### Keywords

coronary artery scoring; calcium scoring; multi-detector CT; vascular calcification; cardiovascular diseases; heart disease risk factors; x-ray computed tomography

## History of the Coronary Artery Calcium Score

### Development

The Agatston Calcium Score was developed in 1990 by Dr Arthur Agatston with most of the work leading to its development completed at Mount Sinai Medical Center (Miami Beach, FL) during the late 1980s.<sup>1</sup> Agatston's work was heavily influenced by the Framingham Heart study, but he endeavored to also identify which patients would benefit most from statin-induced lipid reduction therapy. An electron-beam computed tomography (EBCT) scanner was used to provide direct visualization of coronary artery atherosclerotic calcium plaques, quantify calcium, and estimate plaque,

years before a patient would have an acute coronary event. He used a single-slice mode (slice thickness of 3 mm) and a temporal resolution of 100 ms to provide the necessary temporal and spatial resolution to visualize coronary arteries and quantify calcium. Agatston first published his findings in 1990 in the *Journal of the American College of Cardiology* along with the Agatston (Coronary Artery Calcium) score, which is the calcified coronary plaque area multiplied by density factor.<sup>2</sup>

### Early Use

Since 1990, the Agatston score has been increasingly used by physicians to evaluate the atherosclerotic risk for patients. Agatston's article was widely cited, and comprehensive re-

search in the field followed to study the prognostic value of coronary artery calcium (CAC) scoring, with several meta-analyses published in peer-reviewed journals.<sup>3-4, 5-7</sup> Some of the first large cohort studies completed include the Multi-Ethnic Study of Atherosclerosis (MESA), the Dallas Heart Study, and the Heinz Nixdorf Recall study.<sup>8-10</sup>

**Evolution**

Since the introduction of the Agatston score, several other calcium scoring methods have been developed.<sup>11</sup> In 1998, Callister et al was the first to use a calcium volume score, which added the volumes of all coronary calcification slices and was calculated by multiplying calcification area by slice thickness.<sup>11</sup> Calcium mass score measures true calcium mass in the atherosclerotic lesions.<sup>12</sup> A calcium density score, which can be calculated from the Agatston score and calcium volume score, has also been used.<sup>13</sup> The MESA study revealed additional prognostic value of calcium density in patients who had similar calcium volume scores.<sup>14</sup>

**Imaging Modalities to Assess Calcium Score**

**EBCT versus MDCT versus DSCT**

With the recurrent evolution of CT technology, multi-detector helical CT (MDCT) was introduced, largely replacing EBCT. MDCT has become the clinical standard over the last 10-15 years due to lower costs and reduced space requirements. All the quantification methods of coronary calcium in EBCT have been reproduced in MDCT with comparable calcium scoring results, and MDCT has emerged as the most widely used imaging modality.<sup>15,16</sup> Improvements have also been made in radiation technology, lowering the radiation dose exposure to a level of 1 mSv, which led to the development of dual-source CT (DSCT).<sup>13</sup> Studies have shown that, compared to MDCT, DSCT is less susceptible to cardiac motion and reduces the differences between EBCT and MDCT results.<sup>17</sup>

**Risks and Costs**

MDCT has longer exposure times (83 to 210 ms) compared with EBCT (50 to 100 ms), which leads to a higher effective radiation dose. Hence, MDCT exposes patients to higher radiation, 1.0-1.5 mSv in men and 1.1-1.9 mSv in women, as compared to EBCT which has a radiation dose of 0.7-1 mSv in men and 0.9-1.3 mSv in women.<sup>18</sup> Due to increased radiation exposure, models based on BEIR VII resulted in an estimated increase in cancer risk from MDCT (9/100 000 males, 28/100 000 females, for single screening, age 40).<sup>19</sup> Additionally, increased availability of CAC screening could result in unnecessary testing and higher health-care costs. However, MDCT is less expensive than EBCT, which could deliver healthcare to more patients.

**Current Practices for CAC Scoring**

**Risk assessment**

A CAC score helps quantify the atherosclerotic burden for a patient, which helps assess underlying coronary heart disease and predicts the risk for major cardiovascular outcomes. Primary prevention decisions, such as initiating statins or aspirin, can be based on a patient’s individual coronary calcium score.<sup>18,20</sup> Previous studies have shown that patients with a CAC score greater than 100 may have the most benefit when started on aspirin and/or statins, irrespective of their cardiovascular risk profile.<sup>21-22</sup> A Walter Reed Army Medical Center 10-year follow-up study showed that we only need to statin-treat 12 patients with a CAC score greater than 100 to prevent 1 event.<sup>22</sup>

**Equations and Diagnostic Accuracy**

A summary of the equations to calculate various calcium scores discussed above is provided in **Table 1**. An Agatston CAC score greater than 0 has a high sensitivity (98%) and low specificity (40%) to predict stenosis greater than 50%.<sup>23,24</sup>

**Table 1.** Basic Equations to Calculate Calcium Scores

Calcium score	Equation
Agatston CAC score	Calcification area x density factor
Calcium volume score	Calcification area x slice thickness
Calcium density score	Agatston CAC score / [calcium volume score x (1/slice thickness)]

### Score Interpretation and Predictive Value

In 2007, the American College of Cardiology Foundation/American Heart Association (ACC/AHA) consensus guidelines combined the data from 27 622 asymptomatic patients and calculated the relative risk of major adverse cardiovascular events (MACE), which included all-cause mortality, cardiac mortality, and nonfatal myocardial infarction.<sup>3</sup> The results are summarized in **Table 2**.

The 2013 ACC/AHA guidelines classified CAC scoring as a class IIb recommendation for risk stratification of asymptomatic patients.<sup>25</sup> There are 2 accepted methods for interpreting calcium scores: absolute values with fixed cut-offs or age-, gender-, and race-adjusted scores by calculating distribution percentiles using population databases. The MESA data and risk calculator is most commonly used as an adjunct to calcium scoring to improve 10-year coronary heart disease event prediction.<sup>26</sup>

According to McClelland et al, the MESA risk score was markedly enhanced with the addition of CAC scoring (Harrell’s C-statistic 0.80 versus 0.75,  $P < .0001$ ).<sup>26</sup> External validation provided evidence of strong discrimination and calibration, with a C-statistic of 0.78 in the Heinz Nixdorf Recall study and 0.82 in the Dallas Heart Study.<sup>26</sup> Additionally, analyses by Yeboah et al yielded similar results, where the addition of CAC scoring improved the prediction of atherosclerotic cardiovascular disease (ASCVD) events with the Framingham Risk Score and Pooled Cohort Equation.<sup>27, 28</sup> When compared to other biomarkers, such as brachial flow-mediated dilation, ankle-brachial index, carotid intima-media thickness, and high sensitivity C-reactive protein, the addition of CAC scoring to the Framingham Risk Score had

the highest net reclassification improvement (NRI, 0.66) versus the NRI for other biomarkers (0.024 - 0.10). As for the Pooled Cohort Equation, adding CAC to the prediction model for ASCVD events, including stroke, had a categorical NRI of 0.12.

### Age-Based Interpretation of CAC Score

Age-related adjustments are important in the interpretation of a CAC score. This assertion was clearly supported by Mortensen et al who found that the diagnostic value of a 0 CAC score improves with increasing patient age.<sup>29</sup> For example, patients less than 40 years of age with a 0 CAC score had a 32% lower likelihood of future obstructive coronary artery disease while patients greater than 70 years of age with a 0 CAC score had an 82% lower likelihood.<sup>29</sup>

### CAC Scoring for Asymptomatic Patients

#### Screening Decisions for Asymptomatic Patients

The 2019 ACC/AHA guidelines recommended the selective use of CAC scoring to guide management decisions for primary prevention of ASCVD in asymptomatic patients 40-75 years of age.<sup>30</sup> The first step is to evaluate ASCVD risk for asymptomatic patients using the Pooled Cohort Equation, which estimates 10-year ASCVD risk. CAC scoring is a class IIa recommendation for select borderline-risk adults (5% to < 7.5% 10-year ASCVD risk) and intermediate-risk ( $\geq 7.5\%$  to < 20% 10-year ASCVD risk) for guiding primary prevention management decisions, such as starting statin therapy if the risk decision is uncertain.<sup>30</sup> CAC scoring may be indicated if a patient has an underlying co-morbidity. For example, studies

**Table 2.** Calcium Score, Interpretation and Future Risk of Major Adverse Cardiac Events (MACE)<sup>3</sup>

Calcium score	Interpretation/Prognosis
0	No calcium, low risk of future MACE
1-112	Average risk; RR 1.9% (95% CI 1.3-2.8%) of future MACE
100-400	Moderate risk; RR 4.3% (95% CI 3.1%-6.1%) of future MACE
400-999	High risk; RR 7.2% (95% CI 4.2%-9.9%) of future MACE
>1000	Very High risk; RR 10.8% (95% CI 4.2-27.7%) of future MACE

RR = relative risk; CI = confidence interval

**Table 3.** 2019 ACC/AHA Guidelines for Starting a Patient on Statins Based on CAC Score<sup>30</sup>

Calcium score	Decision on prescribing statins
0	Low risk, no need to start statins unless patient has diabetes, a family history of premature coronary heart disease, or is a current smoker
1-99	Favor starting statin especially if age greater than 55 years
> 100 (or 75th percentile)	Reasonable to start statin therapy

have shown the benefit of CAC screening for asymptomatic patients with type 1 and type 2 diabetes.<sup>31,32</sup>

Multiple analyses from the MESA study and the CAC Consortium showed that CAC scoring offers better risk assessment and risk classifications for patients, especially when added to the standard risk factors, such as age, gender, hypertension, and diabetes. For example, the Nasir et al study of the MESA cohort showed that the 10-year number needed to treat (NNT-10) to prevent an ASCVD event in patients recommended for statins was 64 for patients with a CAC score of 0 and 28 for patients with a CAC score greater than 100.<sup>33</sup> For patients considered for statins, the NNT-10 was 223 for patients with a CAC score of 0 and 46 for patients with a CAC score greater than 100. By comparison, in the absence of calcium scoring, the NNT-10 was 138 and 556 for those recommended for statins and those considered for statins, respectively.<sup>33</sup>

**Management for Asymptomatic Patients**

The 2019 ACC/AHA guidelines outlined management decisions based on ASCVD risk and calcium score.<sup>30</sup> In patients with borderline or intermediate ASCVD risk and a CAC score of 0, statin therapy can be withheld, and the patient can be reassessed in 5-10 years in the absence of other higher-risk conditions (family history

of early coronary heart disease, type 2 diabetes, and smoking history).<sup>30</sup> Under similar patient conditions, if the CAC score is between 1 and 99, statin therapy is recommended for patients over age 55. Finally, for patients with a CAC score over 199 (75th percentile or higher), statin therapy is recommended.<sup>30</sup> The guidelines for starting statin based on CAC scores for patients 40-75 years of age and LDL-C greater than or equal to 70 or less than 190 mg/dL are shown in **Table 3**.

The 2017 Society of Cardiovascular Computed Tomography expert consensus statement recommended CAC screening for asymptomatic patients who are 40-75 years of age with the 10-year ASCVD risk between 5 and 20%.<sup>34</sup> The Society of Cardiovascular Computed Tomography also recommended CAC screening for some patients with ASCVD risk of less than 5% (eg, those with a family history of premature coronary artery disease). Guidelines for starting statin and aspirin according to this expert consensus based on CAC score are outlined in **Table 4**.

Besides lifestyle modification and medical therapy, management options for an asymptomatic patient found to have a high CAC score include a cardiac stress test, cardiac imaging, or coronary angiography, which might not be warranted in an otherwise asymptomatic individual.<sup>35</sup> Wu et al studied the rates of cardiovascular

**Table 4.** 2017 Society of Cardiovascular Computed Tomography Expert Consensus on the Clinical Indications for CAC Score<sup>34</sup>

CAC score	Risk	Treatment recommendation
0	Very low risk	Statin not recommended
1-99	Mild risk	Moderate-intensity statin if < 75th percentile; Moderate-to-high-intensity if > 75th percentile
100-299	Moderate risk	Moderate to high-intensity statin + ASA 81 mg
> 300	Moderate-to severe risk	High-intensity statin + ASA 81 mg

Abbreviation: ASA = acetylsalicylic acid

**Table 5.** Rescreening Intervals in Patients With 0 CAC Score<sup>41</sup>

CAC score and 10-year ASCVD risk	Recommended rescreening interval
CAC = 0, < 5% ASCVD risk	5-7 years
CAC = 0, 5% - 20% ASCVD risk	3-5 years
CAC = 0, > 20% ASCVD risk	3 years
CAC = 0, Diabetic or age < 40 years	3 years <sup>42</sup>

testing in asymptomatic patients 1-year post-CAC scoring.<sup>36</sup> The testing rates were higher in patients with CAC scores greater than or equal to 100 (27%), with a rate of 10.3% for exercise stress testing, 8% for single-photon emission computed tomography myocardial perfusion imaging, 7% for stress echocardiography, and 1% for coronary angiography.<sup>36</sup> If a cardiac stress test is positive in an asymptomatic patient with a high CAC score, coronary angiography might be recommended. However, careful consideration and a benefits-versus-risks approach should be taken due to the invasive nature of the procedure. Even if an obstructive lesion is found in an asymptomatic individual, it doesn't identify sites of future myocardial infarction as it is mostly caused by rupture of unstable atherosclerotic plaques.<sup>35</sup> Therefore, the benefit of functional testing and invasive angiography in an asymptomatic patient is questionable, and the prediction of prognostic outcomes is unclear.<sup>37</sup>

### The Power of Zero and Time to Re-scan

Several randomized epidemiologic studies, clinical trials, and large registries, such as MESA, Dallas Heart Study, Heinz Nixdorf Recall, SCOT-HEART, PROMISE, CONFIRM, and SWEDHEART have demonstrated the prognostic value of a 0 CAC score.<sup>38-40</sup> Blaha et al concluded that a CAC score of 0 was the strongest negative risk factor for cardiovascular disease (CVD).<sup>38</sup> Pursani et al showed that a CAC score of 0 was associated with low CVD risk (1.6%) in statin-eligible participants.<sup>39</sup> Another study by Mortensen et al showed that a CAC score of 0 could potentially down-classify elderly statin-eligible patients to statin-ineligible patients.<sup>40</sup> These findings revealed the potential utility of a 0 CAC score. The recommended time for rescreening for patients with a CAC score of 0 based on ASCVD risk is shown in **Table 5**.

The radiation risk associated with re-exposure to EBCT/MDCT scans should be considered and discussed with the patient. These re-screening decisions should be individually tailored based on patient risk factors for a major cardiovascular event.

### Prognostic Outcomes of CAC Scoring in Asymptomatic Patients

There is extensive evidence regarding the prognostic value of CAC for predicting ASCVD and mortality among asymptomatic patients with borderline and intermediate risk. The most convincing data comes from the Budoff et al MESA study in which CAC scores were analyzed in asymptomatic males and females of different ethnicities.<sup>43</sup> The authors reported that the risk-adjusted hazard ratio was 7.7 for a CAC score of 101-300 and the hazard ratio was 9.7 for a score greater than 300.<sup>43</sup> Budoff et al also reclassified their patients because approximately 40% of patients with a CAC score of 400 were not receiving statins, even though statins were indicated in these patients based on their CAC score.<sup>43</sup> The Heinz Nixdorf Recall study followed the patients for 5 years after their CAC screening. In this study, Erbel et al found that relative risk was significantly higher in patients with CAC scores greater than the 75th percentile, compared to patients with CAC scores less than or equal to the 25th percentile.<sup>44</sup> Also, a higher event rate was noted in males (relative risk [RR] = 11) as compared to females (RR = 3) in the study.<sup>44</sup>

Another retrospective, multicenter study followed asymptomatic patients with a CAC score greater than or equal to 1000 and no known CVD for a period of 12 years to compare the prognostic outcomes of patients with lower CAC scores.<sup>45</sup> These authors found patients with a CAC score of greater than or equal to

1000 had higher CVD and total mortality (Hazard ratio [HR] = 5) when compared to patients with a CAC score of 0 and compared to patients with CAC score of 400-999 (HR = 1.7).<sup>45</sup> A low CAC score has also been associated with an improved prognosis of young asymptomatic adults 33-45 years of age with low risk. The CARDIA (Coronary Artery Risk Development in Young Adults) study also found the CAC score to be a strong predictor of mortality.<sup>46</sup>

### Benefits of Early Detection

A coronary calcium scan gives the clinician an early look at the patient's atherosclerotic burden and helps implement early interventions. Patients are more receptive to management strategies following a scan, which can help promote patient compliance. Changes in lifestyle, including a healthy diet and regular exercise, have the potential to slow arterial plaque progression and reduce the risk of future cardiovascular events can be recommended. In addition, drugs including statin and aspirin can be started depending on a patient's individual CAC score. A coronary calcium scan has also proven to be cost-effective, specifically in patients with a family history of premature coronary artery disease (FHCAD). Venkataraman et al studied data from the CAUGHT-CAD (Coronary Artery Calcium Score: Use to Guide Management of Hereditary Coronary Artery Disease) trial to examine the cost effectiveness of coronary calcium scanning in patients with a FHCAD for primary cardiovascular prevention.<sup>47</sup> These authors found a CAC-guided strategy of adding CAC scoring to ASCVD risk assessment for patients with FHCAD pooled cohort equations risk thresholds greater than 2% was more cost-effective than statin-treating all patients with pooled cohort equation risk thresholds greater than or equal to 7.5%.<sup>47</sup>

### Prognostic Outcomes of Coronary Plaque Calcification, Density, and Vulnerability

There are 2 primary types of coronary calcium, intimal calcification, which is associated with advancing age, smoking, hypertension, and hyperlipidemia, and medial calcification, which is due to kidney disease.<sup>48</sup> A higher CAC score indicates a higher plaque burden, but it does not translate into higher plaque vulnerabili-

ty.<sup>48</sup> High-risk plaque features include thin-cap fibroatheroma, necrotic-lipid core, positive remodeling, spotty calcification, low CT attenuation, and napkin-ring sign, which makes the plaque unstable and increases the risk of rupture leading to acute coronary syndrome.<sup>49</sup> Patient outcomes are highly dependent on calcification patterns, calcified nodules associated with thick-cap fibroatheroma, higher plaque volume, and lower MACE,<sup>50</sup> while spotty calcification increases plaque vulnerability.<sup>51-53</sup> Factors associated with high plaque density are age, high-density lipoprotein-cholesterol, and statins, while high body mass index and diabetes are typically associated with decreased plaque density.<sup>54-57</sup> Higher plaque density is associated with greater plaque stability, which reduces future risk of MACE.<sup>55,58-60</sup> Studies have found CAC density to be inversely associated with MACE and CAC volume to be positively associated with MACE.<sup>61</sup> Consequently, it has been proposed that calcium volume score adjusted for density score would be superior to the Agatston score or volume score alone for cardiovascular risk assessment. For example, Bhatia et al conducted an analysis of MESA participants and found that higher CAC density leading to lower MACE depends on the CAC volume.<sup>54</sup> These authors observed that their low-volume, high-density group had lower MACE risk than the low-volume, low-density group, but event rates for high-volume, low-density and high-volume, high-density groups were similar.<sup>54</sup> In fact, Bhatia et al proposed a CAC volume cut-off point of less than or equal to 130 mm<sup>3</sup>.<sup>54</sup> In other words, in patients with CAC volume of less than or equal to 130 mm<sup>3</sup>, CAC density was associated with MACE reduction, but an association between CAC density and MACE was not seen in patients with a CAC volume of greater than 130 mm<sup>3</sup>. Currently, the Agatston CAC score is the standard CAC scoring method, but it has a potential for improvement by using the volume score with an adjustment for density for better cardiovascular risk assessment. However, a standardized method to integrate volume and density scores has not been established.

### Coronary Calcium Scan in Specific Populations

#### Race and Gender

Researchers have analyzed and interpreted the

data from MESA and revealed differences in the CAC score across ethnic groups. Bild et al, for example, found that the relative risk of having coronary calcification (Caucasian reference), after adjusting for a range of control variables, was 0.78 in African American patients, 0.85 in Hispanic patients, and 0.92 in Chinese patients.<sup>62</sup> McClelland et al concluded that men had higher CAC compared to women of the same age, and as expected, CAC score also increased with age.<sup>63</sup> Researchers also found that CAC was highest in Caucasian and Hispanic men and women as compared to the same gender counterparts of other ethnicities.<sup>63-65</sup>

### Smokers

Smoking is a significant risk factor associated with poorer cardiovascular outcomes due to its deleterious effects on hypertension, atherosclerosis, hyperlipidemia, and inflammation. Several researchers studied the utility of CAC scoring in smokers. Schulman-Marcus et al reported the prognostic outcomes in smokers with a 15-year follow-up and found higher median CAC scores in smokers versus non-smokers (19 vs 3,  $P < .001$ ).<sup>66</sup> Non-smokers were also significantly more likely to have a CAC score of 0 when compared to smokers (47.8% vs 38.7%, respectively,  $P < .001$ ).<sup>66</sup> For any CAC score, smokers had a higher adjusted hazard ratio or mortality risk ( $HR = 4.67$ ,  $P < .001$ ) compared to non-smokers ( $HR = 3.07$ ,  $P < .001$ ).<sup>66</sup> McEvoy et al divided smokers and non-smokers into CAC score categories and found higher mortality hazard ratios for smokers.<sup>67</sup> Specifically, these authors reported hazard ratios (non-smoking reference) of 3.8 for a CAC score of 1-100; 3.5 for a CAC score of 101-400; and 2.7 for CAC scores greater than 400.<sup>67</sup> Simply put, smoking was associated with higher mortality for any given CAC score.<sup>67</sup> Shaw et al found that smokers had a CAC score that was 72 points higher on average, compared to non-smokers.<sup>68</sup> These authors also stratified smokers by age and revealed that smokers less than 50 years of age with a high-risk CAC score were 4 to 9 times more likely to die compared to non-smokers. In addition, a CAC score greater than 400 decreased the life expectancy by 4.8 years in smokers less than 50 years old.<sup>68</sup> These studies illustrate the prognostic value of CAC scoring in the smoking patient population and its utility in risk stratification.

### Summary and Conclusion

CAC scoring was first introduced in 1990 to visualize coronary calcium plaque and estimate atherosclerotic burden, and it is strongly associated with coronary heart disease/MACE events. EBCT was initially introduced for CAC measurement, but with recent technological advancement, MDCT and DSCT are widely used due to lower costs. In the ensuing decades, CAC scoring has evolved from a basic screening modality to a national guideline-recommended approach to guide management decisions. Preventive strategies, such as statin and aspirin, can be initiated in adults aged 40-75 years at intermediate 10-year ASCVD risk ( $\geq 7.5\%$  to  $< 20\%$ ) and in selective borderline risk ( $5\%$  to  $< 7.5\%$ ) individuals, such as those with a family history of premature coronary artery disease. The addition of CAC scores to other risk stratification scores, such as the Framingham Risk Score and the Pooled Cohort Equation, has the potential to refine risk predictions of ASCVD events. CAC provides an early opportunity to define cardiovascular risk and implement early management strategies, such as lifestyle changes and statins/aspirin, both of which can slow plaque progression and reduce the incidence of poor outcomes. Additionally, CAC scoring can promote patient compliance. When physicians encounter an asymptomatic individual with a positive CAC score, they should emphasize to the patient that atherosclerosis is reversible with proper risk factor management, such as exercise, healthy diet, or anti-hyperlipidemic and anti-platelet therapies. Functional cardiac testing, cardiac imaging, and invasive coronary angiography are justified for an asymptomatic individual with a positive CAC score after a comprehensive risk versus benefit consideration as they will otherwise not be indicated in these individuals.

A CAC score of 0 is a promising marker of low cardiac event rates, has high negative predictive value, and can be used to avoid starting preventive therapies. Higher CAC scores and CAC progression are directly proportional to higher coronary heart disease/CVD hazard ratios and all-cause mortality. It is recommended to consider statin for a CAC score of 1-99 and to start statin for a score greater than or equal to 100. Careful interpretation of the CAC score is essential as its diagnostic accuracy depends on patient characteristics, such as age. Primary

risk prevention and the decision to start statin should be personalized based on several risk factors and co-morbidities, such as smoking, hypertension, diabetes mellitus, and obesity, which independently increase the risk of a future MACE event. It is recommended to add CAC to cancer screening imaging modalities, such as NCCT for lung cancer and mammography for breast cancer screening. Higher CAC density leads to lower MACE based on CAC volume, hence the Agatston CAC score use of plaque density as a multiplier is sub-optimal. This highlights the importance of integrating CAC volume and density scores into CAC scoring and perhaps the development of a new CAC scoring system.

### Future Directions

CAC scoring has revolutionized preventive cardiovascular medicine and has the potential to be incorporated in everyday clinician-patient discussions and prevention strategies. Further studies are needed to elucidate the role of CAC scoring in risk reduction therapies in specific populations, such as diabetics. It is also anticipated that other calcium scores, such as the calcium density score, can be obtained simultaneously with the CAC score and will be integrated into clinical practice as a new predictive marker of atherosclerosis. However, it remains contentious whether high- or low-density calcium plaques correlate to worse CVD outcomes. Recent studies have shown that higher CAC density may in fact be protective as dense calcium deposition without a large lipid core might stabilize the plaque.<sup>69</sup> Future studies are essential to better understand this phenomenon and its clinical relevance, opening the possibility that a new methodology could be established for optimal cardiovascular risk assessment by integrating CAC volume score adjusted for CAC density.

Another promising area for future research is to determine the risk of a future CVD event based on the location of coronary plaque. It will be revealing to explore whether plaques in left main coronary arteries and proximal coronary arteries impart greater risk as proximal plaques have been shown to be more susceptible to rupture and cause occlusion.<sup>70,71</sup> Studies focusing on the shape and distribution of calcified plaque will also help understand the relative risks of coronary events. A synthesis of avail-

able evidence suggests that CAC will remain an essential tool for personalized cardiovascular care as more data become available. The use of CAC scoring in daily clinical practice has evolved substantially since its introduction in 1990 and will likely be integrated even more into daily clinical practice, leading to improvements in the delivery of patient care.

### Conflicts of Interest

Dr Alexander discloses speaking honoraria from Janssen Pharmaceuticals.

Drs Flynn, Hussain, and Mahmood declare no conflicts of interest.

Drs Mahmood and Alexander are employees of Corpus Christi Medical Center, a hospital affiliated with the journal's publisher.

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