

# The Role of Coronary Artery Calcification Scoring in Primary Prevention of Cerebrovascular Disease

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## Abstract

Atherosclerosis is considered a systemic disease, and its presence in any site of the arterial system in the body raises suspicion of its presence somewhere else. Since atherothrombosis represents the most common cause of stroke, it is important to investigate whether coronary artery calcification, a commonly used measure of cardiac atherosclerotic burden, can be a similarly useful measure of atherosclerotic burden in the brain. This review aimed to summarize the current evidence regarding the role of CAC in the detection and prevention of cerebrovascular disease. CAC is an independent risk factor of stroke development, and using it to supplement traditional risk factors may allow better identification of higher-risk groups. Intermediate risk patients with elevated CAC scores can be started on statin therapy. CAC score may hold promise in identifying patient groups most likely to benefit from aspirin therapy. In addition, it may have a role in the identification of stroke patients who may benefit from closer cardiac monitoring as it can aid traditional scores in the detection of coronary pathology in stroke survivors.

## 1. Introduction

Atherosclerosis is the primary driver of cardiovascular disease, which, according to the World Health Organization (WHO), makes up 31% - nearly 18 million- of deaths worldwide [1]. Importantly, the progressive nature of the disease means that through early detection, we can prevent arterial blockage and consequent ischemia. Early affection of the coronary arteries can be gauged using coronary artery calcification (CAC), and since atherosclerosis is a systemic disease, the affection of the coronaries could imply affection of other arteries, such as the cerebral or peripheral arteries [2-4]. In accordance with the above, several studies have reported a higher prevalence of coronary artery disease (CAD) in patients with symptomatic cerebrovascular disease (CVD), as both entities share a common underlying pathophysiological mechanism of endothelial dysfunction due to atherosclerotic disease [5]. Stroke is a major cause of global morbidity and mortality, and despite a decrease in mortality over the last two decades, the incidence of stroke, as well as stroke-related deaths and disabilities, have increased, with low and middle-income countries bearing much of the brunt [6]. The most common cause of cerebral ischemia is the atherosclerotic narrowing of cerebral blood vessels. Other

causes include extra-cranial emboli, typically originating from the heart, and cerebral venous thromboses. Since atherothrombosis represents the most common cause of stroke, it is vital to investigate the utility of early markers of atherosclerosis, such as CAC, as predictors of stroke [7].

Early in the 1980s, CAC was first detected after the development of electron beam computed tomographic scanning (EBCT), which permitted noninvasive and quantitative detection of CAC [8]. Afterward, the development of multi-detector computed tomography (MDCT) leads to a significant improvement in the direct visualization of coronary arteries and the development of CAC scoring. CAC scoring aims to measure and detect the amount of calcium in the wall of the coronary arteries. It can be presented through the Agatston score or the traditional CAC score, detected on CT angiography CTA [9-11]. Nowadays, the Agatston score is the routinely used scoring for CAC quantification [8]. CAC scoring has proven a useful tool in both the detection and prognostication of significant CAD, as studies have demonstrated a high degree of sensitivity in ruling out significant coronary stenosis, and reduced survival in those with higher calcium scores

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[12,13]. As previously mentioned, atherosclerosis is a systemic disease, and it is precisely this systemic nature that may allow us to extend the usage of CAC from the prevention of the coronary manifestations of atherosclerosis, namely CAD, to the prevention of cerebrovascular manifestations, namely CVA. The aim of this review is to determine the role of CAC scoring in the detection of CVA.

### **1.1. CAC Screening for Cardiovascular Disease Development**

The CAC screening is used to assess the risk of developing cardiovascular diseases; however, it is not recommended for patients with low risk of coronary heart disease or for patients who already had an episode of heart attack, stroke, stent, or bypass surgery. Instead, the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on screening for CAD deem measurement of CAC reasonable for cardiovascular risk assessment in asymptomatic intermediate-risk adults [14]. It was found that amongst the different current markers that are used to reclassify intermediate-risk patients, CAC scoring proved most useful, which is unsurprising given that it is a direct gauge of the dynamic pathological process taking place in the coronary arteries [15]. The use of relevant patient data, such as age, sex, and race, to inform interpretation can further enhance the accuracy of CAC scoring, with age- and sex-adjusted percentiles proving a more useful measure than absolute calcium scoring [16]. It is important to note that, as with a number of other tests, the value of CAC may vary depending on the ethnicity of the target population; for instance, African Americans may have significantly less CAC than white Americans despite a worse metabolic profile, therefore emphasizing the importance of using ethnicity-specific data to guide the interpretation of CAC scores. The Multi-Ethnic Study of Atherosclerosis (MESA) is a commonly used population database that has been used to calculate adjusted percentiles that can better assess patient risk [17-21].

### **1.2. CAC Serial Measurement**

CAC progression monitoring is a subject of debate. It is generally not a recommended measure as no clinical trials have shown demonstrable benefits of serial CAC measurements; furthermore, there is a lack of clear data on how CAC progression can be used to guide the choice of medical therapies [22]. A number of studies have been conducted to assess the effect of statins and other therapies on CAC progression, with conflicting results. Some have shown a reduction in calcium scores after statin therapy, whereas others showed that statin therapy was associated with a progression in CAC scores [23,24]. The postulated mechanism for this paradoxical effect is that statins increase plaque stability by increasing calcium content, thereby reducing the chances of progression to an unstable plaque [23,25-29]. A significant downside of serial CAC measurement would be recurrent radiation

exposure, as the effective dose for CAC measurement by EBCT is 1 mSv for males and 1.3 mSv for females, and by multi-detector row spiral, CT ranges between 1.5-5.2 mSv for male patients and 1.8-6.2 mSv for female patients, with even higher effective dose for patients with a body mass index (BMI) >30 [30,31]. Nevertheless, repeated measurements of CAC may be warranted in patients in whom doing so may help guide the clinician. For instance, in those with a score of zero, measuring CAC score at 5-year may help the provider in timing the initiation of statin therapy [32].

### **1.3. Coronary Artery Calcium as a Predictor of CVA**

Although coronary heart disease has a significant and well-established association with ischemic stroke development, the association between CAC and stroke development was not recognized until recently. Initially, analysis of the Rotterdam study failed to show improved CVA prediction by CAC scoring, and analysis of the MESA study had shown that intimal media thickness (IMT), but not CAC, was a significant predictor of stroke in a multivariate model including both variables [33,34]. The findings in the MESA cohort had corroborated earlier findings, which had shown intimal medial thickness (of the common carotid) to be a more specific marker of stroke risk [35]. A more recent analysis was that of the Heinz Nixdorf Recall (HNR) cohort, which showed that CAC could be a particularly useful measure of stroke risk in younger demographics [36]. A more recent analysis of the MESA trial had shown CAC to be a statistically significant predictor of stroke risk; however, unlike the analysis of the HNR cohort, CAC scoring was more predictive in the elderly rather than in the young [37].

### **1.4. Coronary Artery Calcium for the Detection of CAD in Stroke Patients**

Coronary disease exerts a significant toll in stroke patients, with studies showing a high prevalence of CAD in stroke patients, in addition to elevated myocardial infarction risks even in the absence of a cardiac history [38]. Investigators have attempted to quantify the risk of coronary disease in stroke patients through the development of risk scores, such as the five-point PRECORIS score, which is adequate in the detection of severe (>50%) occult stenosis of the coronaries [39,40]. Nevertheless, the application of the score still has some limitations, as more than half the patients with a score >4 have no occult coronary stenosis. The supplementation of the PRECORIS score with additional measures, namely CAC, can improve the predictive ability of the model in two ways: First, it can enhance the detection of severely stenosed patients in whom further investigations may be warranted. Second, it can improve the identification of those without severe stenosis, and therefore reduce additional unneeded investigations that would carry burdens of their own Table [41].

Study ID	Study design	Country of origin	Total patients	CAC assessment method	Assessed arteries	Main Finding
Elias-Smale [34]	a prospective, population-based study	Netherland	2153	MDCT	CAC, carotid artery and aortic arch calcification	A strong association between calcification of the aforementioned arteries with CHD development but not with CVD development.
Folsom [33]	Prospective study	USA	6698	MDCT and cardiac-gated electron-beam computed tomography scanner	CAC and Carotid intima-media thickness	Carotid intimal thickness showed a greater association with Stroke development than CAC.
Newman [35]	Prospective study	USA	559	EBCT	CAC, common and internal carotid artery thickness	Both CAC and CCA-IMT were associated with Stroke development, although it was higher with CCA-IMT.
O Gibson [37]	Prospective study	USA	6,779	EBCT and MDCT	CAC	CAC was found to be an independent predictor for stroke and TIA development, and it can be used to identify the subjects who can undergo a preventative therapy such as statins.
Hermann [36]	Prospective study	Germany	4180	EBCT	CAC	CAC was able to predict the risk of stroke independent of atrial fibrillation. CAC was also able to differentiate stroke risk between low and intermediate FRS categories.

**CAC:** Coronary Artery Calcification; **MDCT:** Multiple Detector Computed Tomography; **EBCT:** Electron Beam Computerized Tomography; **CHD:** Coronary Heart Disease; **CVD:** Cerebral Vascular Disease; **CCA-IMT:** Common Carotid Artery Intima-Media Thickness; **FRS:** Framingham Risk Score

**Table: Summarizes Some of the Previous Studies that Demonstrated the Association between CVA and CAC**

### 1.5. The Effect of Adjustable Risk Factors on the CAC Score

Several factors have been shown to increase CAC, including obesity and smoking. Young adults with a higher waist girth (men  $\geq 84.3$  cm; women  $\geq 75.5$  cm) have twice the risk of developing CAC the HNR study has shown that current smoking was positively associated with CAC. Interestingly lifetime of not smoking would show benefits in reducing the risk of developing CAC. However, it is known that lifestyle factors alter early atherosclerotic vascular disease risk; therefore, it cannot be determined whether CAC regression through lifestyle modification is an independent risk factor for lowering the risk of CAD and CVA [42]. Due to the importance of CAC in the prediction of adverse cardiovascular events, much research has been done to identify how various lifestyle factors may affect it. Amongst those factors is obesity, as

young adults with a higher waist girth are more likely to have CAC [43]. In addition, other well-described risk factors of stroke, such as smoking, have been shown to increase the risk of developing CAC [44]. In addition, exercise has been reported to be associated with CAC, with higher CAC scores being more common in sedentary groups [45].

Interestingly, the same study showed that the detrimental effects of a lack of exercise were accentuated in those with a higher CAC score, as all-cause mortality was low in those with a CAC of zero regardless of exercise, but significantly increased in those who had higher CAC scores and did not perform an exercise. These results indicate that not only can CAC scoring be used as a reflection of the effect of various well-known risk factors of cerebrovascular

disease, but that the CAC score in and of itself may act to modify the effect of lifestyle interventions on mortality; therefore, CAC scores may help physicians identify patient groups most likely to benefit from certain lifestyle modifications. As previously mentioned, the impact of statins on CAC is not consistent amongst studies; however, CAC scores can be used to inform the initiation of statin therapy, particularly in intermediate-risk patients. Since statins are well known to reduce the risk of stroke, CAC can be said to play an important role in the primary prevention of CVA [46]. In addition, aspirin therapy, which has a limited role in the primary prevention of CVD, may be guided with CAC. Analysis of the MESA study showed that participants with a CAC score of greater than 100 were much more likely to benefit from aspirin therapy than those with a CAC score of 0, as aspirin resulted in a greater decrease of cardiovascular events (including stroke) in the higher CAC group. Given the concerning risk of bleeding that may arise due to aspirin use, better guidance of aspirin therapy using CAC scoring may allow optimal patient selection and thus lead to improved outcomes [47].

## 2. Conclusion

This review aims to summarize the existing evidence regarding the role of CAC in the prediction of CVA. Currently, available data shows that CAC is a viable predictor of CVA risk, and that utilizing it (In addition to well-established stroke risk factors) may allow improved risk stratification, therefore allowing clinicians to better tailor their approach to each patient. In addition, CAC may also guide better management in patients with a pre-existing history of stroke, as using it in addition to other validated measures, such as the PRECORIS score, may similarly aid the clinician in the identification of those at risk of CAD, which is an important cause of morbidity in stroke survivors.

## Highlights

- Coronary Artery Calcification (CAC) is a risk for atherosclerotic plaque formation.
- CAC score can highly predict the risk of cerebrovascular accidents development.
- Intermediate risk patients can be reclassified into other groups using the CAC score.
- CAC score plays an important role in the primary prevention of stroke development.

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