

# CT Coronary Calcification: What Does a Score of “0” Mean?

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**Abstract** Calcium score (CS) is a useful tool in evaluating the risk of cardiovascular events in asymptomatic patients. The absence of detectable calcification determines excellent cardiovascular prognosis, with event rates lower than that of negative stress studies, probably due to the latter’s inability to detect nonobstructive coronary artery disease (CAD). There are few primary prevention medications that would be cost-effective in such a low-risk patient population. The interval for retesting patients with zero CS is still open for debate but it should not be in less than 4 to 5 years. CS should not be used to rule out obstructive CAD in symptomatic patients, as its correlation with coronary stenosis is poor and obstructive CAD is commonly found among symptomatic zero CS patients. Most studies have found very low specificity values for CS to detect obstructive CAD in symptomatic patients, meaning it has limited ability to detect the true negative cases (ie, zero CS without obstructive CAD).

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## Introduction

For 20 years the measurement of coronary calcification by noncontrasted cardiac CT has been used for cardiovascular risk estimation [1]. The rationale behind the ability for the calcium score (CS) to predict cardiac events is straightforward: CT can accurately quantify coronary calcification [1, 2]; calcification is very specific (although not very sensitive) for atherosclerosis [3]; the amount of coronary calcium correlates linearly with total coronary plaque burden [2, 4, 5]; and the higher the atherosclerotic burden the higher the probability of a plaque rupture resulting in a cardiovascular event [5–10]. The CS ability to predict cardiovascular events in asymptomatic individuals has been confirmed in many large clinical trials and has been shown to be greater than that of traditional risk stratification tools, such as clinical risk factor assessment and carotid intima-media thickness [8, 11–15].

CS measurements are low risk; the radiation exposure is limited to 1 to 2 mSv, and the test does not require the use of iodinated contrast agents. Conversely, the main intrinsic limitation of coronary calcification as a predictor of cardiovascular events relates to the fact that there are other variables associated with myocardial infarction besides the anatomical existence of the plaque, such as inflammation, rheological forces, and blood coagulability [16, 17]. In addition, coronary calcification represents only one of the components of atherosclerotic plaques and may develop relatively late in the natural history of atherosclerosis [3, 4, 18, 19]. Although the potential contributions of inflammatory, hormonal, metabolic, and physical factors believed to

underlie coronary calcification are still incompletely understood, the process is believed to represent a natural biologic response to arterial wall injury, activated for the purposes of increasing arterial wall stiffness in response to inflammatory injury and undue deformation [4, 18, 20–22]. Therefore, the amount of calcium accumulated in any given coronary arterial segment reflects not only the magnitude of plaque burden, but also the period of time during which plaques were exposed to the factors that underlie calcification, which renders it largely dependent on age. As a result, younger subjects have proportionally higher volumes of noncalcified plaque.

The value of undetectable coronary calcification by CT (ie, zero CS) is discussed below. Most published data consider calcified plaque any cluster of at least three pixels with attenuation of more than 130 Hounsfield units (HU) at coronary topography. However, it should be noted that some experts advocate decreasing this threshold to 90 HU, especially when using multidetector CT technology instead of electron beam CT, although, this would increase an already very high negative predictive value of zero CS for cardiac events at the expense of an already very low positive predictive value.

### **The Excellent Prognosis of Asymptomatic Patients with Zero CS**

CS is best used for screening asymptomatic intermediate-risk patients. Very low risk patients (ie, <5% Framingham 10-year event rate) and high-risk patients (ie, >20% Framingham 10-year event rate) would rarely have their management changed based on the CS, rendering the test not cost-effective [11]. Conversely, intermediate-risk patients frequently have their risk reclassified after a CS [11, 14, 23, 24], and risk estimation is a fundamental part of good patient management.

The absence of detectable calcification determines an excellent prognosis among intermediate-risk asymptomatic patient populations, as has been shown in multiple large-scale clinical trials with long follow-up [13, 15, 25]. A recent meta-analysis of more than 29,000 patients with zero CS with a mean follow-up of 50 months showed that the absence of coronary calcification is associated with excellent cardiovascular prognosis, with an annualized event rate of 0.12% [26••]. This event rate, which could theoretically be extrapolated to 1.2% over 10 years, represents a lower rate than those typically observed after negative nuclear myocardial perfusion studies or good exercise capacity, as demonstrated in Table 1. A substudy of the MESA (Multi-Ethnic Study of Atherosclerosis) cohort with more than 6700 participants has demonstrated that zero CS is also more protective for cardiovascular events than a negative

carotid IMT, and even patients with greater than 75 percentile of IMT but zero CS had less than 1% per year risk for events [27].

### **If Asymptomatic, Having a Zero CS Is Better Than Having a Normal Stress Perfusion Test**

The better performance of a zero CS to rule out cardiovascular events in the long run compared with functional tests most likely derives from the fact that the latter depend on ischemia for coronary artery disease (CAD) detection, missing a large segment of the at-risk population with nonobstructive CAD, who would reliably be detected by anatomical tests such as the CS. The importance of subclinical atherosclerosis is well known and highlighted by the finding that almost half of acute coronary events occur in previously asymptomatic patients [28] and that up to two thirds of ruptured plaques were previously nonobstructive [7]. Stress perfusion tests excel in assessing cardiovascular risk in the short term and are useful as a decision tool regarding coronary revascularization strategies, but screening patients for atherosclerosis instead of perfusion defects provide a longer-term assessment of risk, which is desirable both for better and earlier treatment planning and intervention as well as to minimize costs, as the interval between tests can be longer.

Additionally, because the prevalence of obstructive CAD is very low among asymptomatic individuals, ischemia-dependent test performances are generally poor in this patient population. As an example, we will discuss a 55-year-old asymptomatic woman referred for an exercise electrocardiogram test, which has sensitivity and specificity for obstructive CAD of 68% and 77%, respectively [29]. She has estimated probability of obstructive CAD of 4% [29], resulting in a positive predictive value of 12%. These results would not be much better if this patient underwent an exercise nuclear test, with sensitivity and specificity of 88% and 72%, respectively [29], rendering the positive predictive value 13%. These very low positive predictive values would require unnecessary follow-up studies, burdening the health care system and potentially harming the patient.

### **Zero CS in Diabetic and Other High-Risk Patient Populations**

As noted above, evidence for the usefulness of routinely performing CS scans in high-risk patient populations is still lacking but, if performed, a CS of zero also places these patients previously thought to be at high risk at very low risk for cardiovascular events. One study of 10,377 asymptomatic individuals with no known previous CAD demonstrated that

**Table 1** Annualized event rates of negative CS, negative myocardial perfusion SPECT, and negative exercise stress tests

Study	Patients, <i>n</i>	Follow-up, <i>mo</i>	Primary end point	Total event rate, %	Annualized event rate, %
<b>Zero CS</b>					
Arad et al. [63]	623	43	Cardiac death, myocardial infarction, revascularization	0.32	0.09
Raggi et al. [23]	319	32	Cardiac death, myocardial infarction, revascularization	0.31	0.12
Wong et al. [64]	398	40	Myocardial infarction, revascularization, stroke	1.00	0.30
Kondos et al. [65]	1816	37	Cardiac death, myocardial infarction, revascularization	0.61	0.20
Shaw et al. [25]	5067	60	All-cause death	0.77	0.15
Greenland et al. [12]	316	102	Cardiac death, myocardial infarction	4.40	0.52
Arad et al. [13]	4903	52	Cardiac death, revascularization, peripheral disease, stroke	0.53	0.12
LaMonte et al. [24]	2692	42	Cardiac death, myocardial infarction, revascularization	0.56	0.16
Taylor et al. [66]	1983	36	Cardiac death, revascularization, unstable angina	0.80	0.27
Budoff et al. [15]	11,046	82	All-cause death	0.40	0.06
Becker et al. [67]	379	40	Cardiac death, myocardial infarction	0.00	0.00
Detrano et al. [8]	3409	44	Cardiac death, myocardial infarction	0.23	0.06
<b>Negative stress perfusion</b>					
Hachamovitch et al. [68]	2946	18	Cardiac death, myocardial infarction	1.20	0.80
Vanzetto et al. [69]	1137	72	Cardiac death, myocardial infarction, revascularization >3 mo	3.36	0.56
Gibbons et al. [70]	4649	36	Cardiac death, myocardial infarction, revascularization	3.40	1.13
Hachamovitch et al. [62]	6046	22	Cardiac death, myocardial infarction	0.70	0.38
<b>Good exercise capacity</b>					
Sandvik et al. [71]	487	192	All-cause death	4.90	0.30
Kampert et al. [72]	17,120	96	All-cause death	1.20	0.15
Vanzetto et al. [69]	1137	72	Cardiac death, myocardial infarction, revascularization >3 mo	5.28	0.88
Mora et al. [73]	1724	240	All-cause death	4.70	0.20

CS calcium score; *SPECT* single photon emission computed tomography

diabetic patients (903 in total) with zero CS had the same risk for events of nondiabetic patients after a mean follow-up of 5 years, although roughly 50% of the nondiabetic patients and 25% of the diabetic patients had zero CS [14]. In another study with a mean follow-up of 20 months, 300 diabetic patients with zero CS had the same survival rate of nondiabetic patients with zero CS (98.8% and 99.4%, respectively;  $P =$  not significant) [30]. A Third recent study found that diabetic patients with a CS of zero had no cardiovascular events during the 20 months of follow-up, similar to the nondiabetic patients [31].

Advancing age is an important risk factor for cardiovascular events and because coronary calcification prevalence increases dramatically with age (only 15% of 70-year-old males had zero CS in the MESA cohort), some resist using CS in this patient population. Nevertheless, CS may have important advantages in selected elderly people, because adverse effects related to multiple drug interactions are not uncommon and having zero CS may allow for reduction in the number of drugs prescribed. Vliegenthart et al. [32] demonstrated that after a mean follow-up of 3.3 years, elderly asymptomatic subjects (mean age, 71 years) with zero CS had 0.2% per year risk for hard cardiovascular events.

Almost half the total patient population in their cohort had no coronary calcium. In another study, more than 40% of patients older than 70 years were correctly reclassified in their cardiovascular risk by a CS scan, approximately 40% of those to a lower risk than previously thought [33]. Zero CS is also associated with better future systolic and diastolic left ventricular function [34] and less incidence of clinical depression [35], also important aspects in the elderly.

### CS is Not Useful to Rule Out Obstructive CAD in Symptomatic Patients

Coronary calcification is only marginally related to the degree of coronary stenosis [36••, 37, 38] and it is well known that both obstructive and nonobstructive CAD as well as vascular thrombosis can occur in the absence of calcification [3, 39, 40]. Significant coronary stenoses are frequently noncalcified, and highly calcified plaques are frequently nonobstructive. It is widely assumed that coronary calcification predicts events based on the overall atherosclerosis burden rather than the detection of vulnerable or obstructive plaques.

Taking into consideration that coronary stenosis and calcification are not closely related but both have been shown to predict cardiovascular events, how can one then solve the apparent contradiction of the excellent prognosis of zero CS patients regardless of the presence of coronary obstruction among asymptomatic people? The answer for this apparent paradox lies with disease prevalence. Obstructive CAD among asymptomatic adults is estimated to range from 1% in a 30-year-old woman to 12% in a 70-year-old man [29]. By contrast, in patients presenting with atypical chest pain, prevalence of obstructive CAD is estimated to range from 12% in a 30-year-old woman to 67% in a 70-year-old man [29]. Any prognostic value obstruction has in asymptomatic patients is diluted by its low prevalence.

This is not the case with symptomatic patients, whose prevalence of obstructive CAD may tip this balance to the other side, and even more acutely so among emergency room (ER) chest pain patients, whose symptoms may be due to unstable obstructive coronary plaques. There is wide recognition of the importance of correctly diagnosing ER patients with chest pain and the risks of missed diagnoses [41].

A substudy of the multicenter CORE64 (Coronary Evaluation Using Multi-Detector Spiral Computed Tomography Angiography Using 64 Detectors) trial with patients referred for invasive coronary angiography demonstrated that 19% of the patients with no coronary calcification had at least one  $\geq 50\%$  coronary obstruction as seen by invasive coronary angiography, 15% had at least one  $\geq 70\%$  lesion, and 13% of these patients were revascularized, attesting for the clinical significance of those lesions [36••]. Interestingly, 20% of the totally occluded coronary vessels were not calcified, showing *in vivo* that calcification is dispensable not only for obstruction, but also for plaque rupture and coronary thrombosis. This is not an isolated finding. Many studies have demonstrated that the absence of coronary calcification is not able to exclude obstructive CAD in symptomatic patients (Table 2) [36••, 38, 42–50].

Some controversy has arisen lately concerning the CS test's ability to rule out obstructive CAD in symptomatic patients. Most of the confusion originates on terminology. The role of CS in the ER, if any, is for low CSs (eg, zero) to rule out obstructive CAD, to discharge patients safely home; thus, a CS of zero might be considered positive for identifying no obstructive CAD patients. Therefore, the usual understandings of sensitivity and specificity for CAD detection have to be revisited; in this special case, the high sensitivity CS has for determining obstructive CAD seen on the studies in Table 2 are not helpful because CS has no use as a rule-in test because no one would send patients to invasive angiography exclusively based on a  $\geq 1$  CS. Specificity is the test determinant that would express the ability of negative (zero) CS to identify negative (ie, no obstructive lesions) cases, and one can clearly see that specificity is low across

the studies, highlighting the inability of a zero CS to rule out obstructive CAD. An exception was made for the CORE64 substudy, which took zero CS as a positive test to rule out obstructive CAD (in the spirit of ruling out CAD), thus simply inverting the sensitivity and specificity values.

Another reason CS is not a good test for identifying obstructive CAD is the low prevalence of zero CS among symptomatic patients. Table 2 again shows that most of the studies had less than 20% prevalence of zero CS. Because we are only interested in the negative results as discussed above, performing a test that only yields useful data in 20% of the cases is clearly not ideal.

Therefore, searching for surrogate evidence of stenosis, as is the case with CS, makes the performance of the test rely heavily on the prevalence of obstructive CAD and other biological factors, rendering CS unsuitable for ruling out obstructive CAD in general practice. We believe this cautious approach on CS reflects the application of what we know in pathophysiology to clinical medicine and supports the results of previous studies indicating that symptomatic patients with suspected CAD should not be discharged from the emergency department based solely on the results of coronary calcium scores assessed by unenhanced CT [51].

Furthermore, CS is only a weak surrogate marker of stenosis. To rule out obstructive CAD based on indirect evidence would depend too heavily on obstructive disease prevalence, thus making this strategy difficult to generalize. In fact, this reliance on indirect markers has been proven troublesome in the past, such as young women with atypical chest pain in the ER who were frequently discharged based solely on their low likelihood of obstructive CAD, which was proved to be a mistake and corrected in the late 1900s and early 2000s by awareness campaigns such as The Red Dress headed by the American Heart Association [52].

### How Does a Zero CS Change the Asymptomatic Patient Management?

The excellent short- to mid-term prognosis of asymptomatic zero CS patients renders any primary prevention therapy very unlikely to be cost-effective [53]. Data are missing regarding whether zero CS patients should have their cardiovascular medications withheld, but this may be appropriate nonetheless.

Patients with hypertension or diabetes should be treated to target end points regardless of the CS result, for they have been proven to improve long-term outcomes in numerous primary prevention trials regardless of patient short- to mid-term risk [54, 55]. In selected zero CS patients with drug-related adverse effects, relaxing the therapeutic target may be reasonable.

Primary prevention trials with statins are not as definitive. Data suggest that low-risk patients do not benefit much from

**Table 2** Trials that evaluated the performance of CS for the detection of obstructive coronary artery disease by invasive coronary angiography

Study	Total patients, <i>N</i>	Patients with zero CS, <i>n</i> (%)	Zero CS/stenosis +, <i>n</i> (% of zero CS)	Zero CS/stenosis -, <i>n</i> (% of zero CS)	Sensitivity, %	Specificity, %	Observations
Fallavollita et al. [47]	106	30 (28)	9 (30)	21 (70)	85	45	Only patients <50 years old
Budoff et al. [46]	710	147 (21)	23 (16)	124 (84)	95	44	
Baumgart et al. [45]	57	7 (12)	1 (14)	6 (86)	97	21	Findings corroborated by IVUS
John et al. [50]	368	71 (19)	N/A	N/A	96	31	Retrospective analysis, multicenter study
Bielak et al. [44]	213	40 (19)	1 (3)	39 (97)	99	39	
Knez et al. [49]	2115	326 (15)	8 (2)	318 (98)	99	29	Retrospective analysis
Haberl et al. [43]	133	25 (19)	8 (32)	17 (68)	85	24	
Lau et al. [38]	50	6 (12)	1 (17)	5 (83)	97	25	
Becker et al. [42]	1347	259 (19)	5 (2)	254 (98)	99	31	Predictive accuracy of 64%. Same center and similar population as the study by Knez et al. [49]
Drosch et al. [48]	500	61 (12)	16 (26)	45 (74)	N/A	N/A	Retrospective analysis
Gottlieb et al. [36••]	291	72 (25)	14 (19)	58 (86)	45	91	Multicenter study. Zero CS was considered “positive,” thus inverting the sensitivity and specificity values compared with the other trials

CS calcium score; IVUS intravascular ultrasound; N/A not available

cholesterol-lowering medications, as the number of cardiovascular events prevented by these drugs is too small (if any) and the number needed to treat too high, rendering these drugs probably not indicated in zero CS primary prevention patients unless cholesterol levels are very high [56–58]. Aspirin is also not recommended in primary prevention of patients with zero CS due to its poor relationship of adverse effects to benefit, even if the patient has diabetes. The American Diabetes Association has published guidelines that recommend aspirin in primary prevention only if the patient has a 10-year risk for cardiovascular events greater than 10%, which is not the case for any subgroup of zero CS patients [59]. Of course, lifestyle healthy changes such as exercise, eating habits, and smoking cessation should be encouraged regardless of the CS.

### When Should a Patient with Zero CS Be Retested?

If the patient develops symptoms suggestive of cardiovascular disease he or she should be re-evaluated regardless of a previous zero CS. Remaining asymptomatic, evidence suggests that the CS should not be repeated frequently, certainly not yearly [11, 60, 61••].

One recent study has demonstrated the cumulative rate of “conversion” from a zero CS to  $\geq 1$  CS to be 15% in the

first 4 years and 25% in the fifth year [61••]. The authors conclude that 4 years is the ideal “warranty period” for a zero CS. Although reasonable, their conclusion may be overstated because there are important issues remaining before retesting shall be considered: 1) the overwhelming majority of the patients who converted to  $\geq 1$  CS still remained with less than 100 CS, and are still considered low risk; 2) converting to  $\geq 1$  CS is not the end point, cardiac events are; 3) it has not been demonstrated so far that patients who convert to  $\geq 1$  CS would benefit from any change in therapy; and 4) there is no evidence retesting is cost-effective. Although CS retesting is still a subject of debate, it should be highlighted that subclinical atherosclerosis tests such as CS decrease retesting necessity compared with functional studies, as “warranty” periods for the latter are frequently considered to be 2 years [62].

### Conclusions

Having a zero CS places asymptomatic subjects at very low risk for cardiac events, even if the patient is considered to be at high risk by clinical assessment. There are few primary prevention medications that would be cost-effective in such a low-risk patient population. Zero CS determines better risk stratification and is preferred over



stress perfusion techniques for risk stratification of asymptomatic patients. Whether and when zero CS patients need to be retested is still open for debate, but it should not be in less than 4 to 5 years. CS should not be used to rule out obstructive CAD in symptomatic patients, as its correlation with coronary stenosis is poor and obstructive CAD is frequently found among symptomatic zero CS patients.

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