Circulation

PERSPECTIVE

Zero Coronary Artery Calcium Score

Desirable, but Enough?

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A zero calcium score is desirable, but is it enough to defer therapy given that up to one-third of events will occur in this group? A viewpoint.

Multiple observational studies have demonstrated the utility of the coronary artery calcium score (CAC) in identifying individuals at higher and lower atherosclerotic cardiovascular disease (ASCVD) risk. Given the very low short-term ASCVD event rates in those with a CAC of zero, the concept of the power of zero, downrisking, and the possibility of deferring statin therapy in select individuals has emerged.[1] Although CAC continues to impress in stratifying cardiovascular risk, several aspects regarding zero CAC and the deferral of therapy merit consideration.

About one-fourth to one-third of the total incident cardiovascular disease (CVD) events (Table) occur in those with a CAC of zero, despite some use of lipid-lowering therapy at baseline or during follow-up (in MESA [Multi-Ethnic Study of Atherosclerosis] ≈15% at baseline and 44% during follow-up).[2] Indeed, individuals with a CAC of zero who develop CVD events have been shown to have a higher prevalence of potentially modifiable ASCVD risk factors, such as diabetes mellitus, smoking, or family history of premature ASCVD (on the basis of which the American Heart Association/American College of Cardiology Guidelines on the Management of Blood Cholesterol recommend against the use of CAC to defer care in individuals with the these risk factors[1]). Hence, although, a CAC of zero has favorable short-term prognosis, given the lifetime risk, the long-term benefit of statin therapy cannot be discounted in these individuals. One additional concern is that nuances such as this could be missed by the practicing clinician. In fact, observational studies have not only shown lower odds of aspirin and antihypertensive medication initiation but also lower odds of smoking cessation, increasing exercise, and dietary change in individuals with a CAC of zero, despite a high prevalence of an unfavorable cardiovascular health profile in several of these individuals. Additionally, other than affecting the treatment of dyslipidemia, what else would deescalation entail? Would blood pressure targets or diabetes management also differ?

Certain groups of individuals (especially younger individuals and women) require even more careful attention. The presence of CAC, especially a score of >100, is relatively rare in younger adults (Table). In the CARDIA trial (Coronary Artery Risk Development in Young Adults) cohort,[3] in individuals aged 32 to 46 years, the prevalence of a CAC >0 was only 8.1%, whereas the prevalence of a CAC >100 was 1.8% (Table). Overall, ≈70% to 90% of younger patients are expected to have a CAC of zero (Table). In addition, studies evaluating the utility of CAC in young individuals have relatively short follow-up, the longest being 12 years (Table). Twelve years is not a lifetime for these young individuals whose long-term cardiovascular risk should not be discounted. Atherogenesis as a process

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Table. Prevalence of CAC in Young Individuals Stratified by Sex and CAC Score Across Multiple Cohorts

Demographics	CARDIA[3] (n=3036)	CAC Consortium[4] (n=22 346)	DHS[5] (n=1520)	MESA[2] (n=1947)
Age, y	36-42	30–50	<50	45-54
Female, n (%)	1506 (49.6)	5576 (24.9)	1038 (53.3)	1038 (53.5)
Mean follow-up, y	12.5	12.7	9.2	8.5
All, n (%)				
0	2733 (90.0)	14 660 (65.6)	877 (57.7)	1414 (72.6)
1–100	248 (8.2)	6080 (27.2)	602 (39.6)	17 (21.4)
>100	55 (1.8)	1606 (7.2)	41 (2.7)	116 (6.0)
Female, n (%)				
0	1430 (95)	4603 (82.7)	NR	851 (82.0)
1–100	62 (4.1)	831 (14.9)	NR	170 (16.3)
>100	14 (0.9)	132 (2.4)	NR	18 (1.7)
Events (1000 p-y)				
0	27*	36 (0.2)†	NR	32 (0.9) ‡
1–100	17*	28 (0.8)†	NR	13 (3.8))‡
>100	13*	20 (1.0)†	NR	18 (2.1)‡

CAC indicates coronary artery calcium; CARDIA, Coronary Artery Risk Development in Young Adults; CHD, coronary heart disease; CVD, cardiovascular disease; DHS, Dallas Heart Study; MESA, Multi-ethnic Study of Atherosclerosis; NR, not reported; and p-y, person-years

*Cumulative CHD, stroke, heart failure, and peripheral artery disease.

†CVD death.

‡CHD events.

starts early in life, with studies showing that many individuals demonstrate coronary atheroma between ages 20 and 30 years.[1] Calcified plaque (detected as CAC on computed tomography imaging), however, represents a small proportion of the total plaque burden. Hence, there is a disconnection between zero calcium and zero atherosclerosis, which raises concerns about what age a zero CAC starts to be meaningful. Although the presence of atherosclerosis does not automatically translate to incident ASCVD events, recent studies in patients with familial hypercholesterolemia have suggested that early treatment with statins is beneficial in reducing incident cardiovascular events over >20 years of follow-up. Consequently, if statin therapy is withheld/deferred because of a zero CAC, paradoxically, it is possible that more cardiovascular events may occur in those with a CAC of zero than in those with a low calcium score who are treated with statins.

Women have also been shown to have significantly lower CAC, with 83% to 95% of younger women (age<50 years) demonstrating a zero CAC (Table). Even in middle-aged women, only about one-third demonstrate a CAC of >0. Despite this, about one-third of CVD events occur in those with a CAC of zero and another one-third occur in those with a CAC between 0 and 100.[1] Hence, when considering deferring therapy in individuals with a CAC of zero, several aspects such as age, sex, comorbid risk factors, and lifetime CVD risk should be considered. Furthermore, we should consider whether ignoring one-fourth to one-third of events is prudent given that the therapies withheld, such as statins and blood pressure medications, are relatively inexpensive, safe, and, most important, clinically effective.

Finally a major concern regarding the clinical use of CAC would be how clinicians communicate the results and how this impacts patients' perception of their risk. Clinicians should clearly communicate that a score of zero does not imply that their risk for an event is zero or that they have zero atherosclerosis, but that the application of calcium scoring comes with limitations. They should continue to advocate healthy lifestyle choices irrespective of the CAC. Furthermore, preventive therapies such as statin use and intensive blood pressure control should be discussed and implemented if other risk factors dictate. Clinicians should be mindful that a CAC of zero may provide a false sense of security to the patient who may then perhaps consider that his or her lifestyle choices (including smoking) are acceptable or hinder his or her compliance to medications. If after a discussion and consideration of these factors, the provider and patient defer therapy, repeat CAC testing can be considered in 5 to 10 years.

CAC, when used in the right clinical context, is a powerful risk prediction tool and can help guide therapy. We recognize that statin therapy will not prevent all events and that several factors such as patients' tolerability of statins, treatment preference, and numbers

needed to treat/benefit need to be considered. However, the implications of a CAC of zero are different depending on the age and sex of an individual. Although a CAC of zero in a younger individual is normal and expected, it has a lot more power at an older age. One might say that, like fine wine, the value of a CAC of zero increases with age. Hence, although a CAC of zero is desirable, it is far from perfect, and decisions to defer care should be considered carefully, especially given that one-fourth to one-third of ASCVD events, even in the short term, occur in this group, and long-term risk is not well studied. Clinical context and shared decision making are critical to harness the value of a zero calcium score.

ARTICLE INFORMATION

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