The Fallacy of the Power of Zero

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EDITORIAL COMMENT

The Fallacy of the Power of Zero*

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The coronary artery calcium (CAC) scan is a simple, proven test for detecting and quantifying calcific coronary atherosclerosis, and its use is endorsed by guidelines to better inform primary prevention treatment decisions in many asymptomatic adults.[1] However, because of its inability to detect and quantify noncalcified coronary atherosclerotic plaque, plaque features, or lumen stenosis, CAC testing is rarely used clinically to evaluate symptomatic patients. Studies such as the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) and SCOT-HEART (Scottish Computed Tomography of the Heart) trials, as well as large-scale registries, have demonstrated that a sizable proportion of stable, symptomatic patients with zero CAC have detectable plaque on coronary computed tomography angiography (CTA).[2-4] For patients with zero CAC, the presence of noncalcified plaque, high-risk plaque features, and stenosis on coronary CTA is prognostically superior to CAC testing and has clinical implications for the timing and intensity of preventive therapies.[2-4] Current European guidelines recommend against CAC testing in symptomatic patients (Class III), and recent U.S. chest pain guidelines consider CAC testing (Class IIa) in selected, low-risk patients, in whom no testing (Class I) is recommended as the preferred management strategy.[5,6] Despite the limitations of CAC for diagnosing coronary artery disease (CAD), it is still championed as a binary gatekeeper in symptomatic patients based on its "power of zero," whereby those with zero CAC are reassured of a low likelihood of significant CAD, and those with any CAC undergo additional testing.

Significant technological advances now allow the semi-automated quantification of coronary plaque volume using coronary CTA, which includes quantification of calcified and noncalcified plaque, as well as plaque subtypes such as low-attenuation plaque (LAP).[7] The potential of plaque quantification to improve the prognostic yield of coronary CTA was recently demonstrated in SCOT-HEART, in which the burden of LAP was the strongest predictor of incident myocardial infarction, independent of risk factors, CAC, and stenosis.[7,8] Plaque quantification, although currently an area undergoing significant technical evolution, has also been used to assess plaque progression and the relationship of CAD progression to preventive therapies.[9] Previous studies that assessed the relationship of CAC to plaque burden and stenosis on coronary CTA predominantly used semi-quantitative, visual estimates of CAD burden; follow-up for clinical events was often limited in duration (most <5 years). The progression of coronary atherosclerosis, and its clinical implications, among patients with variable baseline CAC is also not well understood.

In this issue of *JACC: Cardiovascular Imaging*, Hollenberg et al[10] from the PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) registry reported the relationship of CAC scores to coronary plaque volume and subtypes on baseline and follow-up coronary CTA scans in 698 symptomatic patients (mean age 61 years; 45% women) without known CAD. Patients were clinically referred for coronary CTA for both the baseline and follow-up scans (median interscan duration 3.8 years) and were followed for clinical events (death, myocardial infarction, and late revascularization) for a median of 10.7 years in this prospective, multicenter registry. Of note, the current analysis was underpowered for hard clinical events, with only 9.3% of subjects experiencing any event,

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most of which were late revascularizations (>90 days from initial coronary CTA); only 8 subjects experienced death or myocardial infarction.

Among patients with zero CAC (n = 282), the baseline coronary CTA showed coronary atherosclerosis in 41.4%. with a mean plaque volume of 30.4 mm^3. LAP and positive remodeling were present in 18% and 36% of subjects, respectively. Despite the sizable prevalence of noncalcified plaque in those with zero CAC, only 1.4% had a stenosis ≥50% and only 3% experienced a clinical event. On follow-up coronary CTA, patients with zero CAC experienced only a small change in progression or development of calcified plaque (with mean change in CAC score of 4 AU), but progression of noncalcified plaque was common. Patients with zero CAC had an average increase in plaque volume of 25 ± 55 mm^3, with a 5.5:1 ratio for volumetric growth in noncalcified plaque versus calcified plaque. Conversely, patients with high CAC (>400 AU) had a greater increase in plaque volume (180 mm^3) and a 1:15.7 ratio for volumetric growth in noncalcified plaque versus calcified plaque. Therefore, plaque progression varied according to baseline CAC score, in both the volume and type of plaque that developed. In an exploratory analysis, the investigators assessed plaque volume thresholds that conveyed increased risk, but this analysis was limited by few hard events.

The investigators are to be commended for highlighting the interesting pathobiological process involved in plaque progression. They provided further evidence that the development and progression of calcified atherosclerosis occurred relatively late in the disease process, and that the presence of calcified plaque led to the development of further plaque, and calcified plaque in particular. Previous studies showed shown that age, sex, cardiovascular risk factors, and medication use all affected rates of calcified plaque progression. Positron emission tomography studies with 18F-sodium fluoride also showed that there are subgroups of patients with increased 18F-sodium fluoride who had more rapid progression in calcified plaque.[11] These findings suggest that future studies that attempt to define abnormal degrees of CAC and CAD progression should consider the baseline degree of calcification as a marker of CAD maturity and expected plaque compositional progression.

The study had several important limitations, such as its relatively small sample size, low-event rate, and lack of measured risk variables (lipid values, blood pressure) during follow-up. The rates of plaque progression observed were also high, despite the use of contemporary medical therapy, and the underlying rates of plaque progression without treatment were unknown. However, the findings of this important analysis serve to solidify coronary CTA as the computed tomography test of choice in symptomatic patients without known CAD. Although stenosis was uncommon among those with zero CAC, coronary CTA detected predominantly noncalcified coronary atherosclerosis in a sizable proportion of patients with zero CAC, potentially better informing post-test decisions regarding the use and intensity of preventive medications and therapeutic lifestyle changes by patients. Most (57%) of the patients with zero CAC were at a low 10-year atherosclerotic cardiovascular disease risk (<7.5%), such that statin therapy would not be routinely recommended.

It is notable that the prevalence of CAD on coronary CTA in those with zero CAC was higher (41%) compared with most previous studies. For example, in the PROMISE and SCOT-HEART studies, 16% and 17% of patients, respectively, had evidence of coronary atherosclerosis on coronary CTA, despite a CAC score of zero. It was unclear if the higher proportion with CAD and zero CAC in the current study was reflective of the technique used by the investigators and/or the smaller highly selected cohort. It is reassuring that the investigators reported high interreader and intrareader agreement (>95%) for plaque quantification. For volumetric quantification of noncalcified plaque, accurate lumen segmentation and care to avoid including pericoronary adipose tissue are required to ensure accuracy and repeatability.

The current study complements findings from a recent analysis of the Western Denmark Heart Registry.[2] Therein, investigators assessed the proportion of subjects with obstructive (≥50%) CAD on coronary CTA who had CAC score of zero from among 23,759 symptomatic patients (median age 58 years; 54% with zero CAC). Among the cohort, 14% of patients with obstructive CAD (725 of 5,043) had a CAC score of zero, with the prevalence of stenosis in the absence of CAC significantly higher among younger patients. Specifically, 58% of patients with obstructive CAD were younger than 40 years and had zero CAC compared with only 5% in those who were 70 years or older. The presence of obstructive CAD in those without CAC was associated with a significantly increased risk of myocardial infarction and death, with an adjusted HR of 1.80 (95% CI: 1.02-3.19) in subjects younger than 60 years of age who were followed for a median of 4.3 years. These results highlighted the clinical relevance of noncalcified plaque and stenosis in younger patients.

In 2022, contemporary coronary CTA is highly protocolized and increasingly automated in its

acquisition, is frequently performed at radiation doses at or below CAC scanning, and uses low contrast doses (<60 mL) that are associated with low rates of contrast nephropathy. Coronary CTA carries a class I recommendation in both the U.S. and European guidelines as a first-line test in symptomatic patients without known CAD. In this study, Hollenberg et al[10] provided further evidence of the important information that CAC scanning alone misses. Therefore, for symptomatic patients, we are unclear why one would choose CAC, which is a crude measure of only one aspect of CAD designed to assess the probability of stenosis, rather than stenosis itself, over coronary CTA.

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