Coronary Artery Calcium Testing
Exploring the Need for a Randomized Trial

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Coronary artery calcium (CAC) imaging with noncontrast cardiac computed tomography has emerged as a robust method to reclassify atherosclerotic cardiovascular disease (ASCVD) risk.¹ Rigorously conducted observational studies have consistently demonstrated marked increases in ASCVD events in those with elevated CAC.²⁻⁴ In addition, the absence of CAC on cardiac computed tomographic imaging is common and defines a low-risk group who seem unlikely to benefit from ASCVD prevention pharmacotherapies.⁵⁻⁶ There are also modest data demonstrating that CAC-based management leads to improvements in downstream risk factors (cholesterol, systolic blood pressure, and waist circumference).⁷⁻⁸ Similarly, CAC may inform decision making in persons who have difficulty tolerating statin therapy or in those with personal aversion to lifelong statin therapy.⁹ In this context, CAC imaging is endorsed by the American Heart Association and the American College of Cardiology to help reclassify ASCVD risk and guide statin allocation, particularly in persons in whom the patient–doctor risk discussion leads to treatment uncertainty.¹⁰

However, there are no adequately powered prospective clinical trials of CAC-guided ASCVD prevention therapy to inform these guideline recommendations. Indeed, there has never been a trial demonstrating that randomization to preventive therapy using a risk-based assessment (either by risk prediction equations,¹¹ novel biomarkers,¹² or by subclinical atherosclerosis imaging) leads to reduced ASCVD events.¹³ Nonetheless, the limited data we do have suggest that CAC-based treatment allocation, specifically with statin therapy, may lead to improved clinical outcomes.¹⁴ In the single-center St Francis Heart study, participants underwent CAC screening, and those with CAC >80th percentile for age and sex (n=1007) were randomized to placebo or atorvastatin 20 mg daily. Despite a clear trend toward benefit, the trial failed to show a statistically significant difference in the incidence of major cardiovascular events (6.9% versus 9.9%; P=0.08).¹⁵ Likely for this reason, the St Francis Heart trial is, unfortunately, largely ignored.¹² However, the trial was underpowered, and in an exploratory post hoc analysis, subjects with CAC score >400 obtained benefit from statin therapy (8.7% versus 15.0% event rate; P=0.046). Given that ASCVD enjoys such a large proportion of federal research funding, it is surprising that these encouraging initial results have not been confirmed in a larger, more adequately powered contemporary study.

Unfortunately, despite a seemingly clear need,¹⁵ attempts to fund a larger outcomes CAC study have been unsuccessful. The Value of Imaging In Enhancing the Wellness of Your Heart (VIEW) study proposed a multicenter CAC trial with ≤6 years of follow-up for ASCVD events. Eligible subjects were those at low-intermediate cardiovascular risk (10-year Framingham risk score, 5% to 10%) and who had low-density lipoprotein cholesterol levels of <160 mg/dL. However, because of the relatively low risk of this sample, the study team estimated that 30,000 participants would need to be enrolled to ensure sufficient power.¹⁶ An imaging-based study with such a large sample size would represent an enormous undertaking and investment, and currently, the National Heart, Lung, and Blood Institute is unwilling or unable to fund such a study.

Thus, there will be no randomized trial evidence for CAC-based prevention strategies in the near term. Therefore, there is a critical need for alternative strategies evaluating the impact of CAC testing, as well as other risk-based novel biomarkers (eg, high-sensitivity C reactive protein [hs-CRP]), particularly in real-world settings. One such strategy is the use of propensity-based matching to convert observational data into a form more akin to randomized controlled trial data by mimicking the effect of randomization.¹⁷ Using observed covariates, propensity scores match subjects who receive an intervention (eg, CAC) with subjects who do not to balance the distribution of potential confounders of the outcome (eg, ASCVD events) in both groups.¹⁸ However, unlike randomization, this strategy cannot balance unmeasured confounders.

In this issue of Circulation: Cardiovascular Imaging, Shreibati et al¹⁹ present the findings of an excellent and much-needed analysis that leverages a propensity score method to evaluate the clinical impact of CAC imaging relative to the alternatives of hs-CRP testing and lipid screening. The original study sample consisted of a large population of >600,000 Medicare beneficiaries. Over 90% were white, and the mean age was 72 years. Subjects had no claims for ASCVD in the 6 months before the test and were ineligible if they had a diagnosis code of angina, chest pain, dyspnea, or coronary artery disease with the index testing. Thus, although the sample could include some asymptomatic individuals who were actually under secondary prevention because of events >6 months prior, it is likely that the majority of this study sample was in the primary prevention category.
The authors did a superb job matching 4179 subjects from this sample who had CAC testing with near-identical patients who had hs-CRP testing. In sum, they found that persons referred for CAC imaging had increased subsequent stress testing, coronary interventions, and health-care spending, relative to those who had hs-CRP testing. In a comparable propensity score–based study of subclinical atherosclerosis imaging with coronary computed tomographic angiography, we reported similar results (comparing coronary computed tomographic angiography to usual care).17 However, in contrast to our short-term study (18 months), Shreibati et al9 found that CAC imaging was also associated with lower rates of the composite outcome of death, myocardial infarction, or stroke during a median of 3 years’ follow-up (hazard ratio, 0.74; confidence interval, 0.58–0.94; P=0.017). This result is particularly notable given the findings of the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, where hs-CRP was found to identify persons with normal cholesterol levels who derive benefit from statin therapy.20 Thus, although JUPITER was arguably not a trial of true biomarker-based care (it is unknown whether individuals with low hs-CRP would have benefited from therapy21), we know that hs-CRP–guided statin therapy can reduce ASCVD events; therefore, the question is how did CAC perform even better in this real-world study?

First, it is worth noting that there are limitations to the use of claims-based data, and in addition, residual confounding may explain this important finding (eg, providers who order CAC may differ importantly from those who do not). Similarly, this population was far older than those who should typically be considered for CAC testing (according to National Health and Nutrition Examination Survey data, >75% of this study sample should have had 10-year ASCVD risk scores in the elevated ≥7.5% range11 and would warrant statin therapy, typically without any further testing).10 Nonetheless, the hazard ratio of 0.74 was robust and makes intuitive clinical sense, particularly given we know that CAC is superior to hs-CRP at identifying persons with high absolute ASCVD risk and is theoretically far better at identifying those who will benefit from preventive measures.2,5 The extent to which downstream testing and revascularizations versus improved preventive care contributed to the clinical benefit of CAC in this study is unclear. Nonetheless, we think that this innovative analysis convincingly adds further weight to the argument for a trial of CAC–based ASCVD prevention treatment strategies, something the authors themselves justifiably call for. However, novel trial designs may be necessary to make such a trial feasible.

In contrast to the findings in the CAC versus hsCRP comparison, the relative benefit of CAC versus lipid screening was less clear. This apparent contradiction warrants attention. Indeed, should a simple lipid test prove to be as useful as a CAC test, the argument for a CAC trial would be entirely moot. We think that the CAC versus lipid portion of this analysis may harbor problems that limit validity. Importantly, the authors chose to limit the lipid analysis sample to those persons who had lipid testing during a visit with cardiovascular screening as the primary diagnosis code. Although this is understandable in some respects, the vast majority of lipid screening and monitoring is done in different clinical scenarios (particularly in elderly persons with other primary diagnoses, including concomitant ASCVD risk factors). Not surprisingly, by choosing this healthier subgroup, the authors had difficulty matching these individuals to persons who had CAC testing (indeed they were unable to match 25% of the CAC group because <3% of this lipid screening sample was eligible for the match). By removing the best matches from the eligible pool first, the greedy propensity score algorithm used by the authors likely compounded this problem.

In keeping with this, persons eligible for the CAC–lipid match had lower burden of comorbidities than the CAC–hsCRP match (and the subsample of persons chosen for the CAC–lipid match were likely drawn from the lower end of the ASCVD risk spectrum in the CAC sample overall and from the higher end of the risk spectrum in the lipid screening sample overall). This fact will magnify the problem of unmeasured confounding, something a propensity match cannot correct, and could have introduced significant bias. It is possible that this issue should be less of a problem in younger persons, and in fact at the risk of overinterpreting the data, the authors did find that the CAC testing strategy was associated with lower events in the subgroup aged 65 to 70 years, compared with lipid testing (composite end point hazard ratio, 0.51; confidence interval, 0.29–0.91; P=0.022; Table VII in the Data Supplement).1 Thus, we remain to be convinced that a lipid-based strategy will prove as effective as CAC testing.

Ultimately, only a well-designed randomized trial will provide a definitive answer.

Disclosures
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References


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