Coronary Artery Calcium and Cardiorespiratory Fitness: The Simple Keys to Truly Personalized Atherosclerotic Cardiovascular Disease Risk Prediction?

Atherosclerotic cardiovascular disease (ASCVD) risk prediction is the cornerstone of decision-making strategies for the prevention of ASCVD. Whereas guideline recommendations for ASCVD risk prediction are still largely based on the measurement of traditional ASCVD risk factors, there are well-established limitations to this approach, and other predictors of ASCVD risk are needed to better personalize ASCVD risk prediction. Accordingly, the most recent American College of Cardiology/American Heart Association guidelines place added emphasis on refining risk beyond traditional ASCVD risk factors. Coronary artery calcium (CAC), which is a measure of an individual's subclinical burden of coronary atherosclerosis obtained by non–contrast-enhanced cardiac computed tomography, is strongly associated with increased ASCVD beyond traditional ASCVD risk factors; notably, the 2019 American College of Cardiology/American Heart Association primary prevention guidelines provide a IIa recommendation to perform CAC scoring when there is uncertainty among patients with a calculated borderline to intermediate 10-year ASCVD risk (7.5% to <20%). A higher level of cardiorespiratory fitness (CRF) or exercise capacity is also strongly associated with a lower ASCVD risk and all-cause mortality, and indeed, the 2016 American Heart Association Cardiorespiratory Fitness Scientific Statement emphasizes that CRF is a stronger risk factor for incident ASCVD and all-cause mortality than traditional risk factors. In addition to their improvement in ASCVD risk prediction, CAC and CRF tests are widely accessible, relatively low cost, and simple to perform. However, only a small number of studies have examined how the concomitant measurement of both CAC and CRF may improve ASCVD risk prediction.

In this issue of Mayo Clinic Proceedings, Ahmed et al examine whether the measurement of both CAC and CRF together can improve risk stratification for incident major adverse cardiovascular events (MACE), defined as all-cause death, nonfatal myocardial infarction, late revascularization, or hospital admission for heart failure. This study cohort included a total of 1932 patients who had a clinically indicated CAC scan and clinically indicated exercise stress test between January 2015 and September 2021. Approximately half of patients had exercise testing before their CAC scan and vice versa, with a median of 27 days between the 2 tests. Exercise capacity or CRF was defined on the basis of peak metabolic equivalents (METs) derived from symptom-limited treadmill stress testing performed with the Bruce protocol, the most commonly performed protocol in routine clinical practice. Ascertainment of MACE after testing was obtained through electronic health record review and International Classification of Diseases, Ninth Revision and Tenth Revision code search, which was then adjudicated by cardiologists blinded to the CAC and exercise testing results. Both CAC and CRF independently improved ASCVD risk stratification beyond traditional cardiovascular disease risk factors. In addition, CAC score provided additional risk stratification within fitness groups, and prediction models that included both CAC and CRF had the best prediction for MACE. There was no statistical interaction between CAC and CRF.
suggesting that the 2 predict risk independently of each other.

Patients with the lowest exercise capacity (<6 METs) and with CAC score of 400 or higher had the highest incident rate for MACE (77.5/1000 person-years), whereas patients with moderate to high exercise capacity (≥6 METs) and CAC score of 0 had the lowest rate of MACE (4.5/1000 person-years). There was also a higher rate of MACE within each category of CAC for persons with the lowest exercise capacity compared with those with moderate to high exercise capacity. However, there was a smaller difference in event rates across CAC categories for patients with moderate to high CRF, especially among patients with only mild to moderately elevated CAC scores. These findings are similar to results from the Cooper Center Longitudinal Study, which also showed a relatively small difference in cardiovascular disease outcomes across CRF levels for persons with a CAC score of 0 and the largest difference across CAC levels for persons with CAC score of 400 or higher. Conversely, exercise testing appears to have the largest improvement in ASCVD risk estimation among persons with moderate to high CAC scores, with observed event rates approximately 50% lower for patients with moderate to high CRF compared with low CRF. However, whereas patients with a moderate or high CAC score had significant improvement in risk estimation based on their exercise capacity, those patients with a moderate to high exercise capacity and CAC score of 400 or higher still had an absolute event rate consistent with high ASCVD risk and are therefore likely to benefit from preventive pharmacotherapy, such as statin therapy.

A major strength of CAC and exercise capacity/CRF is that they serve as integrated measures of an individual’s cardiovascular disease risk and overall health status. Indeed, beyond cardiovascular disease outcomes, higher CAC scores and lower CRF are associated with increased total mortality and non–cardiovascular disease outcomes, such as cancers. However, CAC and CRF also effectively integrate different and complementary physiologic information. For example, CAC integrates an individual’s duration and intensity of exposure to risk factors along with an individual’s genetic susceptibility to subclinical atherosclerosis. Exercise capacity is dependent on multiple organ systems—including the heart, lungs, skeletal muscles, and nervous system—and genetics, lifestyle, and exercise training. It also serves as a robust measure of an individual’s frailty. Therefore, it makes intuitive sense that these 2 measures of ASCVD risk can together improve risk prediction beyond either measurement alone.

It is noteworthy that although this study categorized patients into 3 CRF groups, the primary results focus on a comparison of patients with low CRF and those with moderate to high CRF. In addition, only 8.4% of patients (n=162) had a low exercise capacity, whereas 54% had a high exercise capacity (≥10 METs), and the absolute number of MACE was relatively low, occurring among only 66 patients during the mean follow-up of 32 months. Accordingly, there are very wide 95% CI ratios for the event rate estimates among patients with low CRF, and the limited number of events precluded investigation of the individual outcomes within the composite MACE definition. In addition, although a number of studies have noted a paradoxical increase in CAC among individuals who perform extreme levels of physical activity and very high CRF but low associated rate of ASCVD, the results presented in this manuscript do not provide sufficient granularity in exercise capacity/CRF to further examine this relationship.

In addition, the cohort is relatively young, with a median age of 56 years, with 42% women and a high prevalence of traditional ASCVD risk factors. Accordingly, although the authors do not present estimated 10-year ASCVD risk, this study cohort
appears representative of what we would expect for middle-aged persons with intermediate ASCVD risk. One of the primary indications for ordering CAC testing is to determine the potential benefit of statin therapy or intensification of statin therapy. However, in this study, 65% of patients were already prescribed a statin, which was likely to be low- or moderate-intensity statin for most patients based on the median low-density lipoprotein cholesterol level of 106 mg/dL. Although the authors did not specifically examine patients receiving statin therapy as a subgroup, these findings showing the utility of CAC for risk stratification among this cohort with a high proportion of patients receiving statin therapy provide further evidence to support the potential utility of CAC scoring among individuals already receiving statin therapy. 16,17 In addition, whereas 62% of patients in this study were referred for risk assessment and presumably asymptomatic, 38% had chest pain or dyspnea prompting cardiovascular testing. However, sensitivity analyses showed similar results across multiple subgroups including asymptomatic patients.

Overall, this study provides further evidence supporting that the complementary information obtained from CAC testing and exercise stress testing/CRF assessment improves ASCVD risk prediction. Whereas CAC improved risk stratification of patients with both low and moderate to high CRF, it appears to be especially useful among persons with low levels of CRF. Conversely, exercise testing appears to have the largest improvement in ASCVD risk estimation among persons with moderate to high CAC scores, although those patients still had an absolute event rate likely to benefit from statin therapy. These large observed differences in event rates by exercise capacity/CRF demonstrate heterogeneity within CAC score groups, and they highlight the need for further research to determine whether an improvement in exercise capacity/CRF among persons with a positive CAC score is associated with a reduction in ASCVD risk.

POSSIBLE COMPETING INTERESTS

The authors report no competing interests.

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