Progression of coronary calcium: not as predictable as 1-2-3

Matthew J. Budoff

Los Angeles Biomedical Research Institute, 1124 W Carson Street, Torrance, CA 90502, USA

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This editorial refers to ‘Progression of coronary artery calcification seems to be inevitable, but predictable - result of the Heinz Nixdorf Recall (HNR) study,’ by R. Erbel et al., on page 2960.

Although coronary artery calcification has long been known to be associated with atherosclerosis—as the process of calcification of a plaque appears to be dependent on active phenomena of mineralization—it is likely that formation of calcium deposits is a highly dynamic process, affected by multiple modulators of mineral metabolism, as well as atherosclerotic risk factors. The investigators of the Heinz Nixdorff Recall Study have cleverly used a model to try to predict the age at which coronary artery calcium (CAC) high-risk thresholds are reached (e.g. the American College of Cardiology Guidelines suggest CAC > 300). By modeling, the explained variance of log-transformed CAC at follow-up was 80.1% and 72.0% in men and women, respectively, and 81.0 and 73.6%, respectively, including risk factors. The authors suggest that CAC largely progresses exponentially, with limited influence from cardiovascular (CV) risk factors, and is predictable, based on the age and sex-related CAC distribution. The age at which CAC high-risk thresholds are reached can be anticipated, which may lead to improved treatment. Theoretically, this information can be used to determine the timing for a second scan, or potentially used to determine when the patient would achieve high-risk status, determining timing for intervention.

While avoiding rescanning has both financial and radiation dose advantages (although the average dose of a calcium scan is comparable to a mammogram and <1 milliSievert), there are two problems with this algorithm that prevent its being used in place of a mathematical model. First, in a study by Erbel et al., 68.1% of patients were in a pre-defined range at five-year follow-up, and 19.4% had higher CAC progression than predicted. Thus, a model that predicts 68% is not unacceptable, but being too dogmatic in the use of a mathematical model will lead to undertreatment in those rapid progressors. Two large-scale studies have demonstrated that rate of progression is a strong predictor of future events, so knowing individual progression rates is paramount. The Multi-Ethnic Study of Atherosclerosis, following 5682 persons over 7.6 years, demonstrated that CAC progression was strongly associated with increased CV events. Among participants with baseline CAC, those with annual progression of >300 Agatston units had adjusted hazard ratios of 3.8 (1.5–9.6) for total and 6.3 (1.9–21.5) for hard coronary heart disease compared to those without progression. Another large-scale study has explored the prognostic impact of CACS progression among 4609 asymptomatic patients who underwent serial non-contrast cardiac CT. In this study, the observed progression of the CAC score was significantly associated with worsening mortality. These larger observational studies, therefore, more strongly support the concept that the continued progression of CAC is associated with increased risk of CV events, independent of baseline score, demographics and traditional CV risk factors. Those patients with new calcifications most likely have ongoing deposition of atherosclerosis, and remain at increased risk of future CV events. Conversely, those with no progression of their calcification scores demonstrate quiescence, and their risk is largely attenuated. More studies of interventions are needed, in order to better demonstrate which therapies most impact those with elevated atherosclerosis as manifested in increasing CAC scores.

Additionally, we have evidence that treatment of increased CAC scores can reduce CV events. Similarly, the St. Francis Heart Study was a placebo-controlled, randomized prospective study of 1005 apparently healthy individuals with a calcium score above the 80th percentile for age and sex on screening CT scans. The study compared the effect of 20 mg daily of atorvastatin, along with vitamins C and E vs. placebo, on progression of CAC by Agatston score. At the end of a mean follow-up of 4.3 years, the progression was similar among treatment arms (~20% per year). Clinical events, however, were significantly reduced by atorvastatin among patients with high CAC scores. The greatest benefit was among those with CAC scores > 400 at baseline (42% relative risk reduction, P = 0.046).

Thus the use of such a model can help decide on when a repeat calcium scan could be considered, but should not replace the scan, as those with more calcification progression than expected can...
be treated more aggressively, and those who have no- or less progression can continue with their current treatment algorithms (Figure 1). Understanding who may need a scan in one, three or five years can certainly help reduce costs and minimize testing: important goals in the current healthcare environment. The algorithms suggested by the Heinz Nixdorf Recall study should also be externally validated in other large cohort studies that employ calcium scoring, such as the Rotterdam Heart, Multi-Ethnic Study of Atherosclerosis or Dallas Heart Study. Similar algorithms could be developed for other screening tests, such as mammography or colonoscopy, rather than adhering to a ‘one time frame fits all’ model, which we too often employ.

References


Figure 1 Individual variations in progression alter risk of events. The progression line represented in red shows an individual who would be high risk, while the green line represents another patient with the same starting calcium score who would be low risk due to slowed progression.