Establishing the warranty of a coronary artery calcium score of zero

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The inherent limitations of traditional risk factor-based cardiovascular disease (CVD) risk assessment [1] have triggered the development and implementation of imaging tests aimed at directly measuring the presence and burden of subclinical atherosclerosis in diverse vascular beds within individual patients. Such individualized disease assessment clearly trumps risk factors as the strongest predictor of incident CVD events and death [2]. The promising results of incorporating such imaging-based risk information into clinical decision-making has led experts to advance a CVD risk assessment paradigm shift from a risk-factor based model to a multi-imaging approach (disease detection).

Among available imaging modalities, coronary artery calcium (CAC) using non-contrast computed tomography is considered one of the most powerful tools for absolute CVD risk assessment in asymptomatic adults [3]. Notwithstanding its essential limitation for ruling out the presence of early non-calcified plaque, CAC has a very high sensitivity for the detection of clinically relevant coronary atherosclerosis in asymptomatic adults [4], which results in a high negative predictive value. Moreover, CAC appears particularly valuable as a prognostic test. Beyond its well-known ability to identify those individuals more likely to have CVD events independent of traditional risk scoring, population studies and large clinical cohorts have shown asymptomatic subjects with zero CAC (CAC = 0) to have an excellent cardiovascular prognosis regardless of their age, sex, ethnic group, and burden of traditional risk factors [5]. Thus, CAC = 0 stands as perhaps the most powerful negative risk factor for near- and mid-term development of coronary events in asymptomatic adults [6]. In a context of population aging and cost-constrained healthcare systems, the accurate identification of “who not to treat” has important public health implications and may lead to large cost savings [7].

Hence, the clinician will find a CAC = 0 particularly informative in the context of CVD risk assessment of asymptomatic subjects considered at “intermediate” risk by traditional risk scores (where therapeutic decision-making is commonly uncertain). Nonetheless, in order to build decision-making around CAC results that might lead to withholding or reducing preventive pharmacotherapies, the clinician requires reliable information regarding the stability of that CAC = 0 over time: i.e., the “warranty period” of that result, during which it is safe to assume that the patient is likely to have persistent CAC = 0, remaining at low risk for CVD events and not in need for further interventions or repeat CAC evaluation. Indeed aging, and thus a longer exposure to risk factors, may lead to the development of coronary atherosclerosis and calcifications in individuals with initial CAC = 0. Previous studies have reported low conversion rates to CAC > 0 after 4–5 years of follow-up (≈ 20%, including 1% conversion rates to CAC > 100) [8] and very low CVD event rates [5,9] in subjects with CAC = 0. Nonetheless, uncertainty regarding when and in which patients this conversion and subsequent risk shift will occur has hampered incorporation of CAC = 0 into clinical guidelines, leading to the continuation of costly treatments with potential side-effects in those unlikely to have events, “just in case”.

1. Defining the warranty period of CAC = 0: a multi—imaging approach

The multi-imaging approach, rooted in the systemic nature of atherosclerosis [10] and the heterogeneity by which it affects different vascular beds, integrates the information provided by complementary, non-invasive diagnostic tests. This approach has been tested for further refining absolute CVD risk assessment beyond CAC in specific subgroups [11], and has recently been

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proposed for predicting CAC conversion – the finding of CAC>0 on a follow-up scan in subjects with an initial CAC = 0.

In this issue of Atherosclerosis, Brodov et al. [12] provided an excellent example of the multi-imaging approach. In a cohort of 1648 subjects with CAC = 0 from the EISNER Registry, thoracic aorta calcium (TAC) scoring was assessed as a predictor of CAC conversion (CAC > 0) after a mean follow-up of 5 years. Subjects with a baseline TAC > 100 had a 37% conversion rate, compared to 22% in the TAC = 0 group. In multivariate analyses TAC > 100 was an independent predictor of CAC > 0. Of note, 77% of the study subjects persisted to have CAC = 0 after a mean follow-up of 5 years and only 1% developed CAC>100, highlighting the durability of CAC = 0.

This is the first study assessing the independent predictive value of specific baseline TAC thresholds for CAC conversion, and provides new evidence supporting the notion of atherosclerosis as a systemic process. Furthermore, among the possible combinations of imaging tests, CAC + TAC appears as one of the most attractive strategies, both as can be assessed using the same CT imaging acquisition protocol and software. Thus, TAC appears as a convenient, non-further-irradiating, inexpensive "second" test, overcoming some of the intrinsic limitations of a multi-modality approach. Nevertheless, important limitations from the results reported by Brodov et al. must be highlighted. Among the group who converted to CAC > 0, just 4.5% had TAC > 100 at baseline, translating into a poor yield for changing clinical decision-making. Moreover, among those with TAC > 100 at baseline, only 37% developed CAC after 5 years of follow-up (i.e. 63% remained at CAC = 0). Furthermore, subjects with baseline TAC > 100 had a mean BMI of 27 kg/m², and at least 65% had other major CVD risk factors. Thus, at least 65% of the subjects with baseline TAC > 100 probably would have benefited from closer scrutiny according to their clinical risk profile alone.

Regardless of the "second" (or successive) test chosen, the use of a multi-imaging strategy for predicting conversion to CAC > 0 raises concerns regarding cost, radiation exposure, and potential downstream testing after incidental findings. From a clinical standpoint the use of multiple tests should provide relevant information and aid decision-making. Having two negative baseline tests should reassure the clinician about the stability of that CAC = 0 over time. Yet, in the study by Brodov et al. the performance of TAC > 100 for detecting CAC > 0 converters must be considered modest. Furthermore, among participants with CAC = 0 and TAC = 0 at baseline, 22% developed CAC during follow-up. What about these patients?

2. Alternative approaches

The need and frequency of repeated testing over time is determined by both the natural history of the disease and the characteristics of the test. CAC scoring is relatively inexpensive, is associated with a low dose of radiation exposure and has a low rate of false negatives. On the other hand, coronary atherosclerosis development and progression [13] is directly affected by lifetime exposure to traditional risk factors. This also holds for subjects with CAC = 0, which is commonly (but not always) the result of either a low risk factor burden or a short life-long exposure at the time of the scan. Accordingly in the study from Brodov et al., baseline diabetes, hypertension and hypercholesterolemia were independent predictors of CAC conversion, consistent with the results from previous studies [14] and with the pathophysiology of atherosclerosis. Of note, baseline diabetes was the strongest predictor of CAC conversion at follow-up, even stronger than TAC > 100.

Thus, an alternative approach to the warranty period of CAC = 0 reverts back to clinical features to identify those subjects more likely to develop coronary atherosclerosis and calcifications over a given period of time. In this context, CAC and risk factor burden provide complementary information, with CAC score defining baseline absolute risk and risk factors determining the "slope" of the risk trajectory over time. This approach yields intuitive, easy-to-follow and personalized follow-up algorithms built on information already available to the treating clinician. Moreover, it allows flexibility, as it can adapt to changes in the patient’s risk profile over time. Indeed, the concept of "warranty" implicitly assumes that the patient will not engage in high-risk activities that would make a negative result unstable. Thus, any warranty period or single-time calcium conversion prediction could be compromised by the onset of new risk factors. In such a context, an approach that emphasizes a fixed warranty period might help overcome the limitations of single-time predictions and enable tailored flexible follow-up strategies.

3. Future directions

Advances in atherosclerosis-imaging technologies in the next years will boost research in this area, expanding our knowledge regarding safety, cost-effectiveness and the potential interplay between imaging tests and predictions based on clinical features. This will be particularly helpful in the electronic medical record era, in which clinicians will be able to leverage vascular disease information from seemingly unrelated tests to improve risk assessment.

In such a context, studies like the one by Brodov et al. will improve our understanding of the additional information provided by different tests/measurements, aiding the selection of clinically relevant information among a wealth of measurements. On the other hand, future studies on the warranty period of negative factors such as CAC = 0 will have to provide clear definitions of the "outcome" (what defines the warranty? – any new CAC, only new-onset increased burden of CAC, or an eventual CVD event?), as well as the acceptable yield of repeat testing (number needed to scan in order to detect a CAC conversion). These questions are nearly completely unexplored.

Until further evidence is available, we should pay careful attention to features that caution us about the need for a closer follow-up in a given patient. Underscoring the role of the patient as the main guarantor of a CAC = 0 operation, we need further exploration of the concept of the necessary warranty period of atherosclerosis imaging results in order to advance clinical decision-making.

Conflicts of interest

None.

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