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A 15-Year Warranty Period for Asymptomatic Individuals Without Coronary Artery Calcium

A Prospective Follow-Up of 9,715 Individuals

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ABSTRACT

OBJECTIVES The aim of this study was to examine the long-term prognosis in asymptomatic individuals with a coronary artery calcium (CAC) score of 0 and its associated warranty period.

BACKGROUND Emerging evidence supports a CAC score of 0 as a favorable cardiovascular short-to intermediate-term prognostic factor.

METHODS A total of 9,715 individuals undergoing CAC imaging were stratified by age, Framingham risk score (FRS), and National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) categories and followed for a mean of 14.6 years (range 12.9 to 16.8 years). Cox regression, area under the receiver-operating characteristic curve, and net reclassification information were used to assess all-cause mortality, discrimination, and reclassification of a CAC score of 0 compared with the FRS and NCEP ATP III, respectively. A warranty period was pre-defined as <1% annual mortality rate. Vascular age was estimated by linear regression.

RESULTS In 4,864 individuals with a baseline CAC score of 0 (mean age, 52.1 ± 10.8 years; 57.9% male), 229 deaths occurred. The warranty period of a CAC score of 0 was almost 15 years for individuals at low and intermediate risk with no significant differences regarding age and sex. A CAC score of 0 was associated with a vascular age of 1, 10, 20, and 30 years less than the chronological age of individuals between 50 and 59, 60 and 69, 70 and 79, and 80 years of age and older, respectively. The CAC score was the strongest predictor of death (hazard ratio: 2.67, 95% confidence interval: 2.29 to 3.11) that enabled discrimination and consistent reclassification beyond the FRS (area under the receiver-operating characteristic curve: 0.71 vs. 0.64, $p < 0.001$) and NCEP ATP III (area under the receiver-operating characteristic curve: 0.72 vs. 0.64, $p < 0.001$).

CONCLUSIONS A CAC score of 0 confers a 15-year warranty period against mortality in individuals at low to intermediate risk that is unaffected by age or sex. Furthermore, in individuals considered at high risk by clinical risk scores, a CAC score of 0 confers better survival than in individuals at low to intermediate risk but with any CAC score.
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In population-based studies, coronary artery calcium (CAC) scoring by computed tomography (CT) accurately stratifies cardiovascular risk in asymptomatic individuals (1–5). Notably, the presence (6,7), extent (8), and progression (9,10) of CAC have been shown to be associated with major adverse cardiovascular events (4,6–10) and death (3,4,10–15), independent of conventional risk factors. Conversely, a favorable prognosis has been observed in the absence of CAC (16–18). The majority of these studies have evaluated the beneficial effect of a CAC score of 0 in cohorts with up to 5 years of follow-up, a time point at which a generally low number of incident adverse clinical events has occurred. However,

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whether a CAC score of 0 confers long-term protection against poor survival incremental to and independent of clinical risk scoring and its associated "warranty period" remains to be elucidated. Further, several recent studies highlighted the important distinction between chronological age and "vascular age," the latter of which adjusts an individual's risk of mortality based on the level of CAC (19,20). To date, the long-term impact of a CAC score of 0 for the estimation of vascular age versus chronological age is unknown. Thus, in the present study, we set out to determine the long-term prognosis associated with a CAC score of 0, comparing the prognosis of a CAC score of 0 with the prognosis obtained by the current clinical prediction models such as the Framingham risk score (FRS) and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), quantifying the "warranty period" for a CAC score of 0, and, last, examining the association of a CAC score of 0 with chronological versus vascular age.

METHODS

STUDY POPULATION. The study cohort comprised 9,715 consecutive asymptomatic individuals without known coronary artery disease (CAD). All individuals were referred by their physicians for CAD evaluation and underwent CAC imaging with electron beam computed tomography (EBCT) at a single site. All individuals provided informed consent to undergo EBCT, and the study was approved by the Human Investigations Committee at the Tennessee Heart and Vascular Institute.

RISK FACTOR COLLECTION. All study participants were queried for the following baseline cardiovascular risk factors: 1) cigarette smoking was considered to be present if a subject was an active smoker at the time of scanning; 2) dyslipidemia was considered to be present for any individual reporting a history of high total cholesterol, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, high triglycerides, or current use of lipid-lowering therapy; 3) diabetes was defined as baseline use of antidiabetic medication or a history of elevated blood glucose measurement of >126 mg/dl; 4) hypertension was defined as a self-reported history of high blood pressure or the use of antihypertensive medication; and 5) family history of premature CAD was determined by asking individuals whether any member of their immediate family (i.e., parents or siblings) had a history of fatal or nonfatal myocardial infarction and/or coronary revascularization in a male relative younger than 55 years of age or a female relative younger than 65 years of age.

EBCT SCREENING PROTOCOL. Subjects underwent EBCT on either a C-100 or C-150 Ultrafast CT scanner (Imatron, South San Francisco, California). With a tomographic slice thickness of 3 mm, a total of ~40 sections were obtained beginning at the level of the carina and proceeding caudally to the level of the diaphragm. Images were obtained with a 100-ms/slice scanning time, with image acquisition electrocardiographically triggered at 60% to 80% of the R-R interval. A calcified lesion was defined as more than 3 contiguous pixels with a peak attenuation of at least 130 Hounsfield units. Each lesion was then scored using the method developed by Agatston et al. (21) (Agatston units). The estimated radiation dose was ~1 mSv.

ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcium
CAD = coronary artery disease
CI = confidence interval
CT = computed tomography
EBCT = electron beam computed tomography
FRS = Framingham risk score
HR = hazard ratio
NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III

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