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A 15-year warranty period for asymptomatic individuals without coronary artery calcium: a prospective follow-up of 9715 individuals

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Abstract

Objective—To examine long-term prognosis of a zero coronary artery calcium (CAC) score among asymptomatic individuals and its associated warranty period.

Background—Emerging evidence supports CAC=0 as a favorable cardiovascular short-to-intermediate term prognostic factor.

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Methods—9715 individuals undergoing CAC imaging were stratified by age, Framingham risk score (FRS) and Adult Treatment Panel III (NCEP ATP III) categories and followed for a mean of 14.6 (12.9–16.8) years. Cox regression, area under the receiver operating characteristic curve (AUC) and net reclassification information (NRI) were used to assess all-cause mortality, discrimination and reclassification of CAC=0 compared with 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—Among 4864 individuals with baseline CAC=0 (mean age 52.1±10.8 years; 57.9% male), 229 deaths occurred. The warranty period of CAC=0 was almost 15 years for individuals at low and intermediate risk with no significant differences regarding age and gender. CAC=0 was associated with a vascular age of 1, 10, 20, and 30 years below chronologic age for individuals between 50–59, 60–69, 70–79, and ≥80 years, respectively. CAC score was the strongest predictor of death (HR 2.67, 95% CI 2.29–3.11) that enabled discrimination and consistent reclassification beyond FRS (AUC 0.71 vs. 0.64, p<0.001) and NCEP ATP III (AUC 0.72 vs. 0.64, p<0.001).

Conclusions—CAC=0 confers a 15-year warranty period against mortality among individuals at low-to-intermediate risk, which is unaffected by age or gender. Furthermore, in individuals considered at high-risk by clinical risk scores the presence of CAC=0 confers better survival than in individuals at low-to-intermediate risk but with any CAC.

Keywords

Coronary artery calcium; prognosis; warranty period; mortality; computed tomography

INTRODUCTION

In population-based studies, coronary artery calcium (CAC) scoring by computed tomography (CT) accurately stratifies cardiovascular risk for asymptomatic individuals.[1–5] Notably, CAC presence,[6,7] extent,[8] and progression[9,10] have been shown to be associated with major adverse cardiovascular events[4,6–10] and death,[3,4,3,10–15] 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 salutary effect of a CAC = 0 in cohorts with up to 5 years of follow-up, a time point where a generally low number of incident adverse clinical events has occurred. However, whether CAC = 0 confers long-term protection against poor survival incremental and independent to clinical risk scoring, and its associated “warranty period,” remains to be elucidated. Further, several recent studies have highlighted the important distinction between chronologic and “vascular age”, the latter of which adjusts an individual’s risk of mortality based upon the level of CAC.[19,20] To date, the long-term impact of CAC = 0 for the estimation of vascular age versus the chronologic age is unknown. Thus, in the present study, we set out to determine the long-term prognosis associated with a CAC = 0, comparing the prognosis of CAC = 0 to the prognosis obtained by the current clinical prediction models such as the Framingham risk (FRS) and the Adult Treatment Panel III (NCEP ATP III) scores, quantifying the “warranty period” for CAC=0 and lastly, examining the association of CAC = 0 to chronologic versus vascular age.

METHODS

Study population

The study cohort comprised of 9715 consecutive asymptomatic individuals without known coronary artery disease (CAD). All individuals were referred by their physicians for CAD evaluation and underwent CAC testing electron beam computed tomography (EBCT) at a single site. All individuals provided informed consent to undergo EBCT and the study received approval from the Human Investigations Committee.

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 anti-diabetic medication or had a history of elevated blood glucose measurement of >126 mg/dl use; 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 <55 years or a female relative <65 years.

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 approximately 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 >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 approximately 1 mSv.

Study outcome

The primary endpoint of this study was death from all causes. Ascertainment of mortality status was conducted by individuals masked to baseline historical data and EBCT results, and was verified using the Social Security Death Index. The United States Social Security Death Index is a national registry of all deaths that have occurred in the United States, allowing for 100% mortality ascertainment among study participants.

Definition of warranty period

In accordance with societal guidelines, an annual mortality rate below 1% was employed to define individuals as low risk.[22] For the purposes of this study, a warranty period was

defined as the time an individual remained within the low risk category; conversely, reported values of annual mortality rate above 1% signified warranty period cessation.

Statistical methods

Categorical variables are presented as counts with proportions and continuous variables as mean ± SD. The Pearson chi-square test was employed for comparison of categorical variables. Between-group comparisons for continuous variables were computed using the independent samples t-test or the Mann-Whitney U test as appropriate. Multivariable Cox proportional hazard regression models reporting hazard ratios (HR) with 95% confidence intervals (95% CI) were performed to examine and compare the risk of death from all-causes among individuals. The latter model adjusted for age, gender, cigarette smoking, and cardiovascular morbidities including diabetes, hypertension, dyslipidemia, and family history of premature CAD.

The relationship between a CAC = 0 and mortality was determined as a function of varying cardiovascular risk as determined by widely employed clinical risk scores. Cox regression models stratified individuals according to pre-defined categories as quantified by low (<10%), intermediate (10% to 20%), and high (>20%) risk using 10-year FRS and NCEP ATP III scores.[3,23] Linear regression models were used to estimate the vascular age using patients' chronologic age as the dependent variable and the CAC score as the independent variable.[19] Group differences between vascular age and chronologic age were plotted. Additionally, for each corresponding category of age, annual mortality rates were calculated. Discriminatory power of CAC over FRS and NCEP ATP III was evaluated using areas under the receiver operator characteristic curve (AUC)[24] and compared using the DeLong method.25 Reclassification was determined using category-free net reclassification improvement (NRI) indices.[26] Statistical analyses were performed using STATA version 12.0 (StataCorp LP, College Station, TX, USA) and SAS version 9.3 (SAS Institute Inc., Cary, NC). A two-tailed P-value <0.05 was considered statistically significant.

RESULTS

Study population

Of 9715 individuals (mean age 53.4±10.5, 59.3% male) undergoing CAC screening, 4864 (mean age 52.1±10.8 years; 57.9% male) had a CAC = 0. At a follow-up mean of 14.6 (12.9–16.8) years, there were 936 (9.6%) deaths in the study population. Of deaths, 229 (4.7%) and 707 (14.6%) occurred among individuals with a CAC = 0 and CAC > 0, respectively. Demographic characteristics of the study sample are summarized in Table 1. Overall, prevalent hypertension, dyslipidemia, smoking status, diabetes, family history of premature coronary artery disease (CAD), FRS and NCEP ATP III, were higher among individuals with CAC > 0 versus CAC = 0. Survival was higher for CAC = 0 (95.1% vs. 83.7%, P<0.001).

CAC and long-term prognosis

In multivariable analyses, CAC > 0 was the strongest predictor of death in overall population beyond individual cardiovascular risk factors, FRS and NCEP ATP III and it was

associated with a nearly 3-fold (HR 2.67, 95% CI 2.29–3.11) risk of death (Table 2). The presence of diabetes (HR 2.53, 95% CI 1.74–3.69), active smoking (HR 1.95, 95% CI 1.50–2.53), and hypertension (HR 1.58, 95% CI 1.21– 2.06) were associated with increased risk of mortality among individuals with CAC = 0. In the presence of any CAC, the risk increased proportionally with the severity in the CAC score but independently of the Framingham Risk Score (FRS) and the risk model provided by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) (Table 3). Men and women showed similar survival and mortality risk either in the presence or in the absence of CAC (Figure 1 A and B, Supplemental).

Warranty period of CAC = 0

Figure 1 describes the 15-year cumulative mortality rate among all study individuals, and those considered low risk by FRS, NCEP ATP III, absence of CAD risk factors and CAC = 0; individuals with CAC = 0 experienced the lowest rates of mortality. Independent of FRS (Figure 2A) or NCEP ATP III class (Figure 2B), a CAC = 0 was associated with a favorable prognosis. Risk of all-cause mortality was higher among individuals with CAC > 0 and low cardiovascular risk (FRS = HR 3.3, 95% CI 2.49–4.32; NCEP ATP III = HR 3.09, 95% CI 2.45–3.90), as compared with those with CAC = 0 and high cardiovascular risk (FRS = HR 2.8, 95% CI 2.05–3.92; NCEP ATP III = HR 2.94, 95% CI 2.15 –4.01).

Figure 3 shows the annual mortality rates for individuals with CAC = 0 and CAC > 0. A CAC = 0 was associated with >15 year warranty period, with the observed rate of mortality remaining <1% during the entirety of follow-up. Mortality rates in individuals with CAC = 0 were non-linear in nature, with a lower event rate (mean 0.3% ± 0.08% events/year) during the initial 12 years that accelerated during the 13th (0.4% events/year) and 14th (0.58% events/year) years. Figure 4 depicts the warranty period of a CAC = 0 in select subgroups. CAC = 0 was associated with a warranty period of 15 years for individuals below the age of 60 years, with no apparent disparity among genders. The observed duration of the warranty period of a CAC = 0 was slightly shorter for those ≥60 years, and ceased after 14 years of follow-up. Despite CAC = 0, individuals considered at high cardiovascular risk by clinical risk, experienced a significantly shorter warranty period (5–6 years) than individuals at low-to-intermediate risk. However, the warranty period for high-risk categories with CAC = 0 was even longer than individuals at low-to-intermediate risk with a CAC > 0.

Vascular age in individuals with CAC = 0

A CAC = 0 was associated with a lower vascular versus chronologic age, a finding more pronounced for individuals of increasing age and for men versus women (Figure 5 A). As an example, the vascular age afforded by CAC=0 for a man ≥80 years of age was equivalent to the chronologic age of a 50 year old man within the general population. The annual mortality rate observed for patients with CAC=0 was lower than the equivalent category of chronologic age, in the general population (Figure 5 B).

Incremental predictive value of CAC for individuals with CAC > 0

Compared with the base models of FRS or NCEP ATP III alone, discrimination improved significantly (Area under the receiver operating characteristics curve [AUC] 0.71 versus

0.64, and 0.72 versus 0.64 for FRS and NCEP ATP III, respectively, p<0.001 for both) when CAC was added to the FRS or NCEP ATP III. The addition of CAC to the FRS or NCEP ATP III also resulted in significant reclassification of events and non-events among individuals (both P<0.001). Irrespective of risk prediction category, CAC improved risk classification for those at risk versus not at risk for incident mortality (P<0.001) (Table 4).

DISCUSSION

In the present study, we extensively examined the long-term prognostic utility of CAC imaging in a large cohort of asymptomatic individuals with 15 years of follow-up. We observed the presence of CAC to be a strong predictor of incident mortality, even when considering robust clinical risk scores by Framingham or NCEP ATP III methods. Importantly, we identified a very low risk state that lasted for the duration of follow-up. The low risk associated with a CAC = 0 persisted to more than 15 years for individuals <60 years of age, and to 14 years for individuals ≥60 years of age, with no apparent disparity among genders. Importantly, the warranty period conferred by CAC = 0 was similar for individuals of low- or intermediate- clinical risk by FRS and NCEP ATP III. Individuals considered at high clinical risk but with CAC = 0, had a higher warranty period than those at low- or intermediate-clinical risk with any CAC. Conversely, the presence and severity of CAC were independently associated with increased mortality risk by the FRS and the NCEP ATP III. Finally, a CAC = 0 was associated with a vascular age that was approximately 30 years lower than chronologic age for older individuals and was associated with a significant lower annual mortality rate than the equivalent chronologic age category. Taken together, these findings indicate the robustness of a CAC = 0 to identify individuals disposed to a particularly propitious outcome, and may be useful as an adjunctive measure to everyday clinical risk assessment.

The present findings support as well as expand the extant literature[16–18] that have investigated the incremental utility of CAC imaging for the evaluation of asymptomatic individuals at risk for cardiovascular disease. The high prevalence of a CAC = 0 in individuals classified as intermediate-to-high risk based by clinical risk scores suggests that such scores are highly imperfect in identifying persons at elevated risk of mortality.[27,28] To this end, the present study detected a significant higher risk of mortality for individuals with a CAC > 0 who were considered low risk by clinical score, with respect to those with CAC = 0 who were considered intermediate or high risk. Yet, while robust in risk prediction, a CAC = 0 was significantly less effective at conferring a long-term warranty for individuals considered high risk by FRS and NCEP ATP III. Thus, while current guidelines support the use of CAC imaging among asymptomatic individuals at intermediate cardiovascular risk,[29] the present study suggests a long-term incremental value of CAC>0 for individuals initially considered to be at low risk but who are subsequently reclassified as at high cardiovascular risk based on CAC testing. Whether there is a clinical benefit of identification of a shorter warranty period of 5–6 years for individuals considered to be high risk by FRS or NCEP ATP III requires further examination in health outcomes studies.

In this study, the beneficial prognosis of a CAC = 0 is further supported by evidence of a vascular age reduction compared to chronologic age, with an associated improvement in

prognosis. Though it is generally accepted that the prevalence of coronary plaque burden and mortality rate increase with advancing age, the presence of a CAC = 0 may be effective as an index of "vascular youth."[19,20] These study findings validate the concept of "vascular youth" as determined by a CAC = 0, wherein individuals >50 years of age may be reassured that their coronary vasculature is "younger" than those of their peers, and that this auspicious finding confers a good long-term prognosis.

These study findings are of high clinical importance. Given the 15-year warranty of a CAC = 0 for individuals at low-to-intermediate clinical risk irrespective of gender and age—a period only mildly attenuated for older patients ≥60 years—the use of CAC may be instrumental for avoiding unnecessary testing even amongst individuals generally considered at higher peril for unheralded adverse clinical events. While some may speculate that the prognostic security of a CAC = 0 may offer an opportunity to attenuate medical therapies, our study findings apply only to coronary rather than cardiovascular assessment in other vascular beds such as the carotid circulation. Thus, the current results should not be interpreted as supporting a practice of therapy diminution or cessation as this matter is beyond the scope of our investigation. Future large-scale studies examining this concept should first be performed.

This study is not without limitations. Despite the large study sample-size, long-term follow-up, and prospective evaluation of study individuals, the single-center design of the present study may have introduced unobserved biases related to selection. In this regard, future population-based studies with long-term follow-up will be important to help confirm the present study findings. Further, CAC was performed only once for the present study and the rates of CAC progression were not accounted in the determination of the CAC = 0 warranty period. It remains conceivable that individuals who experience accelerated or retarded CAC progression may possess different warranty periods, and future studies should be performed to examine this. Also, the long-term mitigating effects of medical therapy and lifestyle modification and how they might influence the relationship between CAC and mortality cannot be accounted for in this investigation. Hence, forthcoming studies that utilize time-varying clinical measures in patients with known CAC values are now needed. Finally, we employed all-cause mortality as the primary endpoint for this study and thus, our analysis is unable to offer information regarding the impact of CAC specifically on cardiovascular morbidity and mortality, such as that used for the 2013 ACC/AHA guidelines.[30] However, the use of mortality disentangles the study from ascertainment or misclassification bias, and represents the hardest end-point to be evaluated in population studies. Indeed, the lack atherosclerotic cardiovascular disease-specific mortality in our study may have only contributed to an underestimation of the real impact of CAC on cardiovascular risk.[31]

CONCLUSION

A CAC = 0 confers a 15 year warranty period against mortality that is unaffected by age or gender, with a significant reduction in vascular over chronologic age. These findings are consistent in individuals with low and intermediate risk. In individuals considered at high risk by clinical risk scores the presence of CAC = 0 confers a longer warranty period compared to individuals at low- or intermediate- risk in presence of any CAC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Conflict of Interest

Dr. Min has served on the medical advisory boards of GE Healthcare, Arineta, Astra Zeneca, and Bristol-Myers Squibb; Speakers' Bureau of GE Healthcare; and received research support from GE Healthcare, Vital Images, and Phillips Healthcare. Dr. Min serves as a consultant to Astra Zeneca and HeartFlow. Dr. Truong received grant support from St. Jude Medical, American College of Radiology Imaging Network, and Duke Clinical Research Institute.

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PERSPECTIVES

Competency in Medical Knowledge

Traditionally, coronary artery disease (CAD) has been assessed in terms of measures of stenosis severity. Characterization of atherosclerotic plaque characteristics, in addition to stenosis severity, may improve the diagnosis and prognostic risk assessment of patients with CAD. Features suggesting high-risk seen with computed tomography include atherosclerotic plaque as well as coronary artery calcification volume and density and others, such as low attenuation plaque, positive remodeling and spotty calcification. Conversely, absence of coronary artery calcium is protective against coronary events over long period of follow up.

Translational Outlook

Additional clinical studies are required to determine the optimal methods for reporting CAD measures of stenosis or atherosclerosis, as well as to determine their prognostic implications and optimal approaches to therapy.

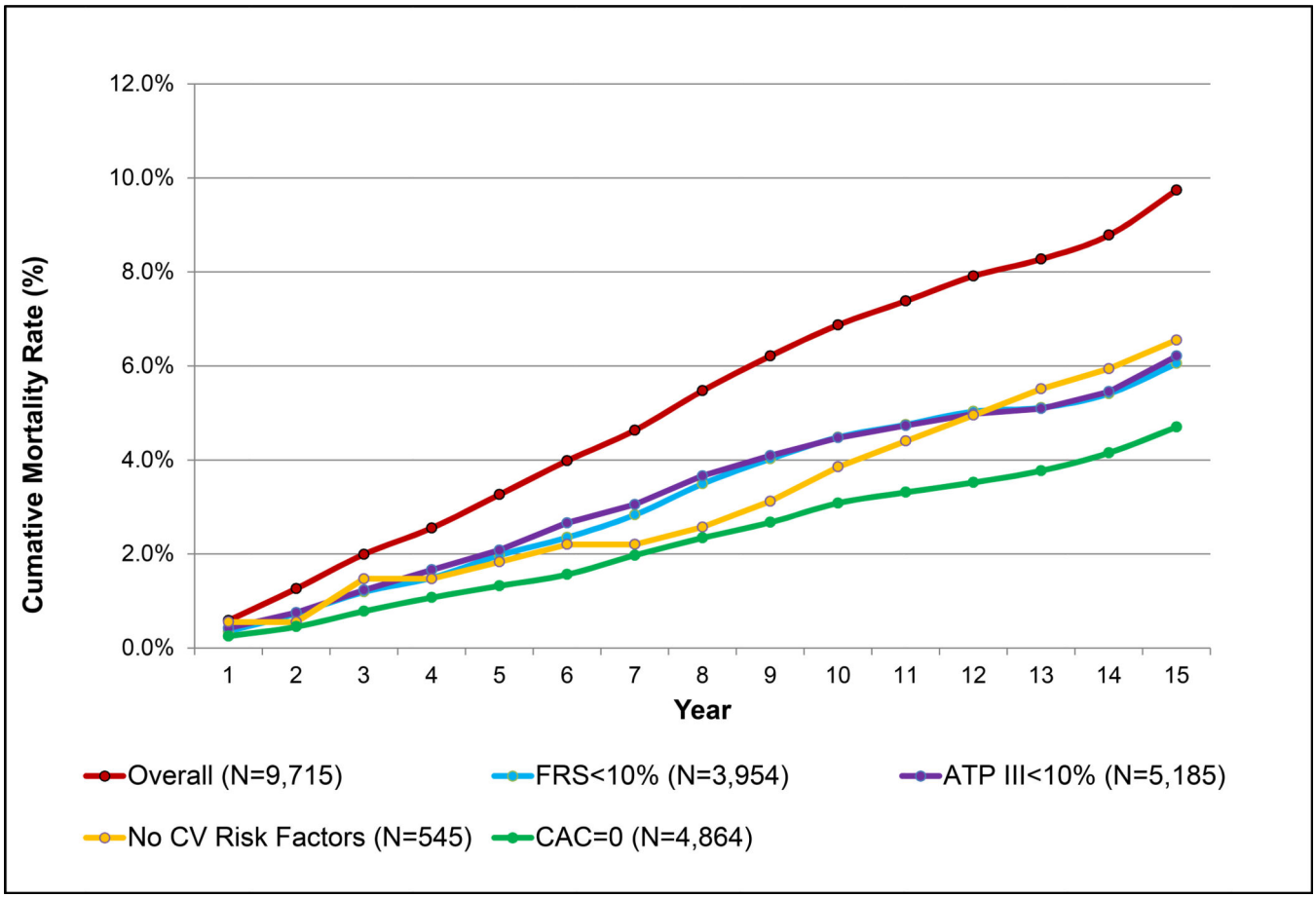

Figure 1. 15-year cumulative mortality rate for the study period

15-year cumulative mortality rate according to the overall study population and individuals considered low risk by Framingham Risk (blue line), National Cholesterol Education Program Adult Treatment Panel III (purple line), the absence of any CAD risk factor (yellow line), and CAC = 0 (green line).

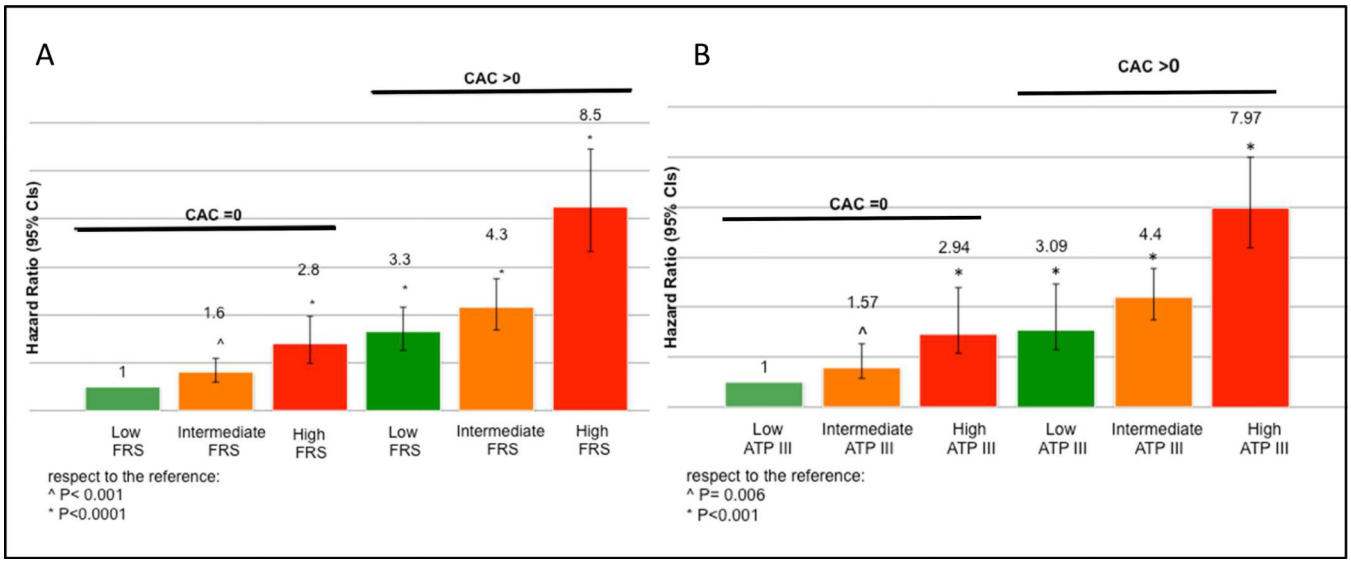

Figure 2. Hazard ratios for risk of all-cause mortality

Hazard ratios for risk of all-cause mortality among individuals with and without coronary artery calcification according to: **(A)** Framingham Risk Score, and **(B)** National Cholesterol Education Program Adult Treatment Panel III.

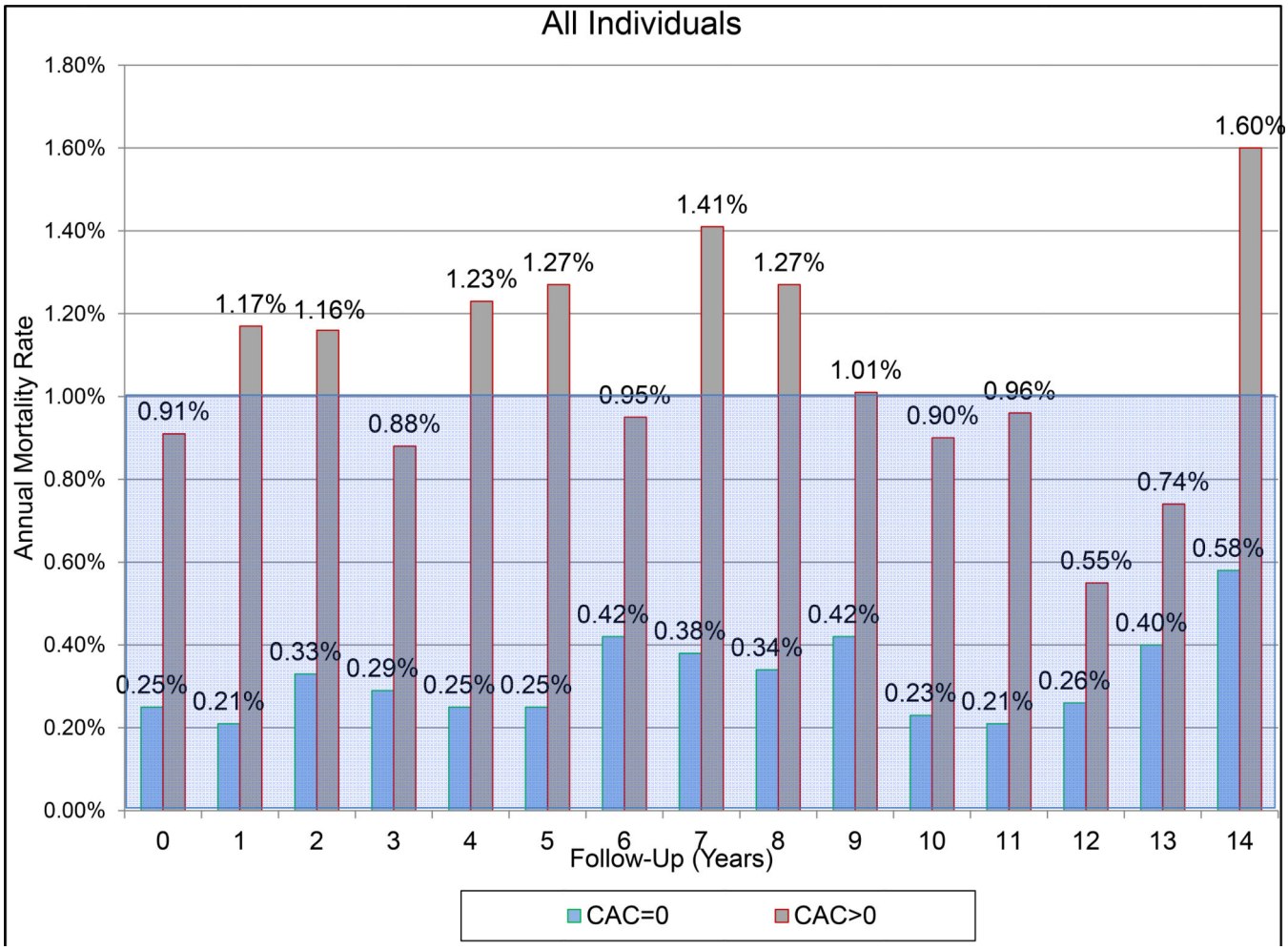

Figure 3. Annual mortality rate during the study period

An annual mortality rate below 1% was employed in order to classify individuals at low-risk of cardiovascular events.

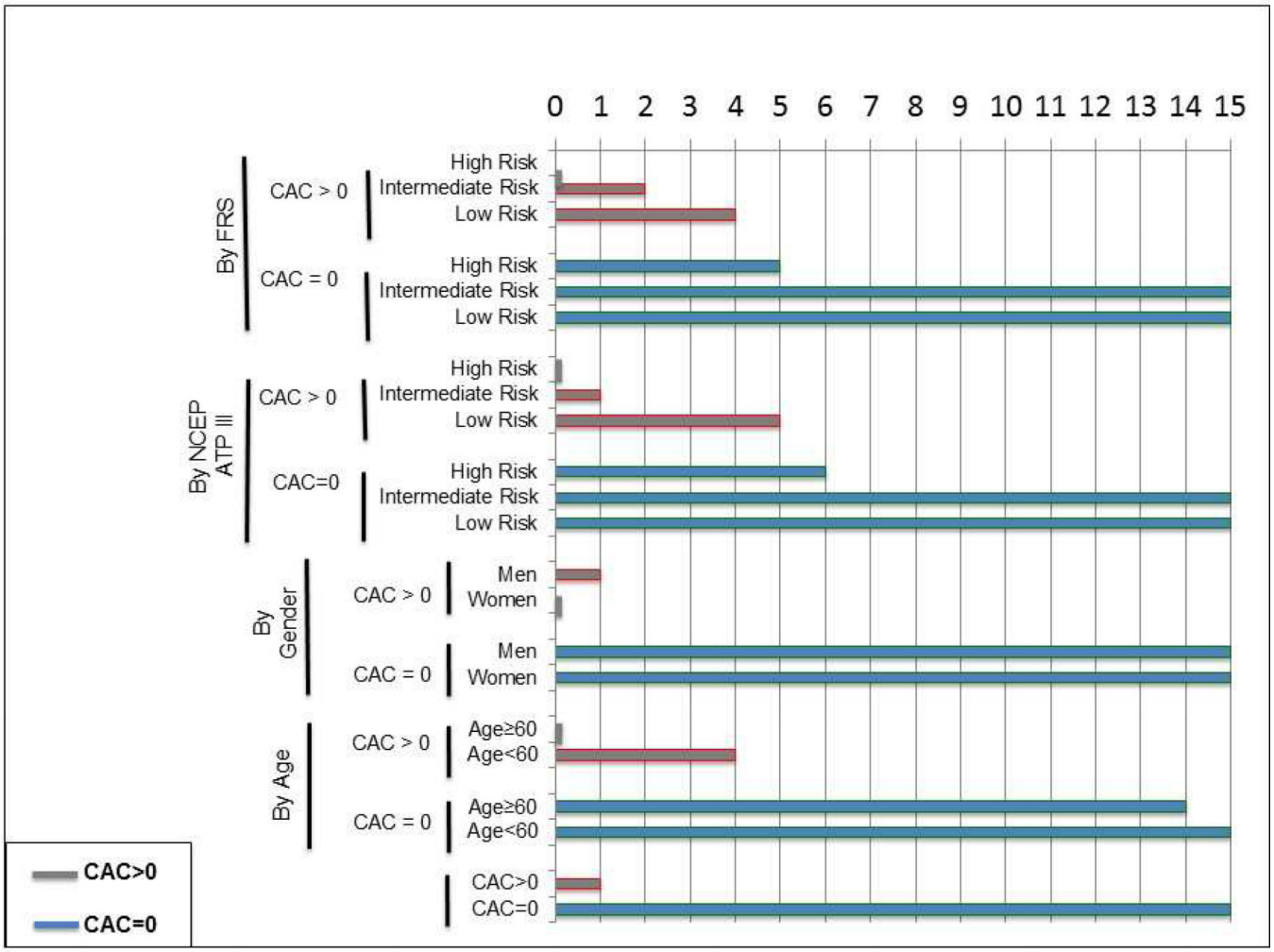

Figure 4. Observed warranty period for absence of CAC compared with the presence of CAC

Observed warranty period (time to exceed 1% risk) for a CAC = 0 compared with the presence of any coronary artery calcium across 15 years of follow-up among 9715 asymptomatic individuals stratified by coronary artery calcium score, age, gender, Framingham risk score (FRS) and National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III).

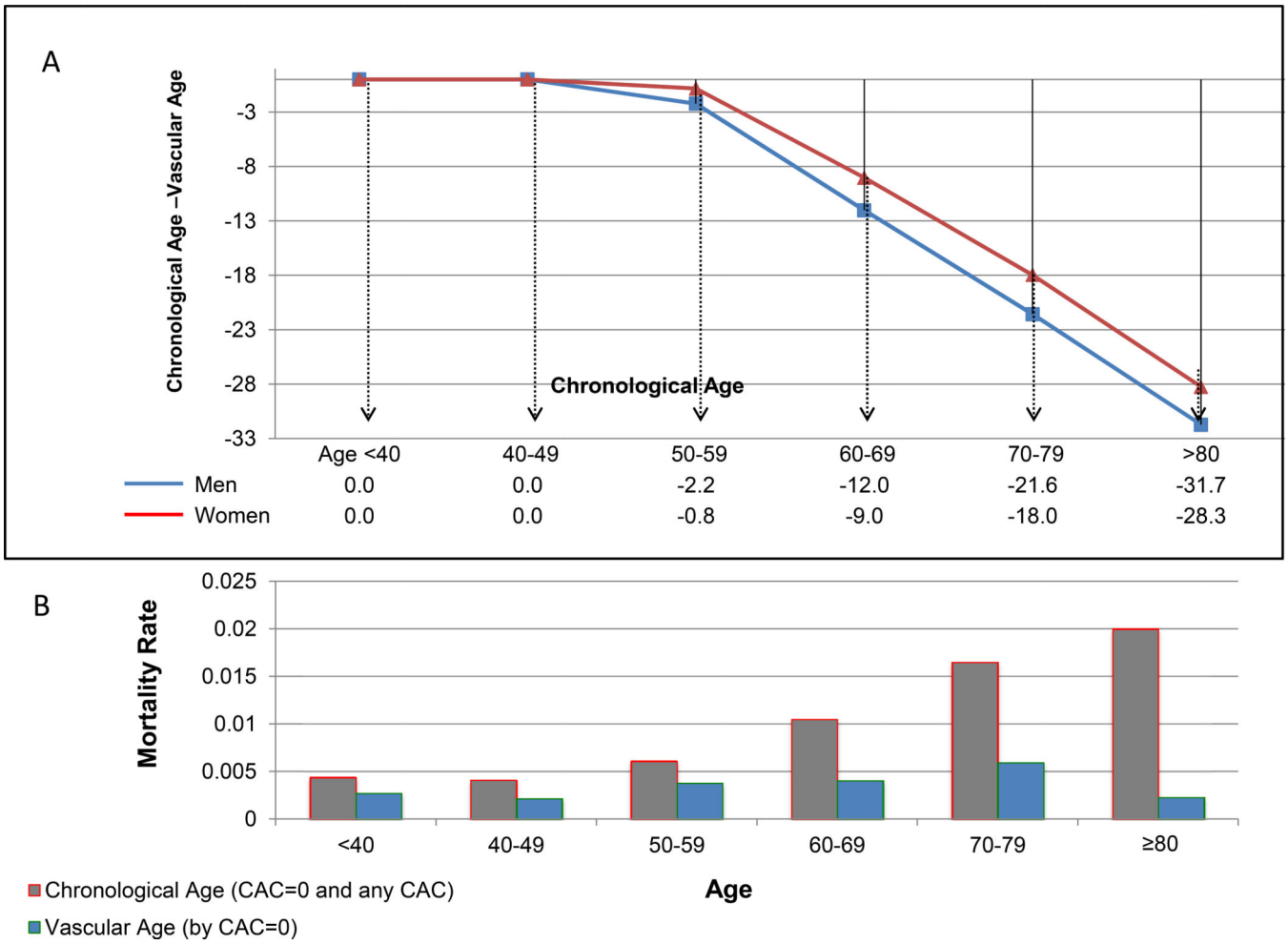

Figure 5. Differences between chronologic and vascular age

(A) Differences between chronologic versus vascular age in patients with zero coronary artery calcium score and **(B)** the corresponding annual mortality rate.

Table 1

Clinical characteristics of the study sample

(Risk Factor Cohort)	Overall (N=9715)	CAC=0 (N=4864)	CAC>0 (N=4851)	P value
Mean Age ± SD	53.4±10.5	52.1±10.8	54.6±10.0	<0.001
Male Gender	59.3%	57.9%	60.8%	0.003
Hypertension	43.4%	36.8%	50.1%	<0.001
Dyslipidemia	62.6%	57.8%	67.3%	<0.001
Diabetes	8.3%	5.7%	11.0%	<0.001
Smoking	39.3%	33.6%	45.0%	<0.001
Family History of Premature CAD (%)	68.7	69.7	67.7	0.03
Death	936 (9.6%)	229 (4.7%)	707 (14.6%)	<0.001
15 year survival	89.6%	95.1%	83.7%	<0.001
FRS[23]				<0.001
Low (<10%)	40.7%	50.0%	31.4%	
Intermediate (10–20%)	41.3%	37.3%	45.3%	
High (>20%)	18.0%	12.7%	23.3%	
NCEP ATP III[3]				<0.001
Low (<10%)	53.4%	62.9%	43.8%	
Intermediate (10–20%)	27.7%	23.7%	31.8%	
High (>20%) or DM	18.9%	13.4%	24.4%	

Abbreviations: CAC, coronary artery calcium; DM, diabetes mellitus; FRS, Framingham Risk Score; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.

Table 2

Predictors of all-cause mortality in asymptomatic individuals with and without coronary artery calcification.

	Model 1		**Model 2**			
	Overall (N=9715)		**CAC=0 (N=4864)**		**CAC>0 (N=4851)**	
	Univariable	**Multivariable**	**Univariable**	**Multivariable**	**Univariable**	**Multivariable**
CAC>0	3.36 (2.89–3.90) p<0.001	2.67 (2.29–3.11) p<0.001	NA	NA	NA	NA
Age	1.04 (1.04–1.05) p<0.001	1.04 (1.03–1.05) p<0.001	1.03 (1.02–1.04) p<0.001	1.03 (1.02–1.04) p<0.001	1.05 (1.04–-1.05) p<0.001	1.05 (1.04–1.05) p<0.001
Female	1.05 (0.93–1.20)	0.96 (0.84–1.09)	1.08 (0.83–1.40)	1.01 (0.78–1.32)	1.10 (0.94–1.27)	0.93 (0.80–1.09)
Gender	p=0.42	p=0.54	p=0.58	1.02 p=0.92	p=0.23	p=0.37
Hypertension	1.90 (1.67–2.16) p<0.001	1.61 (1.41–1.84) p<0.001	1.68 (1.30–2.18) p<0.001	1.58 (1.21–2.06) p=0.001	1.66 (1.43–1.94) p<0.001	1.62 (1.39–1.89) p<0.001
Dyslipidemia	0.81 (0.71–0.92) p=0.002	0.69 (0.60–0.79) p<0.001	0.93 (0.72–1.21) p=0.60	0.83 (0.63–1.08) p=0.16	0.66 (0.57–0.76) p<0.001	0.65 (0.56–0.75) p<0.001
Diabetes	2.98 (2.54–3.49) p<0.001	2.22 (1.89–2.61) p<0.001	2.84 (1.97–4.11) p<0.001	2.53 (1.74–3.69) p<0.001	2.48 (2.08–2.97) p<0.001	2.15 (1.79–2.57) p<0.001
Family History	0.75 (0.65–0.85) p<0.001	0.76 (0.67–0.87) p<0.001	0.93 (0.70–1.23) p=0.61	0.93 (0.70–1.23) p=0.61	0.71 (0.61–0.83) p<0.001	0.71 (0.61–0.83) p<0.001
Smoking	1.91 (1.68–2.17) p<0.001	1.79 (1.58–2.04) p<0.001	1.92 (1.48–2.48) p<0.001	1.95 (1.50–2.53) p<0.001	1.64 (1.41–1.90) p<0.001	1.77 (1.52–2.05) p<0.001
	Model 3		**Model 4**			
FRS, per 5% risk increase[23]	1.21 (1.18–1.24) p<0.001	1.17 (1.15–1.20) p<0.001	1.17 (1.11–1.24) p<0.001	1.18 (1.11–1.24) p<0.001	1.17 (1.14–1.20) p<0.001	1.17 (1.14–1.21) p<0.001
NCEP ATP III per 5% risk increase[3]	1.29 (1.25–1.34) p<0.001	1.23 (1.19–1.28) p<0.001	1.28 (1.19–1.37) p<0.001	1.28 (1.19–1.37) p<0.001	1.21 (1.17–1.27) p<0.001	1.22 (1.17–1.27) p<0.001

Model 1 adjusted for presence of coronary artery calcium, age, gender, and cardiovascular morbidities, including cigarette smoking, diabetes, hypertension, dyslipidemia and family history of premature coronary artery disease. **Model 2** adjusted for age, gender, and cardiovascular morbidities, including cigarette smoking, diabetes, hypertension, dyslipidemia and family history of premature coronary artery disease. **Model 3** adjusted for presence of coronary artery calcium, and family history of premature coronary artery disease. **Model 4** adjusted for family history of premature coronary artery disease.

Abbreviations: CAC, coronary artery calcium; FRS, Framingham Risk Score; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.

Table 3

Hazard Ratio analysis of 15-years all-causes mortality in asymptomatic individuals according to the coronary artery calcification score.

	Overall (N=9715)		
	Univariable	**Multivariable**	
	HR	**Adjusted for FRS**	**Adjusted for NCEP-ATPIII**
CAC 0	1.00 (ref)	1.00 (ref)	1.00 (ref)
CAC 1–99	2.21 (1.86–2.64) p<0.001	2.08 (1.74– 2.48) p<0.001	2.03 (1.70–2.42) p<0.001
CAC 100–399	3.85 (3.19 –4.66) p<0.001	3.42 (2.83– 4.14) p<0.001	3.32 (2.74 –4.02) p<0.001
CAC 400–999	5.98 (4.84–7.39) p<0.001	4.93 (3.98–6.12) p<0.001	4.81 (3.87 – 5.97) p<0.001
CAC ≥1000	8.66 (6.79–11.05) p<0.001	6.79 (5.29–8.72) p<0.001	6.99 (5.46– 8.95) p<0.001

Abbreviations: CAC, coronary artery calcification; FRS, Framingham risk score; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III. [3]

Table 4

Net reclassification improvement with the addition of coronary artery calcium scoring to a model including the Framingham Risk Score or National Cholesterol Education Program Adult Treatment Panel III score

	NRI	95% CI	P-Value	%Events correctly reclassified	Event P-Value	%Non-events correctly reclassified	Non-event P-Value
Overall Cohort (n=9715)							
FRS + CAC	0.58966	0.5251–0.6542	<0.0001	29%	<0.0001	30%	<0.0001
NCEP ATPIII + CAC	0.57966	0.5149–0.6444	<0.0001	28%	<0.0001	30%	<0.0001
Low cardiovascular risk							
FRS + CAC	0.52561	0.3961–0.6551	<0.0001	12%	0.07	41%	<0.0001
NCEP ATP III + CAC	0.49967	0.3878–0.6116	<0.0001	13%	0.02	37%	<0.0001
Intermediate cardiovascular risk							
FRS + CAC	0.46417	0.3611–0.5672	<0.0001	23%	<0.0001	23%	<0.0001
NCEP ATP III + CAC	0.51544	0.3955–0.6354	<0.0001	28%	<0.0001	23%	<0.0001
High cardiovascular risk							
FRS + CAC	0.58347	0.4709–0.6961	<0.0001	40%	<0.0001	18%	<0.0001
NCEP ATP III + CAC	0.55956	0.4494–0.6698	<0.0001	37%	<0.0001	19%	<0.0001

Abbreviations: NRI, net reclassification improvement; CAC, coronary artery calcium; FRS, Framingham Risk Score;[23] NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.[3]

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