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Interplay of Coronary Artery Calcium and Traditional Risk Factors for Predicting CVD/CHD Mortality: The Coronary Artery Calcium Consortium

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ABSTRACT

Background: While coronary artery calcium (CAC) is a known predictor of short-term all-cause mortality, there is a paucity of data on long-term and cause-specific outcomes. We sought to evaluate the association and burden of CAC with long-term cause-specific mortality across the spectrum of baseline risk.

Methods: The CAC Consortium cohort is a multi-center cohort of 66,636 individuals free of established coronary heart disease (CHD) who underwent CAC testing. The following RFs were considered: (1) current cigarette smoking, (2) dyslipidemia, (3) diabetes mellitus, (4) hypertension, and (5) family history of coronary heart disease.

Results: During 12 ± 4-year follow-up, 3,158 (4.7%) deaths occurred, and 32% were cardiovascular disease (CVD) deaths. Participants with CAC ≥400 had a significantly increased risk for CHD and CVD mortality (hazard ratios of 5.44 (95% CI: 3.88-7.62) and 4.15 (95% CI: 3.29-5.22) respectively) compared to CAC =0, whereas participants with ≥3 RFs had a smaller increased risk for CHD and CVD mortality (hazard ratios of 2.09 (95% CI: 1.52-2.85) and 1.84 (95% CI: 1.46-2.31) respectively) compared with 0 RF. Across RF strata, CAC added prognostic information. For example, participants with no RF and CAC ≥400 had significantly higher all-cause, non-CVD, CVD, and CHD mortality rates compared with individuals with ≥3 RFs and CAC =0.

Conclusion: Across the spectrum of RF burden, a higher CAC score is strongly associated with long-term all-cause mortality and a greater proportion of deaths due to CVD and CHD. Absence of CAC identifies people with a low risk over 12 years of follow-up, regardless of RF status.

Key words: Coronary artery calcium; risk factors; mortality.

INTRODUCTION

Appropriate risk assessment is a critical first step in risk assessment and subsequent management decisions for cardiovascular disease (CVD) - the leading cause of death in the US and worldwide.[1] Most risk assessment algorithms including the Pooled Cohort Equations atherosclerotic cardiovascular disease (ASCVD) risk algorithm use a traditional risk factor (RF) -based approach to estimate 10-year ASCVD risk to guide preventive pharmacotherapy.[2,3] Despite the value of traditional RFs, and the utility of the Pooled Cohort Equations as a starting point for risk estimation, many high-risk individuals and many low-risk individuals are mischaracterized as low-risk and high-risk respectively by the traditional RF-based algorithms leading to overuse or underuse of preventive strategies.[4–9]

The 2018 AHA/ACC cholesterol guidelines provided a class IIa recommendation for coronary artery calcium (CAC) testing among individuals in whom a risk-based treatment decision is unclear.[3] CAC scans measure atherosclerotic burden in the coronary arteries using routine low-radiation non-contrast cardiac-gated computed tomographic scans. CAC scoring has been proposed as an integrative measure of the life-time cumulative exposure to traditionally measured, non-traditionally measured, and unmeasured risk factors linked to the development of coronary atherosclerosis.[10,11] Prior studies have demonstrated that CAC significantly improves risk prediction above and beyond conventional risk factors (RFs) in time period extending up to an average follow-up of 10 years.[6,12–19]

To date there are few studies that have demonstrated the relationship between traditional RF burden and CAC in predicting ASCVD events and all-cause mortality over 5-10 years of follow-up.[6,13,17] However, none have been sufficiently powered to elucidate the association of presence and higher burden of CAC with cause-specific mortality across the spectrum of baseline risk determined by traditional risk factors over longer-term follow-up. As a result, in this study we aimed to examine the association of CAC on cause-specific mortality across baseline risk and identify the prognostic value of high CAC among individuals who have no reported RFs and CAC =0 among high risk patients in the largest cohort of clinical CAC scoring yet assembled.

METHODS

Study Participants

We used the Coronary Artery Calcium Consortium (CAC Consortium) for this study.[20] The study cohort consisted of 66,636 consecutive asymptomatic individuals free of known coronary heart disease (CHD), referred for non-contrast cardiac-gated CAC testing at 4 different institutions from 3 states in the US (Los Angeles and Torrance, CA; Minneapolis, MN; and Columbus, OH) between 1991 and 2010. Consent for participation in research was collected at the individual centers at the time of CAC scanning, and Institutional Review Board approval for coordinating center activities including death ascertainment was obtained at the Johns Hopkins Hospital. Patients were

determined to be free of coronary heart disease based on patient history and prior evaluation by the referring physician.

Since the study participants were referred by a physician for the assessment of subclinical atherosclerosis, they represent a clinical population rather than a random sample of the general population. Comparison of the CAC Consortium with National Health and Nutrition Examination Survey (NHANES) 2001-2002, Multi-Ethnic Study of Atherosclerosis (MESA), and Framingham Offspring/3rd Generation have been previously published.[20] The CAC Consortium has a higher percentage of males (67%) compared to these other cohorts (44-48%) and a predominantly white population (89%). The prevalence of the traditional CVD risk factors is otherwise similar to MESA except for a mildly higher prevalence of hypertension (45% vs 31%), diabetes (13% vs 7%), and smoking (13% vs 10%) in MESA compared to the CAC Consortium.

Individual patient level data on demographics, cardiovascular risk factors, medications, and symptoms were collected at the clinical visit associated with the referral for CAC testing, from a semi-structured in-person interview at the time of the CAC scan, and/or from established diagnosis recorded in the electronic medical record.[20]

Risk Factor Data Collection

The following risk factors were considered: (1) hypertension was defined as a self-reported or existing medical record diagnosis of

hypertension, or current treatment with anti-hypertensive medication; (2) dyslipidemia was defined as a prior diagnosis of primary hyperlipidemia, prior diagnosis of dyslipidemia (elevated triglycerides and/or low high-density lipoprotein-cholesterol (HDL-C)), treatment with any lipid-lowering drug, or low-density lipoprotein-cholesterol (LDL-C) >160 mg/dL, HDL-C <40 mg/dL in men and <50 mg/dL in women, or fasting triglycerides >150 mg/dL in those with concomitant lipid values; (3) current cigarette smoking was defined as smoking at the time of CAC assessment; (4) diabetes mellitus was defined as a self-reported or existing medical record diagnosis of diabetes or treatment with oral hypoglycemic drugs or insulin; (5) family history of coronary heart disease was predominantly determined by the presence of a first degree relative with a history of CHD, whereas the Columbus, OH site (11% of the study population) used a definition of premature family history (<55 years old in males relative and <65 years old in female relative). Multiple imputation was conducted in the case of partially missing risk factor data using a previously published algorithm.[20] 28% of the cohort had at least one risk factor data missing, all analyses were repeated in the subpopulation with non-missing risk factor information.

Computed Tomography data

Non-contrast cardiac-gated CT scans for CAC scoring were performed at each individual site according to a common standard protocol for each scanner technology. Most patients (approximately 93%) were scanned using electron beam tomography (EBT), while more recent CAC data at two sites

was obtained using multidetector CT (MDCT). Prior studies have demonstrated no clinically meaningful differences between CAC score derived from EBT versus MDCT scanners.[21] In total, approximately 13% of patients were scanned with the Imatron C-100 scanner, 38% with the C-150, 38% with the C-300, and 3.5% with the e-Speed scanner (GE-Imatron). The remaining scans (7%) were performed on a 4-slice MDCT scanner (Somatom Volume Zoom, Siemens Medical Solutions) and the General Electric LightSpeed VCT 64-slice platform (GE Healthcare). CAC was quantified using the Agatston method in all patients.[22]

Follow-up and death ascertainment

Mean follow-up time for the cohort was 12 ± 4 years with maximum follow-up across sites ranging from 13.6 to 22.5 years. Ascertainment of death was conducted by linkage to the Social Security Death Index (SSDI) Death Master File (DMF) using an algorithm previously validated in The FIT Project.[23] Cause of death was obtained via coded death certificates obtained from the National Death Index (NDI). Cause of death was reported as ICD-9 and ICD-10 codes, and grouped as previously described.[20] Internal validation studies against known deaths identified via the electronic medical record revealed >90% specificity for identifying known deaths, with estimated sensitivity of 72-90%. A detailed comparison of death rates in the CAC Consortium with the U.S. Census and MESA has been previously published.[20] The death rate in the CAC Consortium dataset was mildly but systematically lower compared to the white population from the MESA study, however

differences were diminished to -11.7% when limiting to those within income above the poverty level, which maybe more representative of the CAC Consortium. The death rates in the CAC Consortium were lower than the general U.S. White Population, similar to what prior comparisons of research studies and clinical patients to the general unselected population.[23]

Statistical Methods

The baseline characteristics of patients are presented as means ± standard deviation for continuous variables (age) and proportionate frequencies for categorical variables for the entire population and by the prespecified CAC score group (0, 1-100, 100-400 and ≥400).[24] Age was compared across increasing CAC score groups using analysis of variance tests and proportional frequencies of other risk variables were compared across increasing CAC score groups using $\chi 2$ analysis.

Graphical analysis was used to display crude mortality, as well as proportion of deaths due to CHD vs. CVD vs. non-CVD, across RF and CAC score groups. Annualized mortality rates were estimated by dividing the number of all-cause/cause-specific deaths by the total number of person-years at risk. Cumulative hazard analysis was performed using individual subject time-to-all-cause/cause-specific mortality data. The Nelson-Aalen estimator was used to generate the cumulative probability of mortality curves stratified by categories of CAC scores and RFs. Cox proportional hazard regression models, adjusted for age and sex, were used to calculate

hazard ratios and 95% CIs to evaluate the effect of CAC or RF burden on all-cause and cause-specific mortality. Harrell's Concordance statistic (C-statistic) was estimated as a summary measure of risk discrimination. $P<0.05$ was considered statistically significant for all the analyses.

To evaluate the prognostic value of high CAC among low risk patients (no RFs) and CAC =0 among high risk patients (≥3 RFs), annualize mortality rates, and multivariable-adjusted hazard ratios were compared stratified by level of RF burden and CAC score group. In sensitivity analysis, all analyses were performed using only non-imputed risk factor data for comparison. All statistical analyses were performed using STATA version 14 (STATA Corp, College Station, TX).

RESULTS

The mean age of the study population was 54 ± 11 years, and 67 % were men. Overall, 17% of the study population had 0 RF, 36% had 1 RF, 32% had 2 RFs, and the rest 15% had ≥3 RFs. Approximately 45% of the study population had a CAC =0, 31% had a CAC score of 1-100, 13% had a CAC score of 100-400, and 11% had a CAC score of ≥400. The baseline characteristics of the study population by CAC score strata are shown in the Table 1. With increasing CAC strata, the percentage of men, hypertension, diabetes, and dyslipidemia increased. Among individuals with a CAC score 0, 56% were male, 23% were hypertensives, 4% had diabetes, and 48% had

dyslipidemia. The respective prevalence was much higher among individuals with a CAC score ≥400 (84% male, 50% hypertensives, 15% diabetes, and 66% dyslipidemia).

Figure 1 describes the prevalence of CAC according to the burden of RFs. Among the individuals with no RFs, more than half (56%) had CAC =0, while 28%, 10%, and 6% had CAC scores of 1-100, 100-400 and ≥400 respectively. Whereas among ≥3 RFs 30%, 31%, 19%, and 20% had CAC scores of 0, 1-100, 100-400, and ≥400 respectively. The patients were more likely to have higher CAC scores as the number of risk factors increase. Only 6% had a CAC scores ≥400 among no RFs, while 8%, 12%, and 20% had CAC scores ≥400 among 1 RFs, 2 RFs, and ≥3 RFs respectively.

Burden of CAC on all-cause and cause-specific mortality across baseline risk

A total of 3,158 (4.74%) deaths were recorded in the total study population over a median (interquartile range) follow up of 12.5 (10.6 to 14.1) years. A total of 971 deaths (31%) were secondary to CVD and 524 (16%) of those were due to CHD. Table 2 depicts the annualized all-cause and cause-specific mortality rate with increasing RF burden and CAC score group. The annualized all-cause mortality rate was 1.61 (95% CI, 1.49-1.74) death per 1000 person-years for those with CAC =0 as compared with 3.10 (95% CI, 2.88-3.31), 6.24 (95% CI, 5.79-6.73), and 13.16 (95% CI, 12.40-13.96) deaths per 1000 person-years among those with CAC scores of 1-100,

100-400, and ≥400, respectively (an 8-fold increase in the annualized all-cause mortality rate among individuals with a CAC score of ≥400 as compared to individuals with CAC =0).

A 16-fold increase in the annualized CVD mortality rate and a 24-fold increase in the annualized CHD mortality rate among individuals with a CAC score of ≥400 as compared with individuals with CAC =0. The annualized CVD mortality rate was 0.33 (95% CI, 0.27-0.39) death per 1000 person-years for those with CAC =0 as compared to 0.77 (95% CI, 0.67-0.89), 2.01 (95% CI, 1.76-2.29), and 5.22 (95% CI, 4.75-5.74) deaths per 1000 person-years among those with CAC scores of 1-100, 100-400, and ≥400, respectively. The annualized CHD mortality rate was 0.14 (95% CI, 0.10-0.18) death per 1000 person-years for those with CAC =0 as compared to 0.35 (95% CI, 0.29-0.43), 1.08 (95% CI, 0.91-1.30), and 3.19 (95% CI, 2.83-3.60) deaths per 1000 person-years among those with CAC scores of 1-100, 100-400, and ≥400, respectively.

Whereas, the annualized all-cause mortality rate per 1000 person-years was 2.8 (95% CI, 2.54-3.09) among individuals with 0 RFs as compared with 3.20 (95% CI, 3.00-3.41), 3.97 (95% CI, 3.74-4.22), and 6.60 (95% CI, 6.11-7.04) deaths per 1000 person-years among those with 1, 2, and ≥3 RFs, respectively. A 2-3-fold increase in the annualized all-cause mortality rate and 3-4-fold CVD/CHD mortality rate was seen among individuals with ≥3 RFs as compared with those with 0RFs (table 2).

Table 3 provides the hazard ratios for all-cause and cause-specific mortality with increasing RF burden and CAC scores group. The hazard ratios for all-cause mortality were 1.41-fold increased, and cause-specific mortality were 1.84-fold (CVD mortality) and 2.09-fold (CHD mortality) increased for ≥3 RFs when compared to no RF after adjusting for age, sex, and CAC scores. There was no statistically significant difference in hazards ratios among individuals with 1 or 2 RF when compared to no RF, the hazard ratios were 1.23 to 2.47-fold for all-cause mortality, 1.43 to 4.15-fold for CVD mortality, and 1.47 to 5.44-fold for CHD mortality with increasing CAC scores after adjusting for age, sex and RF burden.

Addition of CAC to models containing age, sex, and RFs for predicting all-cause and cause-specific mortality resulted in a significant improvement in C-statistic, from 0.78 to 0.79 for all-cause, 0.81 to 0.83 for CVD, and 0.83 to 0.85 for CHD mortality respectively.

Prognostic value of high CAC among low risk individuals and CAC =0 among high risk individuals

Figure 2 and Table 4 show the annualized mortality rate with increasing CAC scores according to the burden of traditional risk factors. We observed the lowest all-cause and cause-specific mortality rates among individuals with no RFs and no CAC, while the group of individuals with a CAC score of ≥400 and ≥3 RFs had the highest all-cause and cause-specific mortality rates. Notably, individuals with no RF and CAC score of ≥400 had a

high CVD mortality rate of 4.65 deaths per 1000 person-years as compared to 0.56 deaths per 1000 person-years among individuals with ≥3 RFs and absent CAC. Individuals with no RF and CAC score of ≥400 also had a high CHD mortality rate of 2.45 deaths per 1000 person-years as compared to 0.22 deaths per 1000 person-years among individuals with ≥3 RFs and absent CAC. Similarly, individuals with no RF and CAC score of ≥400 had a high all-cause mortality rate of 11.50 deaths per 1000 person-years as compared to 2.25 deaths per 1000 person-years among individuals with ≥3 RFs and absent CAC.

Figures 3-4 depict the absolute percentage and proportion of all deaths attributable to specific causes (non-CVD, CHD, and non-CHD CVD) mortality. As shown in Figure 3b, across all the risk factor groups the proportion of deaths due to CHD/CVD increased significantly across the CAC score groups (Proportion of CHD mortality was 7%-10% among CAC =0 vs 21%-29% among CAC ≥400), and the non-CVD proportion decreased significantly. Among individuals with ≥3 RFs and a CAC =0, 75% of the deaths are caused due to non-CVD causes. On contrary, there was a less pronounced increase seen in the CHD/CVD mortality with increase in the RFs burden with in each CAC score group (as seen in Figure 4: among individuals with CAC =0, the CHD mortality was 7% among 0 RF vs 10% among ≥3 RFs). Supplemental Figures 1-4 show increased all-cause, non-CVD, CVD, and CHD cumulative hazard curves with increasing CAC scores at each level of baseline RF burden. Among those with CAC =0 at baseline (n=29,757), all-cause

cumulative mortality estimated at 20 years was under 3.5%, CVD cumulative hazards was under 0.8%, and CHD cumulative hazards was under 0.3% regardless of risk factor burden (Supplemental Figure 5).

Further analysis of hazard ratios for mortality of CAC score stratified by underlying RF burden after adjusting for age and sex showed that participants with CAC ≥400 had a 1.84 to 3.2-fold higher risk of all-cause mortality across increasing number of risk factors compared to those with CAC =0 and 1.6 to 2.6-fold for non-CVD mortality. While the hazard ratios for CVD and CHD mortality were 3.2 to 5.1 and 3.8 to 8.7-fold higher in CAC ≥400 when compared to CAC =0 across increasing risk factors (Table 5). By comparison, Cox regression analyses adjusted for age and sex, only ≥3 RFs were associated with a higher hazard ratio of all-cause, CVD or CHD mortality when compared to 0 RF among individuals with a positive CAC score, while no such higher risk was observed among individuals with no CAC (Table 6).

In sensitivity analyses, adjustment for the study site did not change the results, and additional analyses showed identical conclusions when only the non-imputed dataset was used.

DISCUSSION

In this large multi-center cohort of 66,636 asymptomatic individuals we have demonstrated that CAC predicts all-cause, CVD, and CHD mortality better across the spectrum of traditional risk factors over a median follow-up

of 12 years. Our study determined that there is a significant heterogeneity in subclinical coronary atherosclerosis across increasing RFs. At each baseline risk level, the CAC score is associated with the all-cause, CVD, and CHD mortality rates. Moreover, the absence of CAC projected extremely low mortality rates in follow-up duration extending beyond 12 years. Our study adds to the current literature in many ways. This is by far largest study, one of the few studies, to our knowledge, which documented CVD and CHD mortality, which may be considered more relevant outcomes to assess risk prediction with CAC as compared with all-cause mortality. Building upon prior mortality studies, the even stronger association of CAC with CVD/CHD mortality when compared with all-cause mortality, further challenges the exclusive use of traditional risk factors in the assessment of cardiovascular risk to determine the intensity of primary prevention strategies.

Absence of Traditional CVD Risk Factors and Elevated CAC

Prior studies have described significant heterogeneity in CAC burden and subsequent risk for adverse cardiovascular event and all-cause mortality risk among those without established ASCVD. Nasir et al,[13] in a retrospective study of the predominantly white and middle-aged asymptomatic individuals referred for CAC scanning for the assessment of subclinical atherosclerosis, demonstrated 43% of the participants to be at low-risk due to absence of any underlying traditional risk factors and within this subgroup, 48% had a detectable CAC and 6% had a CAC >400. They have also depicted, among these low-risk individuals, those with a detectable CAC were at a higher risk

for mortality, and an incremental risk with increasing CAC score. These findings were validated by Silverman et al[6] in the prospective Multi-Ethnic Study of Atherosclerosis (MESA), where 32% of those without any underlying traditional risk factors had CAC >0, 5% had a very high CAC of greater than 300. Kaposi et al.[25], in a meta-analysis of 5 population based studies showed that among asymptomatic low-risk women (10-years ASCVD <7.5 %), CAC was present in 36%. They demonstrated that individuals with a CAC score of 1-100 had a higher annual mortality rate when compare to those without CAC, 3.07 vs 1.41 per 1000 person-years, while those with a CAC >100 had 9.68 events per 1000 person-years.

The results from our study are consistent with these prior studies and, by virtue of study size, able to extend by providing cause-specific mortality information over a longer follow-up time in the cohort of clinical CAC scoring yet assembled. Approximately 17% (11,428) of the participants in our cohort had no RF, and among them, 44% had a detectable score and 6% had a CAC of ≥400. We have also found the individuals with a positive CAC had a higher annual all-cause and CVD/CHD mortality rate as compared to those without CAC. Importantly, our study findings also demonstrated a significantly elevated CHD mortality rate of 2.45 deaths per 1000 person-years among CAC ≥400 subgroup with no RF, which is nearly 7-fold greater than that of all individuals with no RF (0.37 per 1000 person-years).

High Burden of Traditional Risk Factors and CAC =0

While high CAC scores can be useful in identifying high-risk individuals among those with no RF, equally important is the fact that the absence of CAC confers a low risk for future CVD events and mortality across the range of RF burden. A favorable prognosis of CAC =0 (power of zero) has been established by a low short-term CVD and all-cause mortality seen in a meta-analysis,[26] large prospective study,[27] and a multiethnic prospective study[28] over a follow-up extending up to 5 years. The power of zero was further validated by Blaha et al,[29] who showed that nearly half of the individuals meeting eligibility for statin therapy based on Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) criteria had no CAC and experienced an extremely low event rate, with an unfavorable estimated number needed to treat for 5 years of 549 to prevent 1 CHD event compared with 42 among those with the presence of CAC. Silverman et al[6] and Nasir et al[13] have demonstrated a lower event rate among individuals with CAC =0 across RF burden.

Our results are consistent with the prior studies demonstrating a very low all-cause mortality rate among individuals with CAC =0. In addition, our study adds to the current literature by highlighting that majority of deaths (80%) in a long-term follow-up among those with CAC =0 are a result of non-CVD causes and therefore resulting in extremely low CVD and CHD mortality rates. Our results also exhibited a much lower CHD death rate of 0.22 deaths per 1000 person-years among CAC =0 group with ≥3 RFs as compared to 0.70 CHD deaths per 1000 person-years among individuals with no RF but

any CAC. These findings are extremely reassuring for a favorable cardiovascular prognosis, irrespective of underlying traditional risk factor burden even in longer term follow-up, among whom more flexible treatment goals may be pursued with a focus on lifestyle interventions and potentially deferring the use of costly pharmacotherapy or subsequent imaging tests.[30] Such a strategy could enable focus on individuals who are indeed at a high risk to develop disease instead on those who may have been misclassified as high risk by RF burden alone, as truly high-risk individuals are most likely to benefit from more aggressive preventive therapies.

STRENGTHS and LIMITATIONS:

Strengths of the study include cause-specific mortality data and long duration of follow-up. This is the first study to our knowledge which assessed the interplay of CAC and risk factors with CVD and CHD mortality as the end points over a median follow-up of 12 years. While earlier studies only reported all-cause mortality, CVD/CHD mortality data are more relevant outcomes for clinical cardiovascular risk prediction to help guide prevent CVD therapies as opposed to all-cause/non-CVD mortality.

Our study has a few limitations. There is a potential for referral bias and the study sample does not represent a random sample of the population, since all the participants in the study were referred by a physician for CAC scanning based on clinical factors. We do not have data on incidental

findings or subsequent treatment of patients after CAC scoring, which may impact the natural history of the CHD and CVD. However, treatment of higher risk patients with preventive medications would tend to bias our prognostic results toward the null. Due to limitation inherent in vital status ascertainment in the United States, the CAC Consortium may underestimate mortality by up to 30%, although this would be non-differential across CAC/RF groups. Another potential weakness includes recall bias from self-reporting of risk factors information. However Hoff et al[31] have shown a good reliability of self-reported histories of CHD risk factors in self-referred individuals for EBCT screening, however because the CHD risk factors were self-reported as binary variables, the potential residual confounding cannot be ruled out, thus possibly diminishing the strength of association of risk factors with mortality.

CONCLUSION

In summary, our study adds to the current literature the value of CAC testing in a larger cohort of individuals over a longer follow-up time by demonstrating a significantly higher incremental risk especially for CVD and CHD mortality with increasing CAC scores. Our study also underscore data 'power of zero' with majority of deaths non-CVD in nature in this extended follow-up in absence of CAC. Whether the proposed paradigm shift in CVD risk assessment and subsequent management decisions based on CAC

detection for risk prediction for targeted risk factor modification will result in more appropriate allocation of resources and improve outcomes need to be addressed in future randomized studies.

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Figures

Figure 1.

Title: Prevalence of CAC Score Groups According to the Burden of RF in CAC Consortium.

Legend:
Abbreviations: CAC, coronary artery calcium; RF, risk factors.

Figure 2.

Title: Mortality Rate with Increasing CAC Scores According to the Burden of RF in CAC Consortium.

Legend: mortality rate expressed as per 1000-person years.
Abbreviations: CAC, coronary artery calcium; RF, risk factors.

Figure 3a.

Title: Cause-Specific Percentage Mortality of Individuals with Increasing CAC Score According to the Burden of RF in CAC Consortium.

Legend:
Abbreviations: CAC, coronary artery calcium; RF, risk factors.

Figure 3b.

Title: Proportion of Cause-Specific Mortality with Increasing CAC Score According to the Burden of RF in CAC Consortium.

Legend:

Abbreviations: CAC, coronary artery calcium; RF, risk factors.

Figure 4.

Title: Cause-Specific Percentage Mortality of Individuals with CAC =0 According to the Burden of RF in CAC Consortium.

Legend: the proportion of each type mortality is given within each bar.
Abbreviations: CAC, coronary artery calcium; RF, risk factors.

Supplemental Figures

Supplemental Figure 1.

Title: Nelson-Aalen All-cause Cumulative Hazard Curves by CAC Scores across Increasing RF Burden in CAC Consortium.

Legend:
Abbreviations: CAC, coronary artery calcium; RF, risk factors.

Supplemental Figure 2.

Title: Nelson-Aalen Non-CVD Cumulative Hazard Curves by CAC Scores across Increasing RF Burden in CAC Consortium.

Legend:
Abbreviations: CAC, coronary artery calcium; CVD, cardiovascular disease; RF, risk factors.

S**upplemental Figure 3.**

Title: Nelson-Aalen CVD Cumulative Hazard Curves by CAC Scores across Increasing RF Burden in CAC Consortium.

Legend:
Abbreviations: CAC, coronary artery calcium; CVD, cardiovascular disease; RF, risk factors.

S**upplemental Figure 4.**

Title: Nelson-Aalen CHD Cumulative Hazard Curves by CAC Scores across Increasing RF Burden in CAC Consortium.

Legend:
Abbreviations: CAC, coronary artery calcium; CHD, coronary heart disease; RF, risk factors.

S**upplemental Figure 1.**

Title: Nelson-Aalen Cumulative Hazard Curves by RF Burden Among Individuals with CAC =0 (n=29,575) in CAC Consortium.

Legend:
Abbreviations: CAC, coronary artery calcium; RF, risk factors.

Tables

Table 1. Baseline Characteristics of Study Population by CAC Score Group in CAC Consortium

	Total population 66,636	CAC =0 29,757 (45%)	CAC 1-100 20,534 (31%)	CAC 100-400 9,067 (13%)	CAC ≥400 7,278 (11%)
Age, years	54 ± 11	50 ± 9.2	55 ± 9.5	60 ± 9.5	64 ± 9.7
Sex: Men (%)	67	56	73	78	84
Hypertension (%)	31	23	32	40	50
Dyslipidemia (%)	54	48	57	61	66
Diabetes mellitus (%)	7	4	7	10	15
Current smoking (%)	10	9	10	11	11
Family history of CHD (%)	46	46	46	46	47
CAC score	164 ± 480 (n=42,964)	0 (n=19,087)	28 ± 27 (n=13,221)	211 ± 84 (n=5,935)	1156 ± 976 (n=4,721)
Race					
White (%)	89	89	89	90	89.5
Asian (%)	4	4	3.5	3	3.5
Black (%)	2	2	2.5	2	2
Hispanic (%)	3	3	3	2.5	3
Others (%)	2	2	2	1.5	2

Continuous variable, mean ± SD; Categorical variable (%);
CAC, coronary artery calcium; CHD, coronary heart disease

Table 2. Mortality Rate with Increasing RF Burden and Increasing CAC Scores in CAC Consortium

	All-Cause Mortality	Non-CVD Mortality	CVD Mortality	CHD Mortality
	MR (95% CI)	MR (95% CI)	MR (95% CI)	MR (95% CI)
RF burden				
0 RF	2.80 (2.54-3.09)	2.08 (1.86-2.33)	0.72 (0.59-0.87)	0.37 (0.28-0.48)
1 RF	3.20 (3.00-341)	2.29 (2.13-2.47)	0.90 (0.80-1.02)	0.47 (0.40-0.55)
2 RF	3.97 (3.73-4.22)	2.79 (2.60-3.00)	1.18 (1.05-1.32)	0.60 (0.52-0.71)
≥3 RF	6.60 (6.11-7.04)	4.08 (3.73-4.46)	2.48 (2.21-2.78)	1.48 (1.27-1.71)
CAC scores				
CAC =0	1.61 (1.49-1.74)	1.28 (1.17-1.40)	0.33 (0.27-0.39)	0.14 (0.10-0.18)
CAC 1-100	3.09 (2.88-3.31)	2.31 (2.14-2.51)	0.77 (0.67-0.89)	0.35 (0.29-0.43)
CAC 100-400	6.24 (5.79-6.73)	4.24 (3.87-4.64)	2.01 (1.76-2.29)	1.08 (0.91-1.30)
CAC ≥400	13.16 (12.40-13.96)	7.93 (7.35-8.56)	5.22 (4.75-5.74)	3.19 (2.83-3.60)

RF, risk factors; CAC, coronary artery calcium; MR, mortality rate (per 1000 person-years); CI, confidence interval

CHD, coronary heart disease; CVD, cardiovascular diseases

Table 3. Hazard Ratio for Mortality with Increasing RF Burden and Increasing CAC Scores in CAC Consortium

	All-Cause Mortality	Non-CVD Mortality	CVD Mortality	CHD Mortality
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
RF burden*				
1 RF vs 0 RF	1.02 (0.91-1.15)	1.00 (0.87-1.15)	1.10 (0.87-1.37)	1.10 (0.80-1.52)
2 RF vs 0 RF	1.09 (0.97-1.23)	1.06 (0.93-1.22)	1.18 (0.94-1.47)	1.16 (0.85-1.59)
≥3 RF vs 0 RF	1.41 (1.25-1.60)	1.25 (1.08-1.45)	1.84 (1.46-2.31)	2.09 (1.52-2.85)
CAC scores†				
CAC 1-100 vs 0	1.23 (1.10-1.37)	1.18 (1.05-1.34)	1.43 (1.13-1.80)	1.47 (1.04-2.09)
CAC 100-400 vs 0	1.65 (1.46-1.85)	1.47 (1.28-1.69)	2.34 (1.85-2.97)	2.82 (1.99-3.98)
CAC ≥400 vs 0	2.47 (2.20-2.78)	2.00 (1.74-2.30)	4.15 (3.29-5.22)	5.44 (3.88-7.62)

RF, risk factors; CAC, coronary artery calcium; HR, hazard ratio; CI, confidence interval
CVD, cardiovascular diseases; CHD, coronary heart disease

* Model adjusted for age, sex, and CAC scores

† Model adjusted for age, sex, and RF burden

Table 4. Mortality Rate with Increasing CAC Score across Increasing RF Burden in CAC Consortium

	0 RF	1 RF	2 RF	≥3 RF
	MR (95% CI)	MR (95% CI)	MR (95% CI)	MR (95% CI)
All-cause mortality				
CAC =0	1.42 (1.18-1.71)	1.52 (1.33-1.73)	1.65 (1.42-1.91)	2.25 (1.82-2.80)
CAC 1-100	2.66 (2.20-3.21)	2.80 (2.48-3.17)	3.16(2.80-3.56)	4.08 (3.49-4.77)
CAC 101-400	5.93 (4.78-7.35)	5.79 (5.06-6.63)	5.91 (5.18-6.74)	7.79 (6.70-9.04)
CAC ≥400	11.50 (9.39-14.07)	11.25 (9.96-12.71)	12.11 (10.93-13.41)	17.39 (15.69-19.26)
Non-CVD mortality				
CAC =0	1.18 (0.96-1.44)	1.24 (1.07-1.44)	1.27 (1.07-1.50)	1.69 (1.32-2.17)
CAC 1-100	2.12 (1.84-2.43)	2.11 (1.84-2.43)	2.37 (2.06-2.72)	2.89 (2.40-3.48)
CAC 101-400	4.28 (3.33-5.52)	4.16 (3.55-4.88)	4.15 (3.55-4.85)	4.49 (3.68-5.47)
CAC ≥400	6.85 (5.27-8.90)	6.67 (5.70-7.82)	7.71 (6.79-8.76)	10.04 (8.78-11.49)
CVD mortality				
CAC =0	0.24 (0.20-0.38)	0.28 (0.20-0.38)	0.38 (0.28-0.51)	0.56 (0.37-0.87)
CAC 1-100	0.54 (0.36-0.82)	0.69 (0.54-0.88)	0.79 (0.62-1.00)	1.20 (0.90-1.60)
CAC 101-400	1.64 (1.09-2.47)	1.63 (1.26-2.10)	1.76 (1.38-2.23)	3.30 (2.62-4.15)
CAC ≥400	4.65 (3.38-6.39)	4.58 (3.78-5.55)	4.40 (3,71-5.21)	7.34 (6.27-8.59)
CHD mortality				
CAC =0	0.10 (0.05-0.20)	0.13 (0.08-0.21)	0.15 (0.90-0.24)	0.22 (0.11-0.43)
CAC 1-100	0.22 (0.12-0.43)	0.33 (0.23-0.47)	0.37 (0.26-0.52)	0.52 (0.34-0.81)
CAC 101-400	1.07 (0.65-1.78)	0.77 (0.53-1.12)	0.90 (0.65-1.27)	1.92 (1.42-2.60)
CAC ≥400	2.45 (1.58-3.79)	2.70 (2.11-3.47)	2.53 (0.02-3.16)	4.97 (4.11-6.02)

CAC, coronary artery calcium; RF, risk factors; MR, mortality rate (per 1000 person-years); CI, confidence interval

CVD, cardiovascular diseases; CHD, coronary heart disease

Table 5. Hazard ratio* for mortality with increasing CAC score across increasing RF burden in CAC Consortium

	0 RF n=11,428(17%)	1 RF n=23,726 (36%)	2 RF n=21,276 (32%)	≥3 RF n=10,206 (15%)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
All-cause mortality, n (%)	397 (3.47%)	945 (3.98%)	1038 (4.88 %)	778 (7.62%)
CAC 1-100 vs 0	1.06 (0.80-1.40)	1.15 (0.96-1.39)	1.31 (1.08-1.59)	1.32 (1.01-1.73)
CAC 100-400 vs 0	1.45 (1.05-1.98)	1.59 (1.29-1.95)	1.61 (1.31-1.99)	1.88 (1.44-2.47)
CAC ≥400 vs 0	1.84 (1.32-2.56)	2.18 (1.76-2.69)	2.45 (1.99-3.01)	3.25 (2.51-4.23)
Non-CVD mortality, n (%)	295 (2.58%)	678 (2.86%)	730 (3.43%)	484 (4.74%)
CAC 1-100 vs 0	1.03 (0.75-1.40)	1.08 (0.87-1.34)	1.31 (1.05-1.64)	1.27 (0.93-1.73)
CAC 100-400 vs 0	1.28 (0.89-1.84)	1.44 (1.14-1.83)	1.59 (1.22-1.99)	1.49 (1.07-2.08)
CAC ≥400 vs 0	1.35 (0.91-2.01)	1.65 (1.28-2.13)	2.20 (1.73-2.81)	2.62 (1.91-3.58)
CVD mortality, n (%)	102 (0.89%)	267 (1.13%)	308 (1.45%)	294 (2.88%)
CAC 1-100 vs 0	1.23 (0.65-2.33)	1.48 (0.99-2.23)	1.32 (0.89-1.96)	1.52 (0.90-2.55)
CAC 100-400 vs 0	2.24 (1.15-4.38)	2.27 (1.47-3.48)	1.82 (1.20-2.74)	3.04 (1.84-5.02)
CAC ≥400 vs 0	4.07 (2.10-7.90)	4.33 (2.84-6.61)	3.16 (2.13-4.71)	5.11 (3.13-8.34)
CHD mortality, n (%)	53 (0.46%)	139 (0.59%)	158 (0.74%)	175 (1.71%)
CAC 1-100 vs 0	1.03 (0.38-2.75)	1.40 (0.78-2.52)	1.51 (0.82-2.79	1.70 (0.74-3.87)
CAC 100-400 vs 0	2.80 (1.10-7.17)	2.05 (1.10-3.80)	2.32 (1.24-4.32)	4.53 (2.09-9.81)
CAC ≥400 vs 0	3.83 (1.46-10.04)	4.66 (2.58-8.42)	4.39 (2.41-8.02)	8.66 (4.06-18.44)

CAC, coronary artery calcium; RF, risk factors; HR hazard ratio; CI, confidence interval
CVD, cardiovascular diseases; CHD, coronary heart disease
* Model adjusted for age and sex

Table 6. Hazard ratio* for mortality with increasing RF burden across increasing CAC score in CAC Consortium

	CAC=0 n=29,757 (44%)	CAC 1-100 n=20,534 (31%)	CAC 100-400 n=9,067 (13%)	CAC ≥400 n=7,278 (11%)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
All-cause mortality, n (%)	595 (2.00%)	790 (3.85%)	685 (7.55%)	1,088 (14.95%)
1 RF vs 0	1.03 (0.82-1.30)	1.04 (0.83-1.30)	1.00 (0.78-1.29)	1.02 (0.80-1.29)
2 RFs vs 0	1.05 (0.83-1.33)	1.18 (0.94-1.47)	1.01 (0.78-1.30)	1.12 (0.90-1.41)
≥3 RFs vs 0	1.30 (0.98-1.73)	1.39 (1.09-1.78)	1.28 (0.98-1.67)	1.52 (1.21-1.91)
Non-CVD mortality, n (%)	474 (1.59%)	592 (2.88%)	465 (5.13%)	656 (9.01%)
1 RF vs 0	1.02 (0.79-1.31)	0.98 (0.76-1.27)	1.00 (0.74-1.34)	1.01 (0.75-1.37)
2 RFs vs 0	0.97 (0.75-1.27)	1.10 (0.85-1.42)	1.00 (0.73-1.33)	1.20 (0.89-1.60)
≥3 RFs vs 0	1.17 (0.85-1.62)	1.22 (0.92-1.62)	1.03 (0.75-1.43)	1.48 (1.10-1.99)
CVD mortality, n (%)	121 (0.41%)	198 (0.96%)	220 (2.43%)	432 (5.94%)
1 RF vs 0	1.10 (0.64-1.90)	1.27 (0.78-2.06)	1.01 (0.63-1.64)	1.03 (0.71-1.49)
2 RFs vs 0	1.44 (0.83-2.48)	1.48 (0.92-2.41)	1.07 (0.66-1.72)	1.01 (0.71-1.45)
≥3 RFs vs 0	1.94 (1.04-3.62)	2.07 (1.24-3.45)	1.92 (1.19-3.08)	1.58 (1.11-2.26)
CHD mortality, n (%)	51 (0.17%)	90 (0.44%)	119 (1.31%)	264 (3.63%)
1 RF vs 0	1.22 (0.53-2.79)	1.50 (0.71-3.16)	0.74 (0.40-1.39)	1.15 (0.70-1.91)
2 RFs vs 0	1.29 (0.55-3.03)	1.74 (0.83-3.67)	0.87 (0.47-1.60)	1.11 (0.68-1.82)
≥3 RFs vs 0	1.66 (0.62-4.45)	2.33 (1.06-5.13)	1.81 (1.00-3.29)	2.10 (1.30-3.40)

RF, risk factors; CAC, coronary artery calcium; HR, hazard ratio; CI, confidence interval
CVD, cardiovascular diseases; CHD, coronary heart disease
* Model adjusted for age and sex