Interplay of Coronary Artery Calcification and Traditional Risk Factors for the Prediction of All-Cause Mortality in Asymptomatic Individuals

Nasir et al: Mortality Across Risk Factors and CAC

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Abstract

Background—Current guidelines recommend the use of coronary artery calcium (CAC) scoring for intermediate risk patients, however potential role of CAC among individuals who have no risk factors is less established. We sought to examine the relationship between the presence and burden of traditional risk factors (RF) and CAC for the prediction of all-cause mortality.

Methods and Results—The study cohort consisted of 44,052 consecutive asymptomatic individuals free of known coronary heart disease referred for computed tomography (CT) for the assessment of CAC. The following risk factors were considered 1) current cigarette smoking, 2) dyslipidemia, 3) diabetes mellitus, 4) hypertension, and 5) family history of CHD. Patients were followed for a mean of 5.6 ± 2.6 years for the primary endpoint of all-cause mortality. Among individuals who had no RF, age and gender adjusted cox proportional model identified that increasing CAC scores were associated with 3.00-13.38-fold higher mortality risk. The lowest survival rate was observed in those with no CAC and no RF, whereas those with CAC≥400 and ≥3RF had the highest all-cause fatality rate. Notably, individuals with no RF and CAC≥400 had a substantially higher mortality rate compared to individuals with ≥3RF in absence of CAC (16.89 vs. 2.72 per 1000 person years).

Conclusions—By highlighting that individuals without risk factors but elevated CAC have a substantially higher event rates than those that have multiple risk factors but no CAC, these findings challenge the exclusive use of traditional risk assessment algorithms for guiding the intensity of primary prevention therapies.

Key Words: coronary artery calcium, risk factors, outcome, mortality
Coronary heart disease is the leading cause of death in most developed countries, including the United States. Traditionally, a risk factor-based approach has been used to identify individuals at increased risk for coronary events. For example, the Framingham Risk Score, Adult Treatment Panel III, QRISK and other algorithms have been designed to facilitate clinical risk assessment based on the presence or absence of the “traditional” risk factors\textsuperscript{1-5}. Despite these valuable tools, many high risk individuals are not identified by traditional risk factor-based algorithms\textsuperscript{6-10}.

Measurement of coronary artery calcium (CAC) by cardiac computed tomography (CT) is a noninvasive method of quantifying the burden of coronary atherosclerosis that has been proposed as a tool to enhance traditional methods for risk stratification. Studies have demonstrated that CAC improves risk prediction beyond that of conventional risk factor based algorithms\textsuperscript{11-19} and guidelines now recommend the use of CAC for select low-intermediate risk individuals.\textsuperscript{20,21} However the frequency of high CAC burden as well its prognostic value among very low risk individuals (i.e, without any known risk factors) is unclear. In addition, outcomes of low risk individuals with CAC compared to those considered to have high risk by traditional algorithms has not been reported. Therefore, in this study we sought to examine the interplay between traditional risk factors and CAC for the prediction of mortality in a large asymptomatic cohort to: (a) identify the prognostic value of CAC among individuals who have no reported risk factors; (b) compare the risk of individuals with no risk factors who have CAC with those that have multiple risk factors but no CAC.
Methods

The study cohort consisted of 44,052 consecutive asymptomatic individuals free of known coronary heart disease referred for electron beam tomography (EBT) for the assessment of subclinical atherosclerosis at three different centers in US (Nashville TN, Columbus OH, and Torrance, CA) from 1991 to 2004. Patients were determined to be free of coronary heart disease based on patient history and prior work-up conducted by the referring physician. The combined population was predominantly white and middle-aged.

Study participants were referred by their primary physicians for the assessments of subclinical atherosclerosis and, as such, do not represent a random sample of the general population. All screened individuals provided informed consent to undergo EBT and for the use of their blinded data for epidemiologic research. The general study received approval from the Human Investigations Committee, and separate Committee approval was obtained for the patient interviews, collection of baseline and follow-up data, and corroboration of the occurrence of death. The methods have been previously described in detail.²²

Risk Factor Data Collection

All study participants were given a questionnaire for the collection of demographic and clinical characteristics as well as baseline cardiovascular risk factors. The following risk factors were considered: 1) Current cigarette smoking was considered present if a subject was a smoker at the time of scanning. 2) Dyslipidemia was considered to be present for any individual reporting a history of high total cholesterol, high LDL-cholesterol, low HDL-cholesterol, and/or high triglycerides, or current use of lipid-lowering therapy. 3) Diabetes was defined as the use of oral anti-diabetes medications or insulin. 4) Hypertension was defined as a self-reported history
of high blood pressure or use of antihypertensive medication. 5) Family history of premature CHD was determined by asking patients whether any member of their immediate family (parents or siblings) had a history of fatal or nonfatal myocardial infarction and/or coronary revascularization. Family history of premature CHD was determined by asking patients whether any member of their immediate family (parents or siblings) had a history of fatal or nonfatal myocardial infarction and/or coronary revascularization. In 36,010 (82% of the study population) a premature history of CHD was defined if such events occurred before the age of 55 in male relatives or before the age of 65 in female relatives. In 8,042 (18% of the study population), a premature history of CHD was defined if such events occurred before the age of 55 years for both male and female relatives.

**EBT Screening Protocol**

All subjects underwent EBT on either a C-100 or C-150 Ultrafast computed tomography scanner (GE-Imatron, South San Francisco, CA). Using 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 using a 100 ms/slice scanning time, with image acquisition electrocardiographically triggered at 60% – 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.23.

**Follow-up and Mortality Ascertainment**

Patients were followed for a mean of 5.6 ± 2.6 years (median 5 years, range 1 – 13 years). Ascertainment of mortality was conducted by individuals blinded to baseline historical data and
EBT results. The occurrence of death was verified using the Social Security Death Index. A full Social Security Death Index search was successfully completed in 100% of patients.

**Statistical Methods**

The baseline characteristics of the study population are presented by pre-specified CAC group (0, 1-100, 101-400 and >400) and in aggregate for the entire study population. Age is presented as a continuous measure ± SD and other risk variables are expressed as proportional frequencies. Age was compared across increasing CAC groups using analysis of variance techniques, and proportional frequencies of other risk variables were compared across increasing CAC groups using chi-square analysis. A p-value <0.05 was considered statistically significant.

Annualized all-cause mortality rates were estimated by dividing the number of deaths by the number of person-years at risk. In addition, survival analysis was conducted using individual subject time-to-all-cause mortality data. Curves representing the cumulative probability of survival were generated using Kaplan-Meier estimates stratified by categories of increasing CAC as well as by increasing number of RF. The logrank test was used to compare for differences in survival between subgroups. In order to evaluate the effect of CAC or RF burden on all-cause mortality, hazard ratios and 95% confidence intervals were calculated using the Cox proportional hazards regression model, adjusted for age and gender.

We computed receiver-operating characteristic curves (ROC) and tested for equality of the areas under the curves (AUC) to examine whether CAC added incremental predictive value over a baseline model which included age, gender, and risk factors. In a similar fashion we also assessed if increasing number of risk factors and age/gender would add predictive incremental predictive value once CAC was taken into account. In addition, in order to further evaluate the
potential incremental value of using CAC over risk factors and age/gender, the net reclassification improvement (NRI) was calculated by the method previously described by Pencina et al. Since an underlying assumption of this statistic is that individuals in different risk groups are managed differently, the following risk categories were used: (a) Risk factors model – low risk: no RF, intermediate risk: 1-2 RF, high risk: ≥ 2 RF; (b) CAC model – low risk: CAC=0, intermediate risk: CAC 1-100, high risk: CAC>100. When applied to our analysis, the NRI thus estimates the extent to which persons that died were appropriately reclassified up (or inappropriately classified down) as well those who survived were appropriately reclassified down (or inappropriately classified up). All statistical analyses were performed using Stata version 10 (STATA Corp, College Station, TX).

Results

The clinical characteristics of the 44,052 subjects are shown in Table 1. The mean age of the study population was 54±10 years, and 54% were men. More than one third (43%, n=18,819) of the subjects reported no RF. A total of 19,898 patients (45%) had no CAC on screening EBT, whereas 14,181 (32%) had CAC scores of 1-100, 5,739 (13%) had CAC scores of 101-400, and 4,234 (10%) had CAC>400. As shown in Figure 1, more than half of individuals with no RF had CAC=0 (53%), whereas those with RF were less likely to demonstrate CAC=0. Coronary artery calcium scores of 1-100, 101–400, and >400 were seen in 32%, 10% and 6% individuals with no RF. In comparison, the respective prevalence was 32%, 19% and 17% among those with ≥3 RF.

Overall, there were 901 deaths (2.05%) in the total study population over a mean follow-up of 5.6 ± 2.6 years (median 5.0 years, range 1-13 years). The annualized mortality rate was
1.84 deaths per 1000 person-years (95% CI: 1.62 – 2.09) for those with no RF as compared to 4.13 (95% CI: 3.60-4.75), 5.78 (95% CI: 5.07-6.59), and 9.11 (95% CI: 8.00-10.38) deaths per 1000 person-years among those with 1, 2, and ≥3 RF respectively. On the other hand, the annualized mortality rate was 0.87 deaths per 1000 person-years (95% CI: 0.72-1.06) for those with CAC=0 as compared to 2.97 (95% CI: 2.61-3.37), 6.90 (95% CI: 6.02-7.90), and 17.68 (95% CI: 5.93-19.62) deaths per 1000 person-years among those with CAC scores 1-100, 101-400 and ≥400, respectively.

Table 2 compares the hazard ratios for all-cause mortality for increasing RF as well CAC scores. After taking into account age, gender and CAC scores, the hazard ratio for all-cause mortality ranged from 1.72-3.15 fold with increasing RF’s. In comparison, the respective hazard ratios with increasing CAC scores categories compared to those without any CAC were 2.52-7.52 fold higher (Table 2). The risk factor and CAC scores interaction term was significant (p=0.002) and as a result the hazard ratios of CAC were further presented stratified by underlying risk factor burden. In Cox proportion hazards regression, after adjusting for age and gender, increasing CAC scores were more strongly associated with all-cause mortality among those with no RF as compared to individuals with RF as shown in Table 3. Figure 2 shows reduced survival curves with increasing CAC score at each level of baseline RF burden. Figure 3 show that the lowest event rate was observed in those with no CAC and no RF, whereas those with CAC≥400 and ≥3RF had the highest all-cause mortality rate. Of note, individuals with no RF and CAC≥400 had a much higher mortality rate compared to individuals with ≥3RF but absent CAC (16.89 per 1000 person years vs. 2.72 per 1000 person years). Similar trend was noted when in addition age (men ≥45 years and women ≥45 years) was also considered as a RF (Appendix)
Among those with CAC=0 at baseline (n=19,895) the respective median 5 year all-cause survival was 99.7%, 99.3%, 99.3% and 99.0% with presence of 0, 1, 2 and ≥ RF respectively.

In age-gender adjusted Cox regression analyses, increasing risk factors were associated with a higher hazard ratio of all-cause mortality across all CAC score categories (Table 4).

When predicting all-cause mortality, the addition of CAC to a model containing age, gender, and risk factors resulted in a significant incremental improvement with the ROC curve increasing from 0.76 (95% CI 0.75-0.78) to 0.81 (95% CI, 0.79-0.82). Finally, in comparison to a model based on the number of traditional risk factors present, the model utilizing CAC resulted in a net reclassification improvement of 0.36 (p<.001). (Appendix)

Discussion

In this large cohort of 44,052 asymptomatic subjects followed for a median of 5 years we demonstrate that among individuals without risk factors but elevated CAC (who are generally not candidate for aggressive prevention) had a significantly higher mortality rates than individuals with multiple risk factors but no CAC. These findings challenge the exclusive use of traditional risk assessment algorithms for determining the intensity of primary prevention therapies and suggest that selected groups of patients without risk factors may benefit from further risk assessment and/or preventive therapies.

Value of CAC Testing in Very ‘Low Risk’ Individuals

Previous studies have examined the prevalence and significance of subclinical atherosclerosis in individuals traditionally considered to be at low risk for events. Michos et al.
showed that 84% of women with significant CAC were classified as low risk for cardiovascular events\textsuperscript{25} and Greenland et al. found that in a group of subjects with few or no RF, 53% had detectable CAC and 19% had CAC >300.\textsuperscript{13} In another study, Laksiki et al demonstrated that 32% of women classified as low risk have detectable CAC and 4% have a CAC $\geq$ 300\textsuperscript{26}. They were also able to show that among low risk women, those with CAC were at increased risk for cardiovascular events as compared to those without CAC. The findings from our study are consistent with these reports: 43\% of the subjects in our cohort had no RF, and within this subgroup, 48\% had detectable CAC and 6\% had a CAC >400.

Other studies have shown similar results: Shaw et al. demonstrated that the 5-year mortality rate for patients with few or no RF was 0.9\% among subjects with a CAC score of <10 but increased to 3.9\% among individuals with a CAC score $\geq$1,000\textsuperscript{12}. They also demonstrated that subjects at low risk by traditional risk assessment models with CAC $\geq$1,000 had a higher 5-year mortality rate (3.9\%) than subjects at high risk with CAC <10 (2.8\%)\textsuperscript{12}. However, Greenland et al. did not observe an increased event rates in the low risk - high CAC group; probably due to a small sample size (for the low risk group n= 98)\textsuperscript{13}. Despite this, subjects at intermediate risk with CAC $\geq$300 were at greater risk for coronary events or nonfatal myocardial infarction than subjects at high risk without CAC.

Our study adds to current literature by evaluating for the first time the value of subclinical atherosclerosis screening for the first time in the largest cohort of individuals with no risk factor and demonstrating an incremental increase in risk of all-cause mortality with increasing CAC scores. These findings have important implications for guidelines regarding identifying appropriate candidates for CAC testing. Although prior guidelines only recommended CAC testing for select intermediate risk individuals with 10 year risk of 10-20\%\textsuperscript{20}. 
updated guidelines have now acknowledged the of CAC testing for further risk stratification in lower risk individuals and had reduced the threshold to include individuals with estimated 6-10% risk of CHD in next 10 years. However, current guidelines recommends against CAC testing in those with 0-1 risk factors. Our study findings suggest that CAC testing even among those with no RF provides important prognostic information which can be instrumental in guiding preventive therapies. Nevertheless, our findings need to be validated in additional settings before any changes in the guidelines for CAC testing are adopted. Current efforts are underway to test this hypothesis in large prospective studies as well as to evaluate if this approach can potentially be cost effective. In the context of potentially expanding the widening the eligibility criteria for population to be considered candidate for screening, issues such as identifications of “incidentalomas” requires thoughtful consideration which may result in potential unnecessary downstream testing and health care costs.

Power of Zero in Traditional ‘High Risk’ Individuals

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 very low risk for future CVD events and mortality across all range of risk factor burden. Sarwar et al. in a meta-analysis showed that among 29,312 individuals without evidence of CAC, only 0.56% of subjects without CAC experienced a cardiovascular event during a mean follow-up period of fifty-one months. These findings were confirmed in a large retrospective study and a multi-ethnic prospective study demonstrating a very low event risk with absence of CAC in asymptomatic individuals. In a recent study Malik et also recently demonstrated that more than one thirds of individuals with DM (38%) have no detectable CAC and minimal CVD events in nearly 6 years of followup. Blaha et al also showed that nearly half of the individuals meeting
eligibility for statin therapy based on JUPITER criteria had no CAC and experienced an extremely low event rate, with an unfavorable estimated number needed to treat for 5 years (NNT5) of 549 to prevent one CHD event compared to 42 among those with presence of CAC31.

In this regard, the absence of CAC can be used to identify individuals with an extremely low risk in whom lifestyle interventions may be advocated while safely deferring the use of costly pharmacotherapy32. Such a strategy could enable us to focus on individuals with actual disease (as opposed to ones who have risk factors but may never develop any substantial coronary atherosclerosis) as they are the ones in whom the majority of clinical events will occur in and are most likely to benefit from more aggressive preventive therapies.

Limitations

There are a few limitations to this study. First, all patients were referred for CAC screening and therefore do not represent a random sample of the population. In general, patients referred for CAC scans may be at higher risk compared to age-matched patients from the general population. If this were the case in the present study, the finding of excellent survival amongst patients with zero CAC could be considered even more striking. A second potential weakness is the self-reporting of risk factors. Data collected by self-report is limited by patient recall and thus subject to recall bias. Although Hoff et al has shown a good reliability of self-reported histories of CHD risk factors in self-referred individuals for EBT scanning33, because the CHD risk factors were self-reported, the potential “residual confounding” cannot be ruled out, thus possibly diminishing the strength of association of risk factors with mortality. Nevertheless, in spite of the fact that risk factors may be under reported, the absence of CAC was still associated
with favorable prognosis across all levels of risk factors. Because of the aforementioned limitations, our findings need to be verified in cohorts with well measured risk factors.

Our models do not include the cause of death and, as such, some mortality events may not be related to atherosclerotic disease. However, all-cause mortality is an appropriate end point to follow, since when one accounts for both cardiac and systemic forms of the disease, nearly 3/4 of all deaths have been related to atherosclerosis\textsuperscript{34}. Furthermore, this end point is unaffected by reporting and misclassification bias potentially introduced by death reports\textsuperscript{35}.

In addition, more detailed conclusions in our study are not possible due to the lack of cardiovascular-specific mortality data. Although coronary heart disease remains the most common killer in industrialized countries, it is not possible to ascertain the proportion of deaths that are cardiovascular in origin. While CAC is presumed to influence mortality mainly via cardiovascular mechanisms, other risk factors such as smoking, hypertension and diabetes contribute to all-cause mortality via additional non-cardiovascular mechanisms (i.e. lung disease and kidney dysfunction). Finally, the NRI with CAC reported in our study is slightly higher than those seen in other prospective studies, and can be due to the fact that risk factors were not directly measured.

**Conclusion**

Our study findings support a paradigm shift in CVD risk assessment from risk factor based approach to detection of subclinical atherosclerosis burden as evident by the fact that a significant proportion of those with no RF have a severe amount of coronary atherosclerosis and have a high risk for all-cause mortality. The higher precision of CAC relative to risk factors for identifying at risk individuals may be due to the fact that CAC is a “measure of actual
“disease” that occurs further down the causal pathway than the presence of risk factors which are mere surrogates for this process. Whether this paradigm shift will eventually result in more appropriate allocation of resources and reduce the overall economic health care costs is yet to be answered and needs to be addressed in future randomized trials.

**Disclosures**

Dr Budoff is on the Speaker Bureau of General Electrics (GE).

**References**


Table 1. Baseline characteristics of study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>54±10</td>
</tr>
<tr>
<td>Gender (female) (%)</td>
<td>46%</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>24%</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>5%</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>30%</td>
</tr>
<tr>
<td>Family history of premature CHD (%)</td>
<td>37%</td>
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<td>Current Smoking (%)</td>
<td>14%</td>
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</table>
Table 2. Hazard ratio for all cause mortality with Increasing CAC Scores and Increasing RF Burden

<table>
<thead>
<tr>
<th>Risk Factors (RF)*</th>
<th>Hazard Ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 RF vs. 0 RF</td>
<td>1.72 (1.41-2.09)</td>
</tr>
<tr>
<td>2 RF vs. 0 RF</td>
<td>2.10 (1.73-2.55)</td>
</tr>
<tr>
<td>≥3 RF vs. 0 RF</td>
<td>3.15 (2.59-3.84)</td>
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</table>

<table>
<thead>
<tr>
<th>Coronary Artery Calcium (CAC) Scores**</th>
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<tbody>
<tr>
<td>CAC 1-100 vs. 0</td>
</tr>
<tr>
<td>CAC 101-400 vs. 0</td>
</tr>
<tr>
<td>CAC &gt;400 vs. 0</td>
</tr>
</tbody>
</table>

*Adjusted for Age, gender & CAC Scores

**Adjusted for Age, gender & Risk Factors
Table 3. Hazard ratio for all cause mortality with Increasing CAC Scores Across Increasing RF Burden

<table>
<thead>
<tr>
<th></th>
<th>0 RF (n = 18,819, 43%)</th>
<th>Any RF (n = 25,233, 57%)</th>
<th>1 RF (n = 10,093, 23%)</th>
<th>2 RF (n = 8,754, 20%)</th>
<th>≥3 RF (n = 6,386, 14%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hazard Ratios (95% CI)</strong></td>
<td>All Cause Mortality (%)</td>
<td>104 (0.52%)</td>
<td>650 (2.58%)</td>
<td>200 (1.98%)</td>
<td>223 (2.55%)</td>
</tr>
<tr>
<td><strong>CAC 1-100 vs. 0</strong></td>
<td>2.99 (1.94-4.61)</td>
<td>2.18 (1.65-2.87)</td>
<td>1.56 (1.00-2.53)</td>
<td>2.30 (1.40-3.78)</td>
<td>2.40 (1.47-3.91)</td>
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<tr>
<td><strong>CAC 101-400 vs. 0</strong></td>
<td>4.78 (3.01-7.58)</td>
<td>3.44 (2.59-4.57)</td>
<td>3.73 (2.36-5.92)</td>
<td>3.26 (1.95-5.45)</td>
<td>2.68 (1.60-4.48)</td>
</tr>
<tr>
<td><strong>CAC &gt;400 vs. 0</strong></td>
<td>13.39 (8.66-20.69)</td>
<td>5.80 (4.40-7.63)</td>
<td>5.58 (3.54-8.79)</td>
<td>5.88 (3.58-9.66)</td>
<td>4.58 (2.79-7.53)</td>
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*Adjusted for Age, gender*
Table 4. Hazard ratio for all cause mortality with Increasing Risk Factors Across Increasing CAC Burden

<table>
<thead>
<tr>
<th>CAC=0</th>
<th>CAC&gt;0</th>
<th>CAC 1-100</th>
<th>CAC 101-400</th>
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<tr>
<td>n = 19,898, 45%</td>
<td>n = 24,154, 55%</td>
<td>n = 14,181, 32%</td>
<td>n = 5,739, 13%</td>
<td>n = 4,234, 10%</td>
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<td>Hazard Ratios (95% CI)</td>
<td>Hazard Ratios (95% CI)</td>
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</tr>
<tr>
<td>All Cause Mortality (%)</td>
<td>104 (0.52%)</td>
<td>797 (3.30%)</td>
<td>234 (1.65%)</td>
<td>207 (3.61%)</td>
</tr>
<tr>
<td>1 RF vs. 0</td>
<td>2.73 (1.63-4.56)</td>
<td>1.73 (1.37-1.84)</td>
<td>1.84 (1.23-2.80)</td>
<td>2.58 (1.17-2.06)</td>
</tr>
<tr>
<td>2 RF vs. 0</td>
<td>3.00 (1.71-5.25)</td>
<td>2.28 (1.86-2.80)</td>
<td>3.01 (2.06-4.40)</td>
<td>2.62 (1.72-3.99)</td>
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<td>≥3 RF vs. 0</td>
<td>5.40 (3.07-9.49)</td>
<td>3.50 (2.84-4.30)</td>
<td>5.62 (3.88-8.14)</td>
<td>3.71 (2.42-5.67)</td>
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*Adjusted for Age, gender
Figure Legends

Figure 1. The prevalence and extent of coronary artery calcium in asymptomatic patients according to Burden of Traditional Risk Factors

Figure 2. Kaplan Meier Survival Curves by CAC Scores Across Increasing RF Burden

Figure 3. Mortality Rate (per 1000 person-years) With Increasing Coronary Artery Calcium Scores according to Burden of Risk Factors
Figure 1. The prevalence and extent of coronary artery calcium in asymptomatic patients according to Burden of Traditional Risk Factors

P<0.0001

0 RF  
N=18,819

1 RF  
N=10,093

2 RF  
N=8,754

> 2 RF  
N=6,386

CAC=0  
CAC 1-100  
CAC 101-400  
CAC>400
Figure 2. Kaplan Meier Survival Curves by CAC Scores Across Increasing RF Burden

0 RF (n=18,819)

1 Risk Factor (n=10,093)

2 RF (n=8,754)

>2 RF (n=6,386)
Figure 3. Mortality Rate (per 1000 person-years) With Increasing Coronary Artery Calcium Scores according to Burden of Risk Factors

<table>
<thead>
<tr>
<th></th>
<th>0 RF</th>
<th>1 RF</th>
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<th>Total</th>
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<td>1,301</td>
<td>1,371</td>
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<td>CAC&gt;400</td>
<td>1,047</td>
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<td>1,148</td>
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<tr>
<td>Total</td>
<td>18,819</td>
<td>10,093</td>
<td>8,754</td>
<td>6,386</td>
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