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Competing Cardiovascular Outcomes Associated with Subclinical Atherosclerosis (From the Multi-Ethnic Study of Atherosclerosis)

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Abstract

Subclinical atherosclerosis measured by coronary artery calcium (CAC) is associated with increased risk for multiple cardiovascular disease (CVD) outcomes and non-CVD death simultaneously, and we sought to determine the competing risks of specific cardiovascular disease (CVD) events and non-CVD death associated with varying burdens of subclinical atherosclerosis. We included 3095 men and 3486 women from the Multi-Ethnic Study of Atherosclerosis, aged 45–84 years, and from 4 ethnic groups. Participants were stratified by CAC scores: 0, 1–99, and 100. We used competing Cox models to determine competing cumulative incidences and hazards ratios within a group (e.g., among those with CAC = 100) and hazards ratios for specific events between groups (e.g., CAC = 100 vs. CAC = 0). We compared risks for specific CVD events and also compared against non-CVD death. In women, during a mean follow up of 7.1 years, the hazards ratios (HR) for any CVD event compared with a non-CVD death occurring first for CAC = 0 and CAC = 100 were 1.40 (95% CI, 0.97–2.04) and 3.07 (2.02–4.67), respectively. CHD was the most common first CVD event type at all levels of CAC, and CHD rates were 9.5% vs. 1.6% (HR 6.24; 3.99–9.75) for women with CAC = 100 compared with CAC = 0. We observed similar results in men. In conclusion, at all levels of CAC, CHD was the most common first CVD event and this analysis represents a novel approach to understanding the temporal sequence of cardiovascular events associated with atherosclerosis.

Keywords

coronary artery calcium; competing risks

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INTRODUCTION

The objective of our study is to determine the risks for diverse cardiovascular outcomes associated with subclinical coronary atherosclerosis. Standard survival models do not account for joint and competing risks for diverse outcomes; rather, specialized competing Cox models are required. Knowledge of first events is important as emphasis on certain prevention strategies may be more effective for specific CVD outcomes. For example, clinical trials have documented significant reductions in the incidence of stroke and heart failure with antihypertensive therapy.^{1–3} Although global risk reduction is clearly indicated in hypertensive individuals, other preventive measures such as lipid-lowering, smoking cessation, and antiplatelet therapy have not reduced the risk of stroke to the same degree as antihypertensive therapy.^{4, 5} Further, the occurrence of one CVD event may markedly increase the risk for a subsequent event (e.g., myocardial infarction increases the risk of subsequent heart failure). An expert consensus document from the American Heart Association/American College of Cardiology Foundation stated that “it may be reasonable to consider use of CAC measurement in such patients based on available evidence that demonstrates incremental risk prediction information in this selected (intermediate risk) patient group.”⁶ Since the time of that publication, CAC has been shown to improve risk prediction for CHD even in lower-risk populations.⁷ Thus, we sought to determine the first event in individuals with no coronary artery calcification and to compare competing risks for global CVD associated with subclinical atherosclerosis for men and women in the Multi-Ethnic Study of Atherosclerosis.

METHODS

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study supported by the National Heart, Lung, and Blood Institute (NHLBI) and details of the study design have been published elsewhere.⁶ Participants aged 45–84 years were recruited from six field centers: Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota. The participants were white (38%), African-American (28%), Hispanic (22%), and Chinese (12%). All participants gave written informed consent and the study protocol was approved by the Institutional Review Board at each site. Participants were free of clinical cardiovascular disease at the time of the initial examination in July 2000–August 2002.

Blood pressure was measured using a standard Omron sphygmomanometer. Body mass index was defined as the weight in kilograms divided by the height in meters squared. Blood samples were obtained after a 12-hour fast and analyzed for lipid measures and glucose as previously described.⁷ Medication use was determined by self-report. Diabetes mellitus was defined as fasting blood glucose > 126 mg/dl or use of oral hypoglycemics. Current smoking was defined as cigarette smoking within the past 30 days.

The details of MESA CT scanning and interpretation have been previously reported.⁸ Coronary artery calcium (CAC) was assessed by chest computed tomography at the time of the baseline examination, concurrent with collection of demographic, anthropometric, and clinical data. Either a cardiac-gated electron beam computed tomography scanner (Chicago, Los Angeles, New York) or a multidetector computed tomography scanner was used (Baltimore, Forsyth County, St. Paul). A cardiologist or radiologist interpreted all scans at a central reading center (Harbor-UCLA Medical Center) and the Agatston score was calculated.⁹ We then stratified subjects into the following groups by CAC score, similar to what has been previously described:^{10, 11} 0, 1–99, and ≥ 100.

The median follow up time was 7.1 years. At 9–12 month intervals, interviewers contacted participants or family members by telephone to inquire about health status, hospitalizations, outpatient diagnoses of cardiovascular disease, and deaths. All diagnoses were reviewed by two physician members of the MESA Mortality and Morbidity review committee. A CVD event was defined as the first occurrence of death due to coronary heart disease (CHD) or nonfatal myocardial infarction (NFMi) [definite/probable], fatal and nonfatal stroke, transient ischemic attack (TIA), heart failure [definite/probable], or other CVD death (this consists of arrhythmic death not due to CHD and stroke, or peripheral vascular disease). The diagnosis of myocardial infarction was based on a combination of symptoms, electrocardiographic findings, and levels of cardiac biomarkers. The diagnosis of heart failure was pre-defined in MESA and was considered in the presence of clinical signs and symptoms, physician diagnosis and treatment, and imaging. Stroke was defined as a focal neurologic deficit lasting for ≥ 24 hours, or as clinically relevant lesion on brain imaging if duration of symptoms was < 24 hours. Deaths were considered related to definite CHD if they occurred within 28 days after a myocardial infarction, if the participant had experienced chest pain within the 72 hours before death, or if the participant had a history of CHD and there was no known nonatherosclerotic, noncardiac cause of death. We included cases that were considered definite/probable but not “possible” cases. Deaths were considered not related to cardiovascular causes if another etiology was suspected and confirmed by the review committee.

The baseline characteristics were compared by categorical CAC levels separately for men and women, using linear models for continuous variables and chi-square tests for categorical variables. All participants were followed until the occurrence of a CVD event, non-CVD death, or censoring for end of follow up for a mean of 7.1 years. The CVD events considered in the analysis, including myocardial infarction and stroke, carry a high burden of morbidity and mortality; thus, we used non-CVD death as the comparison group as other non-CVD outcomes are unequal in terms of disability and years of life lost.

We calculated adjusted risks for CVD events separately for men and women stratified by degree of subclinical atherosclerosis. We then determined the first event occurring during the follow up time, whether it was a CVD event or non-CVD death. In competing risks analysis, the occurrence of one type of event in a participant precludes consideration of any other event in that participant. If a CVD event occurred on the same day as the day of death, then the CVD event was coded as occurring first. When multiple CVD events were diagnosed as occurring on the same date, we arbitrarily assigned one as occurring first. An individual was assigned with MI as occurring before heart failure (HF) if both were diagnosed on the same date and stroke was assigned as the first event if stroke and HF occurred on the same day. We used the data augmentation method as described by Lunn and McNeil¹² to fit Cox proportional hazards¹³ models for all CVD events combined compared with non-CVD death as a first event, separately in men and women and by degree of CAC. Standard Kaplan-Meier survival analyses are typically used in situations where one event is considered, and the time to event is considered the failure time. In the competing risks model we used in this study, a participant may fail from only one of the competing risks, and the time to the first event is considered the failure time. The hazards and the event-free survival are obtained from the augmented model and the competing cumulative incidence rate is the product of these two quantities. Therefore, we were able to estimate hazards ratios and cumulative incidences for competing CVD events compared with non-CVD death within a given group (e.g., those with higher compared to lower burden of atherosclerosis).

In separate analyses, we used the method described by Fine and Gray^{14, 15} to estimate the subdistribution hazard separately for men and women and by extent of atherosclerosis for each of five competing outcomes: 1) coronary heart disease (CHD) death or nonfatal

myocardial infarction (NFMI); 2) heart failure (HF); 3) fatal or nonfatal stroke or transient ischemic attack (TIA); 4) other cardiovascular death; 5) and non-cardiovascular death. The Fine and Gray model is a modified Cox proportional hazards model that accounts for competing risks for different outcomes. The subdistribution hazards are modeled by keeping the competing risk observations in the risk set with diminishing weights. Thus, the effect estimated from the Fine and Gray model shows the temporal differences between the two groups in terms of subdistribution hazards, reflecting the differing balance of event occurrences over time across the groups. This model also utilizes time-dependent covariates to model the nonproportionality of hazards. We stratified by sex and further adjusted for the effect of age and race. R version 2.10.1 and its competing risk library were used for these analyses. We used SAS version 9.2 to compute event rates for any cardiovascular disease event using standard Cox models, so that we could compare hazards ratios obtained from standard and competing Cox models. We also calculated competing risk models for the outcomes of cardiovascular and non-cardiovascular death. Using two-sided inference testing, P values < 0.05 were considered statistically significant.

RESULTS

The MESA sample for this analysis included 3095 men and 3486 women aged 45–84 years and 1870 men and 1368 women had detectable CAC. Baseline characteristics of the study participants are shown by sex and stratum of CAC score in Table 1. Adverse levels of traditional CVD risk factors were associated with the presence and extent of CAC.

During a mean follow up period of 7.1 years (46,159 person-years), there were 320 CVD events and 157 non-CVD deaths in men and 212 CVD events and 112 non-CVD deaths in women. Figures 1 and 2 show the incidence of first CVD events and non-CVD death in men and women by stratum of CAC score. Table 2 shows competing cardiovascular outcomes and non-cardiovascular deaths in men and women by strata of CAC score, using the method of Lunn and McNeil. In men, within each stratum of CAC score, even CAC = 0, any CVD event was the more likely first event, compared to a non-CVD death. The cumulative incidence of any CVD event occurring first in men with no detectable CAC was 4.0% and the incidence of non-CVD death was 3.1%, for a hazards ratio of a CVD event occurring first of 1.35 (95% CI, 0.87–2.11). The relative magnitude of the hazards ratio for any CVD event compared to non-CVD death was higher in participants with CAC score 1–99 and 100.

In women, any CVD event was most likely to occur first across all strata of CAC, rather than non-CVD death, as shown in Table 2. Similar to men, the relative magnitude of the hazards ratio was higher with increasing burden of CAC. We conducted additional analyses adjusting the hazards ratios obtained from the method of Lunn and McNeil for CVD risk factors (results not shown). The overall pattern was similar but the estimates were less stable.

As shown in Table 3, we used the method of Fine and Gray to show that the hazards ratio of any CVD event occurring first in men with the highest levels of CAC compared with no CAC was 5.69 (95% CI, 4.13–7.85). Analysis of specific CVD events in men showed that CHD/NFMI was the most likely first CVD event across all strata of CAC. The cumulative incidences of CHD/NFMI occurring first in men with the highest levels of CAC and in those with no CAC were 13.9% and 1.8%, respectively, for a hazards ratio of 8.31 (95% CI, 5.25–13.2). Men with CAC score ≥ 100 were significantly more likely to experience HF as a first event, compared to those with no CAC. In women with the highest levels of CAC compared to women with no CAC, the hazards ratio for CHD/NFMI was 6.24 (95% CI, 3.99–9.75). Similar to men, women with the highest levels of CAC had significantly greater hazards for

experiencing HF as a first event. Models 2 and 3 in Table 3 show that the hazards ratios for any CVD event were modestly attenuated by adjustment for age and race and then additionally for CVD risk factors.

We computed hazards ratios separately for stroke, CHD, and any CVD event using Cox regression models, as shown in Table 4, and compared to hazards ratios obtained from the method of Fine and Gray. Since only the first event experienced by a participant is counted in competing Cox models and all events are counted in standard Cox models, we observed that in men, the total number of CVD events using the standard and competing models was 612 and 534, respectively. Although there were modest differences in the magnitude of the hazards ratios for stroke, the overall pattern was that the hazards ratios from the standard and competing models were similar.

We conducted analyses for competing risks for CVD death compared to non-CVD death in men and women (results not shown). In men with no detectable CAC, the cumulative incidences of CVD death and non-CVD death were 0.6% and 3.1%, respectively; the hazards ratio for CVD death compared to non-CVD death was 0.20 (0.10–0.46). The cumulative incidences of CVD and non-CVD death in men with CAC score ≥ 100 were 2.7% and 11.2%, respectively, for a hazards ratio of 0.28 (0.18–0.43). The hazards ratios were attenuated after multivariable adjustment for CVD risk factors. We observed similar associations in women.

DISCUSSION

We observed that participants were more likely to die from non-cardiovascular rather than cardiovascular causes during our follow up period, even among those with the highest levels of CAC. When nonfatal CVD outcomes were included, participants at all levels of CAC were more likely to experience any CVD event compared to non-CVD death. Even nonfatal CVD events are associated with substantial morbidity and impose a tremendous burden on patients and on the healthcare system. Studies of patient preference have shown that the disability associated with a severe stroke is considered by many patients as tantamount to or even worse than death.¹⁶ CVD and stroke are associated with an annual cost of \$297.7 billion and accounted for 16% of total healthcare expenditure in 2008.¹⁷ By comparison, the annual costs associated with benign and malignant cancers are estimated at \$228 billion.¹⁷

In addition to the burden on patients and healthcare system imposed by even nonfatal CVD events, patients with CVD require chronic lifelong treatment and are always considered to be at risk for future events. On the other hand, many non-CVD events can be considered “curable,” such as acute infections or conditions for which screening is routinely performed (e.g., colorectal polyps); these non-CVD events tend to have high rates of cure with minimal risk of recurrence. In comparison with other chronic diseases such as cancer, the effectiveness of CVD prevention strategies has been well-documented. Thus, our results may aid the clinician to determine whether a patient will live long enough to benefit from CVD prevention therapies, or is more likely to die first from a non-CVD death.

Although CVD is the leading cause of death in the United States, cardiovascular etiologies account for 32% of all deaths;¹⁸ thus, the sum of all non-CVD etiologies comprises the majority of deaths. In addition, MESA excluded individuals who had clinical CVD at the baseline examination (i.e., history of myocardial infarction or atrial fibrillation). Therefore, MESA participants were somewhat healthier from a cardiovascular standpoint than a general population aged 45–84 years. Although the hazards ratios obtained from the competing Cox models were similar to those obtained from the standard Cox models, our analysis adds value in knowing the first events in a population. Individuals with a high burden of CAC are

most likely to have CHD as a first event; however, these individuals are also at increased risk for experiencing other CVD events and for non-CVD death as a first event. In addition, participants with no CAC are still at risk for CVD events and not only non-CVD death.

Although global risk reduction based on existing guidelines¹⁹ is clearly indicated for all individuals, specific therapies may be emphasized for primary prevention of certain outcomes, depending on the most likely first event. For example, lipid-lowering therapy, smoking cessation, and anti-platelet therapy have been shown to strikingly reduce the risk of incident CHD, but the risk for incident stroke is not reduced to the same degree.^{4, 5, 20, 21} Further, clinical trials have demonstrated the greatest reductions in incidence of stroke and heart failure with antihypertensive therapy.^{1, 3, 22} Because a first nonfatal CVD event increases the risk for subsequent events, existing guidelines should be followed for secondary prevention.²³

One limitation of our study is the relatively short duration of follow up. Indeed, we predict differences in the hazards ratios obtained from the Fine and Gray method and Cox regression models with further follow up of the MESA cohort. Strengths of this study include a well-phenotyped cohort consisting of men and women in four ethnic groups. The measure of subclinical atherosclerosis has been well-validated⁸ and our stratification was based on a previous MESA publication.¹⁰ The hazards ratios for CHD in the previous analysis were similar for participants with CAC score 101–300 and >300; thus, we combined those participants into a single group for our analyses. The hazards ratios we present from the method of Lunn and McNeil were not adjusted for covariates. We conducted additional analyses to adjust the hazards ratios for cardiovascular risk factors and the overall pattern was similar, although the estimates were less stable.

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Figure 1.
Cumulative incidence of first events by coronary artery calcium score in men

Figure 2.
Cumulative incidence of first events by coronary artery calcium score in women

Table 1

Characteristics of Multi-Ethnic Study of Atherosclerosis participants at year 0

	Men, stratified by CAC score (N = 3095)				Women, stratified by CAC score(N = 3486)			
	0 (N= 1217)	1-99 (N = 905)	100 (N = 973)	P	0 (N = 2109)	1-99 (N = 838)	100 (N = 539)	P
Age (yrs)	57.0 ±9.0	62.6 ±9.6	67.8 ±8.9	< 0.001	58.4 ±9.1	65.4 ±9.6	71.0 ±7.9	< 0.001
Race				< 0.001				< 0.001
• Caucasian	365 (30%)	348 (39%)	504 (51%)		738 (35%)	323 (39%)	256 (47%)	
• Chinese	158 (13%)	121 (14%)	102 (10%)		236 (11%)	112 (14%)	58 (11%)	
• African-American	379 (31%)	229 (26%)	186 (19%)		628 (30%)	217 (26%)	146 (27%)	
• Hispanic	303 (25%)	193 (22%)	187 (19%)		478 (23%)	174 (21%)	82 (15%)	
Systolic blood pressure (mm Hg)	121.3 ± 17.4	126.6 ± 19.1	130.9 ± 20.2	< 0.001	122.7 ± 22.0	130.6± 23.1	137.8 ± 24.0	< 0.001
Body mass index (kg/m²)	27.5 ± 4.3	27.8 ± 4.4	28.1 ± 4.6	0.02	28.6 ±6.2	28.7 ± 6.1	28.6 ± 6.0	0.95
Total cholesterol (mg/dl)	186.9 ± 33.7	189.7 ± 35.6	188.2 ± 35.8	0.2	197.9±35.1	201.9 ± 35.8	204.4 ± 36.3	0.001
HDL cholesterol (mg/dl)	45.0 ± 11.1	44.8 ± 11.8	45.5 ± 12.7	0.47	56.9 ± 15.3	55.1 ± 15.2	56.0 ± 15.5	0.01
Fasting blood glucose (mg/dl)	96.3 ± 27.4	100.3 ± 34.7	104.1 ± 36.3	< 0.001	92.2 ± 25.4	97.2 ± 29.5	99.4 ± 29.2	< 0.001
Physical activity (MET-min/wk)	6957 ± 6797	6507 ± 7576	5917 ± 5941	0.002	5501 ± 5105	4747 ± 4988	4254 ± 3920	< 0.001
Education less than high school	195 (16%)	142 (16%)	148 (15%)	0.18	366 (18%)	185 (22%)	119 (22%)	< 0.001
Income < \$35,000	407 (35%)	308 (36%)	367 (39%)	0.13	907 (45%)	454 (57%)	327 (65%)	< 0.001
Diabetes mellitus	114 (9%)	117 (13%)	183 (19%)	< 0.001	172 (8%)	105 (13%)	96 (18%)	< 0.001
Current smoker	190 (16%)	131 (15%)	124 (13%)	< 0.001	240 (12%)	97(12%)	67 (12%)	< 0.001
Anti-hypertensive medications	254 (21%)	262 (29%)	412 (42%)	< 0.001	589 (28%)	345 (42%)	266 (49%)	< 0.001
Lipid-lowering therapy	119 (10%)	144 (16%)	220 (22%)	< 0.001	224 (11%)	198 (24%)	139 (26%)	< 0.001
History of cancer	57 (5%)	76 (9%)	97(10%)	< 0.001	141 (7%)	74 (9%)	70 (13%)	< 0.001
Liver disease	55 (5%)	33 (4%)	41 (4%)	0.62	65 (3%)	21 (3%)	9 (2%)	0.16
Lung disease	109 (9%)	81 (9%)	85 (9%)	0.94	270 (13%)	98 (12%)	67 (12%)	0.70
Renal disease	18 (1%)	23 (3%)	25 (3%)	0.13	46 (2%)	19 (2%)	11 (2%)	0.95

All values expressed as mean ±SD, or N (column %)

Table 2

Competing cumulative incidences of first CVD events and non-CVD deaths, stratified by CAC score

Hazards ratios and competing cumulative incidences in men and women						
	MEN			WOMEN		
	0 (N=1217)	1-99 (N=905)	100 (N=973)	0 (N=2109)	1-99 (N=838)	100 (N=539)
Hazards ratio for CVD event vs. Non-CVD death within group	1.35 (0.87, 2.11)	1.68 (1.18, 2.38)	2.60 (1.99, 3.41)	1.40 (0.97, 2.04)	1.58 (1.04, 2.40)	3.07 (2.02, 4.67)
Competing incidence by strata of CAC score			Competing incidence by strata of CAC score			
Non-CVD death	3.1%	6.6%	8.5%	2.4%	4.7%	7.3%
CHD death/NFMI	1.8%	6.0%	13.9%	1.6%	4.1%	9.5%
Fatal/Nonfatal stroke	1.2%	2.7%	3.2%	1.2%	3.0%	5.5%
HF	1.0%	1.0%	3.0%	0.5%	0.2%	3.1%
Other CVD death	0%	0.1%	0.3%	0%	0.2%	0.4%
Any CVD event	4.0%	9.8%	20.3%	3.2%	7.6%	18.5%

Hazards ratios obtained using Lunn and McNeil method

CAC = coronary artery calcium, CVD = cardiovascular disease, CHD = coronary heart disease, NFMI = nonfatal myocardial infarction, HF = heart failure

Table 3

Hazards ratios for each specific type of first event across CAC score groups in men and women, adjusted for the occurrence of other possible events.

	MEN			WOMEN		
	0 (N=1217)	1-99 (N=905)	100 (N=973)	0 (N=2109)	1-99 (N=838)	100 (N=539)
	Model 1: Hazards ratio for event (CAC = 0 as referent)			Model 1: Hazards ratio for event (CAC = 0 as referent)		
Non-CVD death	Ref (1.0)	2.01 (1.30, 3.10)	2.78(1.85, 4.17)	Ref (1.0)	1.97(1.27, 3.04)	2.52 (1.58, 4.00)
CHD death/NFMI	Ref (1.0)	3.41 (2.05, 5.65)	8.31 (5.25, 13.2)	Ref (1.0)	2.41 (1.47, 3.97)	6.24 (3.99, 9.75)
Fatal/nonfatal stroke	Ref (1.0)	2.03 (1.03, 3.99)	2.62 (1.39, 4.96)	Ref (1.0)	2.46 (1.39, 4.36)	3.89 (2.20, 6.89)
HF	Ref (1.0)	1.23 (0.52, 2.89)	3.24 (1.61, 6.51)	Ref (1.0)	0.51 (0.11,2.32)	6.45 (2.94, 14.2)
Other CVD death	Ref (1.0)	NA	NA	Ref (1.0)	NA	NA
Model 1: Any CVD event	Ref (1.0)	2.53 (1.77, 3.63)	5.69 (4.13, 7.85)	Ref (1.0)	2.24 (1.57, 3.20)	5.82 (4.23, 8.02)
Model 2: Any CVD Event	Ref (1.0)	2.26 (1.57, 3.25)	4.48 (3.12, 6.42)	Ref (1.0)	1.80 (1.24, 2.63)	3.90 (2.66, 5.73)
Model 3: Any CVD Event	Ref (1.0)	1.99 (1.38, 2.87)	3.65 (2.55, 5.22)	Ref (1.0)	1.63 (1.12, 2.38)	3.18 (2.14, 4.72)

Hazards ratios obtained from Fine and Gray method. Results represent hazards ratios for a given event subtype across CAC score strata (with CAC=0 as the referent), adjusted for the occurrence of other first events.

The model for any CVD event considered possible outcomes of any CVD and non-CVD death only.

Model 1: unadjusted

Model 2: adjusted for age and race

Model 3: adjusted for age, race, systolic blood pressure, total and HDL cholesterol, smoking status, and diabetes CAC = coronary artery calcitium, CVD = cardiovascular disease, CHD = coronary heart disease, NFMI = nonfatal myocardial infarction, HF = heart failure

Table 4

Comparison of hazards ratios from competing models^{*} with standard Cox regression models by CAC in men and women

Event Type	Hazards ratios in Men			Hazards ratios in Women	
Stroke	CAC	Cox regression	Fine and Gray	Cox regression	Fine and Gray
	0	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	1–99	1.81 (0.92,3.56)	1.53 (0.78,2.99)	1.60 (0.88,2.93)	1.52 (0.82,2.82)
	100	1.77 (0.89,3.51)	1.59 (0.84,3.02)	1.71 (0.88,3.30)	1.59 (0.79,3.22)
CHD/NFMI	0	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	1–99	2.71 (1.65,4.46)	2.92 (1.75,4.87)	1.87 (1.12,3.11)	1.97 (1.17,3.33)
	> 100	5.81 (3.61,9.37)	6.31 (3.82,10.4)	4.20 (2.52, 7.00)	4.25 (2.44, 7.40)
Any CVD event	0	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	1–99	2.02 (1.40,2.91)	1.99 (1.38,2.87)	1.64 (1.13,2.37)	1.63 (1.12,2.38)
	100	3.68 (2.59, 5.23)	3.65 (2.55, 5.22)	3.20 (2.20,4.66)	3.18 (2.14,4.72)
Non-CVD death	0	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	1–99	1.35 (0.87,2.09)	1.22 (0.78,1.88)	1.20 (0.76, 1.87)	1.16 (0.73, 1.82)
	100	1.46 (0.95,2.24)	1.15 (0.75,1.76)	1.25 (0.77,2.05)	1.07 0.64,1.78)

^{*} denotes that hazards ratios from competing model obtained using the method of Fine and Gray

All hazards ratios adjusted for age, race, systolic blood pressure, total and HDL cholesterol, smoking status, and diabetes

CAC = coronary artery calcium; CHD/NFMI = coronary heart disease/nonfatal myocardial infarction; CVD = cardiovascular disease