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Abdominal Aortic Calcium, Coronary Artery Calcium, and Cardiovascular Morbidity and Mortality in the Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective—To evaluate the predictive value of abdominal aortic calcium (AAC) for incident cardiovascular disease (CVD) independent of coronary artery calcium (CAC).

Approach and Results—We evaluated the association of AAC with CVD in 1974 men and women aged 45 to 84 years randomly selected from the Multi-Ethnic Study of Atherosclerosis participants who had complete AAC and CAC data from computed tomographic scans. AAC and CAC were each divided into following 3 percentile categories: 0 to 50th, 51st to 75th, and 76th to 100th. During a mean of 5.5 years of follow-up, there were 50 hard coronary heart disease events, 83 hard CVD events, 30 fatal CVD events, and 105 total deaths. In multivariable-adjusted Cox models including both AAC and CAC, comparing the fourth quartile with the 50th percentile, AAC and CAC were each significantly and independently predictive of hard coronary heart disease and hard CVD, with hazard ratios ranging from 2.4 to 4.4. For CVD mortality, the hazard ratio was highly significant for the fourth quartile of AAC, 5.9 ($P=0.01$), whereas the association for the fourth quartile of CAC (hazard ratio, 2.1) was not significant. For total mortality, the fourth quartile hazard ratio for AAC was 2.7 ($P=0.001$), and for CAC, it was 1.9, $P=0.04$. Area under the receiver operating characteristic curve analyses showed improvement for both AAC and CAC separately, although improvement was greater with CAC for hard coronary heart disease and hard CVD, and greater with AAC for CVD mortality and total mortality. Sensitivity analyses defining AAC and CAC as continuous variables mirrored these results.

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Conclusions—AAC and CAC predicted hard coronary heart disease and hard CVD events independent of one another. Only AAC was independently related to CVD mortality, and AAC showed a stronger association than CAC with total mortality.

Keywords

aortic diseases; calcium; cardiovascular diseases; diagnostic imaging; epidemiology

The standard methodology for predicting cardiovascular disease (CVD) risk has used risk scores consisting of traditional risk factors^{1,2} and, in some cases, novel markers as well.³ The General Framingham Risk Score is a risk score used for combined CVD end points.² To improve CVD risk prediction beyond such risk scores, several subclinical CVD measures have been investigated. Data from the Multi-Ethnic Study of Atherosclerosis (MESA) have demonstrated the incremental value of several subclinical CVD measures, including the ankle-brachial index,⁴ carotid intimal medial thickness by ultrasound,⁵ endothelial function,⁶ and coronary artery calcium (CAC).⁷ The incremental value of these measures ranges from modest (endothelial function) to high (CAC). However, among these, only CAC uses ionizing radiation. The independent value of CAC as a risk marker has now been confirmed in multiple studies.⁸ In addition, CAC has been shown to substantially improve classification of risk status in the MESA.⁹ Calcified atherosclerosis in the abdominal aorta (abdominal aortic calcium or AAC) measured in plain lumbar radiographs has also been shown to predict incident CVD.^{10–13} A recent meta-analysis of 10 studies concluded that the association of AAC with CVD was graded and consistent.¹³ However, minimal data exist for the relation of AAC, quantified by computed tomography, with CVD outcomes. In addition, whether AAC predicts CVD independent of CAC is unclear. We report here the association of AAC with cardiovascular morbidity and mortality in the MESA, when CAC was simultaneously considered in CVD risk prediction.

Materials and Methods

Materials and Methods are available in the online-only Supplement.

Results

Table 1 shows the distribution of CVD risk factors, including those used in the General Framingham Risk Score, across the 3 categories of AAC and 3 categories of CAC, and event rates for each of the 4 end points. The Agatston score ranges are given for each of the categories and illustrate the much higher scores for AAC versus CAC, and the skewed distribution of both AAC and CAC. At higher levels of AAC, participants were older, more likely to be white, and had higher blood pressure, and were more likely to be on hypertensive therapy. At higher levels of CAC, these trends were similarly present along with a greater male percentage, lower high-density lipoprotein-cholesterol, and a higher prevalence of diabetes mellitus. Statin use did not differ significantly by level of AAC or CAC. For both hard coronary heart disease (CHD) and hard CVD, incidence rates per 1000 person-years were 1.1 to 3.0 in the CAC and AAC 0 to 50th percentile categories, but increased to 11.1 and 12.1 for hard CHD in the fourth quartile of CAC and AAC, respectively, and 17.1 and 19.2 for hard CVD in the fourth quartile of CAC and AAC,

respectively. Rates in the third quartiles were intermediate and higher for CAC than for AAC. For both CVD mortality and total mortality, higher rates were present for the fourth quartile of AAC, 7.0 and 21.3, respectively, compared with CAC, 5.5 and 18.0, respectively.

Of the 9 possible combined AAC/CAC categories (3 AAC categories multiplied by 3 CAC categories in Table 1), event rates were uniformly low in the 5 categories with either AAC or CAC 50th percentile, constituting 63% of the cohort. Thus, these categories were combined as the reference group for the Kaplan–Meier curves, and the remaining 4 groups were considered individually. Thirteen percent of the cohort was in the group with both AAC and CAC in the highest quartile, whereas in the remaining 3 groups, each contained 8% of the cohort. Figure A shows the rates for hard CHD, and Figure B shows the rates for hard CVD. The highest rates for both hard CHD and hard CVD occurred when both AAC and CAC were in the highest quartile, with the next highest rates for either AAC or CAC alone in the highest quartile, with intermediate rates when AAC and CAC were both in the third quartile. The overall log-rank P value was <0.0001 . Figure C shows the results for CVD mortality. Here, mortality was greatest for the 2 groups with AAC in the fourth quartile, and the group with only CAC in the fourth quartile showed intermediate risk, log-rank P value of <0.0001 . Figure D shows the results for total mortality, where similarly mortality was highest with AAC in the fourth quartile, but with only CAC in the fourth quartile an intermediate risk was present, log-rank P value of <0.0001 .

Table 2 shows the General Framingham Risk Score and ethnicity-adjusted Cox models. Models first show results for the AAC and CAC categories alone, and then to explore the independence of AAC and CAC, a model with AAC and CAC additionally adjusted for each other. Table 2 shows that for CHD, there were significant associations for the fourth quartiles of AAC and CAC, with hazard ratios (HRs) of 4.1 and 6.1, respectively, and that with mutual adjustment both HRs were attenuated but remained significant, with the HR for CAC (4.4) higher than that for AAC (2.4). For CVD, there were significant associations for the fourth quartiles of AAC and CAC, with HRs of 4.0 and 4.2, respectively, and with mutual adjustment both HRs were attenuated but remained significant, with the HR for AAC (2.7) similar to that for CAC (2.9). HRs were also elevated for the third quartile, but significant only for CAC. For CVD mortality, the fourth quartile of AAC showed a strong hazard, HR=7.8, with some attenuation after mutual adjustment, HR=5.9, $P=0.01$, whereas the fourth quartile of CAC showed no significant association after mutual adjustment, HR=2.1, $P=NS$. For total mortality, the HR for the fourth quartile of AAC after mutual adjustment was 2.7, $P<0.001$, whereas the HR for the fourth quartile of CAC was 1.9, $P=0.04$.

Models exploring potential effect modification by sex or ethnicity showed nonsignificant interaction terms, and there was no significant interaction between the AAC and CAC categories. Tests for nonproportional hazards across AAC and CAC categories using Schoenfeld residuals¹⁴ were all nonsignificant.

Table 3 shows the receiver operating characteristic curve (area under the curve or AUC) analyses. Both AAC and CAC increased the AUC for both hard CHD and hard CVD, but the result was significant only for CAC, and when considered together, AAC added little to

CAC. For CVD mortality, the results were reversed with only AAC significant and addition of CAC adding little to AAC. For total mortality, the increase for AAC was greater than CAC, but both were significant, and the highest AUC occurred when both were in the model.

The results of sensitivity analyses using log-transformed continuous measures of AAC and CAC, $\ln(\text{AAC}+1)$ and $\ln(\text{CAC}+1)$, mirrored these results. In models containing both variables, for $\ln(\text{AAC}+1)$, the HR per SD for CHD was 1.5 ($P=0.11$), for CVD 1.5 ($P=0.02$), for CVD mortality 3.3 ($P=0.01$), and for total mortality 1.8 ($P=0.01$). For $\ln(\text{CAC}+1)$, the HRs were 1.9 ($P=0.01$), 1.5 ($P=0.02$), 1.2 ($P=0.54$), and 1.3 ($P=0.04$), respectively. These results confirm the somewhat stronger predictive power of CAC for hard CHD and the much stronger predictive power of AAC for CVD mortality and total mortality.

Following the recommendation of the recently published American College of Cardiology/the American Heart Association guideline on the assessment of cardiovascular risk to inform treatment decisions in patients considered uncertain by quantitative risk assessment,¹⁵ we compared a CAC cut point of 300 Agatston units (the 85th percentile in these data) with the same percentile cut point for AAC (2754). The results are shown in Table 4. With both AAC and CAC in the model, AAC was highly significantly associated for each of the 4 outcomes, with HRs ranging from 2.33 to 3.92, whereas CAC was not significantly associated with any of the 4 outcomes, with HRs ranging from 1.22 to 1.53.

Discussion

Among subclinical CVD measures, CAC has shown the largest HRs for subsequent CVD events.^{7,8} In the MESA, participants with CAC scores in the top quartile (Agatston scores >100) had an ≈ 7 -fold risk of a major coronary event during the first 5 years of follow-up.⁷ However, using relatively crude measures of AAC from standard lumbar radiographs, AAC has also been reported to be strongly associated with future CVD events.¹⁰⁻¹³ We have shown in the MESA that CAC was moderately correlated with AAC in participants with at least some AAC and CAC, with a Spearman correlation coefficient of 0.38 ($P<0.0001$).¹⁶ Here, each calcium measure attenuated the other somewhat, but the fourth quartile for both measures remained independently significant in predicting hard CHD and hard CVD. However, only AAC was predictive of CVD mortality. CAC showed higher AUC values for hard CHD and hard CVD, but AAC showed higher AUCs for CVD mortality and total mortality. There are no prior reports available that have directly evaluated the prognostic value of AAC measured by computed tomography for CVD events with adjustment for CAC and the General Framingham Risk Score simultaneously.

Several other subclinical CVD measures, including the ankle-brachial index,^{4,17,18} carotid intimal medial thickness,^{5,19} endothelial function,⁶ subclavian stenosis,²⁰ and thoracic aortic calcium²¹⁻²⁵ have been reported to show independent predictive value for incident CVD events. Most of these measures have been reported to improve the area under the receiver operating characteristic curve. However, subclinical measures of CVD are correlated with each other,^{26,27} some highly so, and in evaluating a given subclinical CVD measure many

reports have not adjusted for other correlated subclinical CVD measures, leaving the independence of the reported findings in doubt.

For CVD mortality, the independent HR for the fourth quartile of AAC was 5.9 versus 2.1 for CAC. For total mortality, the independent HR for AAC was 2.7, compared with 1.9 for CAC. CAC has been reported to be associated with both CVD and total mortality previously.^{21,24} However, these associations have been of variable strength. The reason for the discrepancy between hard CHD and hard CVD, and fatal outcomes here is unclear. AAC is more common, occurs earlier, is better correlated with risk factors than CAC, and seems to reflect atherosclerotic burden beyond CAC.¹⁶ A possibility is that the strong mortality association for AAC reflects the known significance of the total atherosclerotic burden for mortality beyond the extent of coronary disease per se.¹⁷⁻²¹ Of interest, a recent report from the Framingham study showed that AAC, but not CAC, was significantly associated with total mortality.²⁸

Prior studies that have compared other subclinical CVD measures with CAC within the same cohort have not reported another subclinical measure equal to or superior to CAC in predicting CVD outcomes. Based on the data presented here, AAC could improve risk prediction. People below the 50th percentile for either measure had a low risk of events. These data suggest that AAC would add to CAC in predicting hard CVD and that AAC would be the stronger subclinical CVD measure for improving CVD mortality and total mortality risk prediction.

In the analyses of AAC and CAC in Table 4 where the CAC cut point of 300 recommended in the recent American College of Cardiology/the American Heart Association guideline was compared with the percentile equivalent for AAC, AAC was significant for each of the 4 end points, whereas CAC showed no significant association for any of the end points.

Strengths of this study include standardized and validated protocols in a multiethnic cohort, careful measurement of potentially confounding variables, and follow-up in a cohort free of CVD at baseline. Limitations include the modest number of CVD deaths (30), although the difference in the predictive value of AAC versus CAC for CVD mortality was marked. The cohort studied here was an $\approx 30\%$ subset of the full MESA cohort. However, they were randomly selected and thus representative of the larger MESA cohort. To allow comparable assessment of the extent of AAC in participants, our AAC measure was limited to the distal 8 cm of the abdominal aorta. This choice seems reasonable because previous studies have shown the highest concentration of AAC is near the bifurcation. The MESA cohort was not a random sample of the US population, but MESA was structured for multiethnic representation. Finally, given the sparse data on the predictive value of AAC independent of CAC, our results will need to be replicated by others.

In conclusion, in a multiethnic cohort, both AAC and CAC were independently predictive for hard CHD and CVD. For CVD mortality, only AAC was independently predictive. The apparent predictive value of CAC for mortality was attenuated when AAC was added to the model. Given guidelines for screening for CAC in asymptomatic intermediate-risk people²⁹ and the independent value of AAC in these data, further research should consider whether

the added clinical use of AAC beyond CAC might warrant recommendations for CVD risk assessment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Nonstandard Abbreviations and Acronyms

AAC	abdominal aortic calcium
AUC	area under the curve
CAC	coronary artery calcium
CHD	coronary heart disease
CVD	cardiovascular disease
HR	hazard ratio
MESA	Multi-Ethnic Study of Atherosclerosis
ROC	receiver operating characteristic

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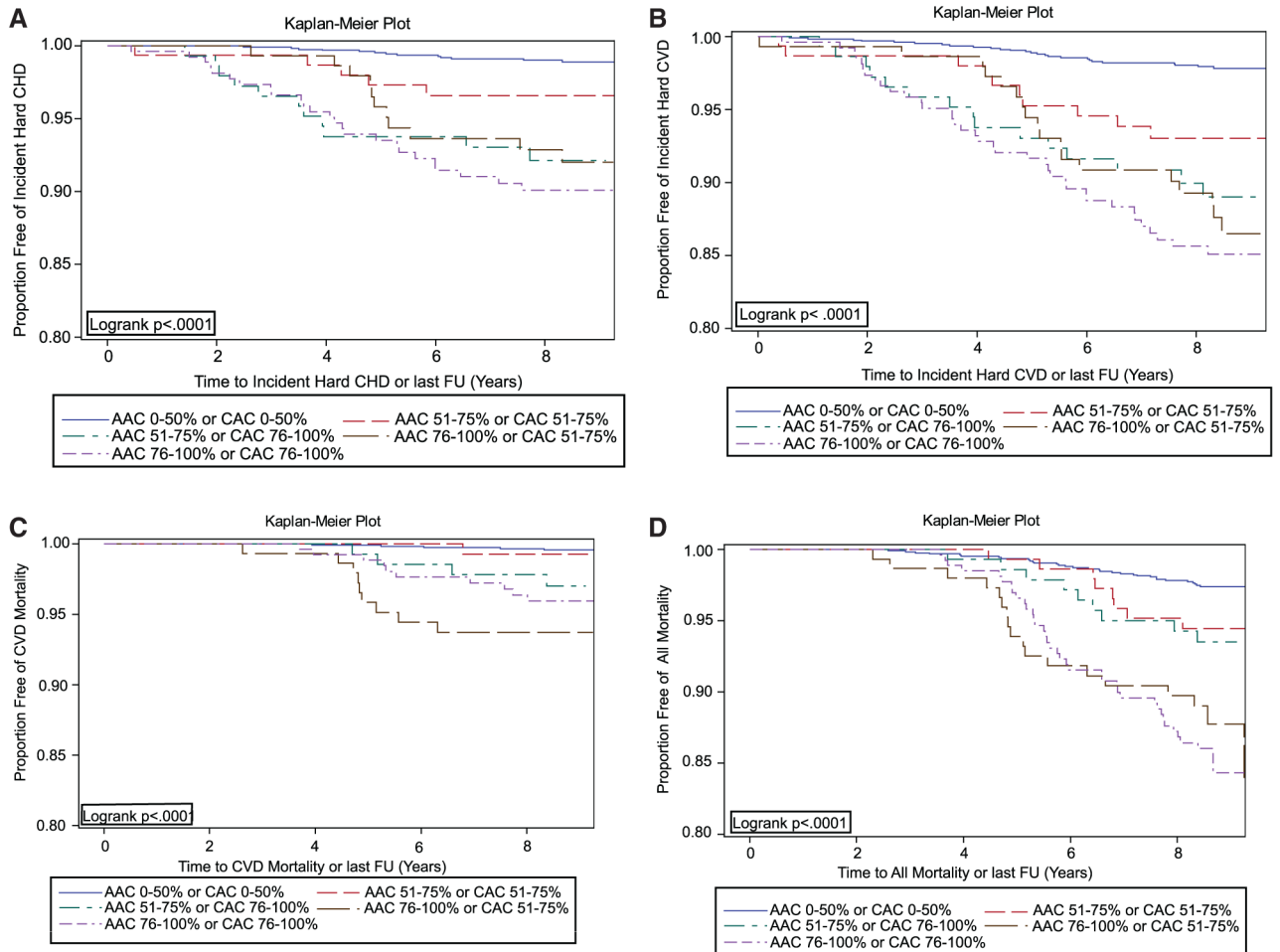
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Significance

In previous studies of subclinical atherosclerosis measures, CAC has shown the strongest independent relationship to CVD events and has similarly shown the greatest increase in CVD risk prediction above standard CVD risk scores based on risk factors. This study is first to report a subclinical atherosclerosis measure, AAC, that shows a similar predictive value to CAC for hard CHD and hard CVD events, and a stronger association than CAC for CVD mortality. Importantly, the predictive values of AAC and CAC are independent and additive, such that overall risk prediction improved when both were measured simultaneously. These results, if confirmed elsewhere, suggest that future recommendations for CVD risk assessment should consider the added clinical utility of AAC measurement.

**Figure.**

Kaplan–Meier curves for abdominal aortic calcium (AAC) and coronary artery calcium (CAC) categories and time to (A) a coronary heart disease (CHD) event, (B) a cardiovascular disease (CVD) event, (C) a CVD death, and (D) all mortality.

Table 1
 Ethnicity, Risk Factors for the General Framingham Risk Score, and Events by Categories of AAC and CAC

Risk Factors	AAC			CAC			P Value Test for Trend
	0-50th Percentile	51st-75th Percentile	76th-100th Percentile	0-50th Percentile	51st-75th Percentile	76th-100th Percentile	
Agatston score range	0-241	242-1437	1438-20 952	0-9	9-136	136-4508	
n	983	491	492	983	491	492	
Age, mean (SD), y	60.4 (8.5)	66.5 (8.8)	71.4 (8.2)	60.9 (8.7)	67.0 (9.3)	69.9 (8.7)	<0.01
Male, n (%)	459 (46.7)	278 (56.6)	253 (51.4)	399 (40.6)	264 (53.8)	327 (66.5)	<0.01
Non-Hispanic white, n (%)	324 (33.0)	204 (41.6)	262 (53.3)	336 (34.2)	200 (40.7)	254 (51.3)	<0.01
Black, n (%)	246 (25.0)	95 (19.4)	70 (14.2)	252 (25.6)	84 (17.1)	75 (15.2)	<0.01
Hispanic, n (%)	271 (27.6)	127 (25.9)	108 (22.0)	258 (25.3)	136 (27.7)	112 (22.8)	0.10
Chinese, n (%)	142 (14.5)	65 (13.2)	52 (10.6)	137 (13.9)	71 (14.5)	51 (10.4)	0.04
Total cholesterol, mean (SD), mg/dL	187.1 (35.4)	183.7 (34.3)	185.9 (37.6)	185.8 (34.7)	188.0 (35.7)	184.2 (37.6)	0.25
HDL-C, mean (SD), mg/dL	52.7 (15.4)	50.2 (14.6)	50.6 (15.2)	52.6 (15.4)	51.0 (15.0)	49.9 (14.8)	<0.01
Systolic BP, mean (SD), mm Hg	119.7 (19.9)	127.3 (21.5)	129.4 (20.1)	120.6 (20.4)	126.6 (20.4)	128.2 (21.0)	<0.01
BP treatment, n (%)	321 (32.7)	237 (48.3)	301 (61.2)	327 (33.3)	237 (48.3)	295 (60.0)	<0.01
Current smoker, n (%)	94 (9.6)	70 (14.3)	56 (11.4)	121 (12.3)	52 (10.6)	47 (9.6)	0.15
Diabetes mellitus, n (%)	65 (6.6)	49 (10.0)	43 (8.7)	64 (6.5)	42 (8.6)	51 (10.4)	0.02
Statins, n (%)	234 (23.8)	94 (19.1)	135 (27.4)	232 (23.6)	115 (23.4)	116 (23.6)	0.98
Events at follow-up							
Hard CHD [*] , per 1000 person-years	1.8 (10)	3.9 (10)	12.1 (30)	1.1 (6)	6.5 (17)	11.1 (27)	
Hard CVD, per 1000 person-years [†]	3.0 (16)	7.9 (20)	19.2 (47)	2.4 (13)	11.2 (29)	17.1 (41)	
CVD mortality, per 1000 person-years [‡]	0.5 (3)	2.9 (8)	7.0 (19)	0.7 (4)	3.9 (11)	5.5 (15)	
Total mortality, per 1000 person-years	4.4 (25)	8.0 (22)	21.3 (58)	4.2 (24)	11.4 (32)	18.0 (49)	

AAC indicates abdominal aortic calcium; BP, blood pressure; CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; and HDL-C, high-density lipoprotein-cholesterol.

^{*} Hard CHD indicates myocardial infarction, resuscitated cardiac arrest, and coronary heart disease death.

[†] Hard CVD indicates myocardial infarction, resuscitated cardiac arrest, stroke, coronary heart disease death, and stroke death.

‡ CVD mortality indicates death from atherosclerotic coronary heart disease, stroke, atherosclerotic disease other than coronary disease or stroke, or other cardiovascular disease not defined.

Table 2

Cox Models for Hard CHD, Hard CVD, CVD Mortality, and Total Mortality for Categorical Definition of AAC and CAC, Adjusted for the General Framingham Risk Score and Ethnicity

	Hard CHD		Hard CVD		CVD Mortality		Total Mortality	
Events	50	83	30	105	1930	1966	1966	1966
Percentile categories	HR	P Value	HR	P Value	HR	P Value	HR	P Value
AAC only, percentile								
0-50th	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
51st-75th	1.49	0.383	1.87	0.069	3.77	0.054	1.43	0.232
>75th	4.06	<0.001	4.00	<0.001	7.83	0.002	3.51	<0.001
CAC only, percentile								
0-50th	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
51st-75th	4.74	0.001	3.67	<0.001	4.03	0.019	2.28	0.003
>75th	6.14	<0.001	4.21	<0.001	3.92	0.021	2.79	<0.001
AAC and CAC, percentile								
AAC 0-50th	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
AAC 51st-75th	1.08	0.875	1.46	0.279	3.11	0.104	1.23	0.506
AAC >75th	2.38	0.038	2.66	0.003	5.89	0.009	2.71	<0.001
CAC 0-50th	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
CAC 51st-75th	3.91	0.006	2.92	0.003	2.75	0.096	1.82	0.037
CAC >75th	4.35	0.004	2.90	0.003	2.10	0.231	1.85	0.036

AAC indicates abdominal aortic calcium; CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; and HR, hazard ratio.

Table 3

AUC for Each of the 4 Outcomes With Addition of Categorical Definitions of AAC and CAC to the Base Model*

Percentile Categories	CHD Hard		CVD Hard		CVD Mortality		Total Mortality	
	AUC	P Value*	AUC	P Value*	AUC	P Value*	AUC	P Value*
Base model [†]	0.749	NA	0.749	NA	0.768	NA	0.716	NA
AAC categories	0.772	0.210	0.772	0.074	0.816	0.037	0.753	0.015
CAC categories	0.807	<0.001	0.793	<0.001	0.802	0.090	0.743	0.037
Both	0.805	0.007	0.796	0.002	0.821	0.053	0.762	0.008

AAC indicates abdominal aortic calcium; AUC, area under the curve; CAC, coronary artery calcium; CHD, coronary heart disease; and CVD, cardiovascular disease.

* Vs base model.

[†] Adjusted for the General Framingham Risk Score and ethnicity.

Table 4

Cox Models for Hard CHD, Hard CVD, CVD Mortality, and Total Mortality for 85th Percentile of AAC (2754) and CAC (300), Adjusted for the General Framingham Risk Score and Ethnicity

	Hard CHD	Hard CVD	CVD Mortality	Total Mortality
Events	50	83	30	105
Total	1930	1930	1966	1966
Percentile categories	HR	P Value	HR	P Value
AAC only, percentile			HR	P Value
0-84th	1.00	Ref.	1.00	Ref.
85th	4.34	<0.001	2.53	0.021
CAC only, percentile			HR	P Value
0-84th	1.00	Ref.	1.00	Ref.
85th	2.15	0.014	1.67	0.198
AAC and CAC, percentile			HR	P Value
AAC 0-84th	1.00	Ref.	1.00	Ref.
AAC 85th	3.92	<0.001	2.33	0.046
CAC 0-84th	1.00	Ref.	1.00	Ref.
CAC 85th	1.42	0.288	1.29	0.552

AAC indicates abdominal aortic calcium; CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; and HR, hazard ratio.