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Abdominal Aortic Calcification Detected on Lateral Spine Images from a Bone Densitometer Predicts Incident Myocardial Infarction or Stroke in Older Women

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Microabstract

Among a cohort of elderly women, abdominal aortic calcification scored on baseline lateral spine densitometric images intended for vertebral fracture assessment was associated with subsequent myocardial infarction or stroke over a median 4 year period, independent of clinical cardiovascular disease risk factors.

Abstract

Introduction: Cardiovascular disease (CVD) risk among older women is not adequately captured by traditional CVD risk factors. Lateral spine images obtained on bone densitometers for vertebral fracture assessment (VFA) can detect abdominal aortic calcification (AAC), an important marker of subclinical CVD. Our objective was to estimate the association between AAC scored on VFA images and subsequent myocardial infarction (MI) or stroke in elderly women.

Methods: Among participants in a randomized controlled trial (women age > 75 years) of clodronate versus placebo, those who sustained an MI or stroke during the median 4 year follow-up study period were selected as cases (n=408), and 408 controls were randomly selected from the remainder of the parent study population. Baseline VFA images were scored for AAC with a previously validated 24-point scale and a newer, simpler 8-point scale.

Results: The odds ratio of incident MI or stroke for those in the middle and top tertiles, respectively, compared to the bottom tertile of AAC score were 1.14 (95% CI 0.79-1.66) and 1.74 (95% CI 1.19 – 2.56) for the 24-point scale and 1.42 (95% C.I. 0.98 – 2.05) and 1.77 (1.22-2.55) for the 8-point scale, adjusted for age, HDL and LDL cholesterol, triglycerides, blood pressure, smoking, renal function, health status, and baseline diagnoses of diabetes mellitus, hypertension, angina, and prior stroke.

Conclusions: Abdominal aortic calcification scored on VFA images is independently associated with incident MI or stroke. Since bone densitometry is indicated for all women age 65 and older, VFA imaging offers an opportunity to capture this CVD risk factor in post-menopausal women undergoing bone densitometry at very little additional cost.

Key Words: Abdominal aortic calcification, myocardial infarction, stroke, vertebral fracture assessment, bone densitometry

Introduction

Coronary heart disease and stroke are the first and third leading causes of mortality among elderly women,[1] and over 60% of women who die of coronary disease have no prior symptoms of the disease.[2] Guidelines have been developed to identify women at higher than average risk of coronary heart disease based on traditional clinical risk factors of elevated blood pressure, dyslipidemias, cigarette smoking, obesity, and diabetes mellitus.[3,4] However, a substantial proportion of those who suffer morbid or fatal cardiovascular disease events are not at high risk when judged by these risk factors.[5-7]

For these reasons, a variety of diagnostic tests for subclinical cardiovascular disease (CVD) have been proposed for use with traditional clinical CVD risk factors to identify a larger proportion of those at high risk of incident CVD events. These include serum c-reactive protein,[8,9] carotid ultrasound to assess carotid intimal thickness,[10,11] measurement of ankle-brachial index,[12,13], and electron-beam computed tomography to detect coronary calcium.[14-17]

Abdominal aortic calcification (AAC) detected on lateral lumbar spine radiographs is also predictive of incident coronary heart disease[13,18] and stroke,[19] independent of traditional CVD risk factors. Lateral spine images obtained on a bone densitometer are increasingly used to detect prevalent vertebral fractures, important BMD-independent predictors of future fracture.[20,21] Bone densitometry is now widely recommended for all women age 65 and older,[22-25] and vertebral fracture assessment (VFA) imaging done at the time of densitometry carries little additional cost (2007 average Medicare Reimbursement $33)[26] and minimal additional radiation exposure (1/100th the effective radiation dose of a lateral lumbar/thoracic radiographs).[27] VFA imaging has also been shown to detect radiographic AAC with reasonable accuracy,[28,29] and offers the potential of identifying subclinical cardiovascular disease in the post-menopausal female population at large.

However, no study to date has investigated whether or not AAC detected on VFA images is associated with any form of incident CVD. Our primary objective was to estimate *ad hoc* the association between AAC scored on baseline VFA images with a previously validated 24 point scale and subsequent myocardial infarction (MI) or stroke in women age 75 years or older participating in a randomized trial of clodronate versus placebo, after adjustment for traditional risk factors.[30] Our secondary objective was to estimate the association with AAC scored with a newer, simplified 8 point scale (AAC-8) and incident MI and stroke.

Materials and Methods

This study was approved by the Park Nicollet Institute Institutional Review Board.

The parent study population consisted of 5,596 Caucasian British women age 75 and older (mean age 80) recruited from general practice registers of South Yorkshire and North Derbyshire in the United Kingdom to participate in a randomized trial of a bisphosphonate drug (clodronate) versus placebo for the prevention of hip and other clinical fractures.[30] Participants were not required to have low bone density or any specific fracture risk factors. Exclusion criteria were prior bilateral hip arthroplasties, concurrent use of any pharmacologic fracture prevention medication, concurrent malignancy, or any other medical condition that would impede informed consent or compliance with study procedures. Participants were followed for a median of 4 years.

For this current investigation, a nested case-control study design was employed. Since those with acute MI or stroke are routinely hospitalized in the United Kingdom, before commencement of the study we chose a combined outcome of fatal and non-fatal incident MI or stroke as our primary measure of incident CVD, in order to assure as complete ascertainment of the outcome as possible. All 408 study participants who had a documented incident MI or stroke during the study follow-up period were selected as cases, and a sample of 408 control subjects were randomly selected from the rest of the study population (**figure 1**). This study design was chosen such that the primary hypotheses could be addressed with adequate power at modest cost, with controls selected to be representative of the entire subset of the parent study population that did not have a myocardial infarction or stroke.

Ascertainment of incident myocardial infarction and stroke

Incident CVD events were recorded as adverse events in the parent RCT at each study follow-up visit done every 6 months. Discharge summaries of all hospitalizations that occurred during the prior 6 months were reviewed at each study visit for serious adverse events, and the cause of all deaths during the study follow-up were ascertained using death reports from the NHS central registry.

Ascertainment of abdominal aortic calcification

All study participants at baseline had a single-energy lateral spine image obtained on a Hologic QDR 4500A densitometer in the supine position for prevalent vertebral fracture assessment (VFA). For this study, baseline VFA images could be located for 807 (98.9%) of the selected cohort (**figure 1**). Of these, 732 (90.7%), including 369 cases and 363 controls, had adequate space anterior to the lumbar spine to include the entire abdominal aorta and thus allow evaluation for AAC. One reader (JTS) evaluated the available soft-copy images for the cases and controls, with a previously validated 24-point scale (AAC-24) and a newer simplified 8-point scale (AAC-8) (**figure 2**). The reader was blinded to case status and all participant characteristics except age.

Details of both the AAC-24 and AAC-8 scales have been published elsewhere. Briefly, in the AAC-24 system, the anterior and posterior aortic walls were divided into four segments, corresponding to the areas in front of the lumbar vertebrae L1-L4. Aortic calcification scored as 0 if there was no calcification, as 1 if one-third or less of the aortic wall in that segment was calcified, as 2 if more than one-third but two-thirds or less of the aortic wall was calcified, or as 3 if more than two-thirds of the aortic wall was calcified. Scores could therefore range from 0 to 6 for each vertebral level, and the total score range was from 0 to 24.[31]

The AAC-8 scale has the same definition of aortic calcification as the AAC-24 scale, but uses a simplified scoring system. In AAC-8, the score is the sum of the total length of calcification for each of the anterior and posterior aortic walls in front of vertebrae L1 to L4. A score of 0 is given if no calcification is seen, 1 if the aggregate length of calcification is $\leq$ to one vertebral height, 2 if that length is > 1 but $\leq$ 2 vertebral heights, 3 if that length is > 2 but $\leq$ 3 vertebral heights, and 4 if the aggregate length of calcification is > 3 vertebral heights.[28] The total score range is 0 to 8. In two previous cohorts, AAC-8 and AAC-24 scale scores have been shown to be highly correlated, but in our experience AAC-8 is faster and easier to score than AAC-24 and may be easier to implement in clinical practice.

Ascertainment of CVD clinical risk factors

All participants in the parent study had systolic and diastolic blood pressure, body mass index, and health status measured by the EuroQol visual analogue scale.[32,33] Past medical events that may increase the risk of fractures, such as prior stroke, and other current self-reported co-morbidities (including diabetes mellitus, hypertension, angina and heart failure) were documented at the baseline study visit. Total hip bone mineral density was assessed at baseline on a Hologic 4500A densitometer. After one quarter of the parent study population had been recruited, smoking status was assessed at baseline for the remainder of the study population. Lipid levels were not assessed duringthe parent study, but sera stored at -40 degrees centigrade was available to measure triglycerides and total, HDL, and LDL cholesterol levels for 704 of those selected as cases or controls for this investigation. For the remainder, all of their stored sera had already been used in other investigations.

Statistical analysis

Baseline characteristics of the cases and controls were compared with chisquare statistics for categorical variables, and with Cochrane t-test statistics for continuous variables. Logistic regression models using SAS 9.1.3 software were used to assess the age-adjusted and multivariable-adjusted associations of AAC-24 and AAC-8 point and incident MI or stroke. Covariates included in the multivariable model were age, systolic blood pressure, LDL and HDL cholesterol, triglycerides, smoking, renal function, treatment assignment (clodronate or placebo), self-reported diagnoses of diabetes mellitus, hypertension, angina, prior stroke, and health status. The multivariable models were done for that subset with complete covariate data, but also with multiple imputation using the PROC MI procedure in SAS 9.1.3 to impute missing covariate data.[34]

This study was designed to have 90% power to detect an odds ratio of 1.75 for the primary outcome incident MI or stroke among those in the top tertile of AAC versus the bottom tertile, using either AAC scale. Although this study was not powered to analyze the association of AAC with incident MI and with incident stroke as separate outcomes, secondary analyses were done to estimate the multivariable-adjusted associations of AAC-8 and AAC-24 with each of these outcomes separately..

An exploratory analysis was also performed examining the association of incident MI or stroke with AAC within tertiles of Framingham Point Score (FPS), an indicator of absolute 10-year risk of coronary heart disease based on age, systolic blood pressure, total and HDL cholesterol, smoking, and treatment of hypertension.[35,36] This was done to qualitatively gauge how predictive AAC may be of incident MI or stroke compared to FPS, and to assess whether or not AAC might identify a subset of elderly women at high risk of incident MI or stroke not identified by FPS.

Results

Among all women in the parent study who did not have an incident MI or stroke, the baseline characteristics of the 408 control patients selected for this study were nearly identical to the 4,780 women that were not selected (data not shown), indicating that a reasonable random subset of the parent population without incident MI or stroke had been selected. Those with an unevaluable VFA image (n=75) had higher body mass index, slightly lower total and LDL cholesterol levels and better renal function, but were similar with respect to case status as those (n=732) with an evaluable VFA image (p=0.40) (**table 1**). Among those with an evaluable VFA image for AAC, cholesterol and triglyceride levels were available for 627 (85.7%) and smoking status for 512 (69.9%). Complete covariate data was available for 420 (57.4%).

Among the cases, 191 women (51.8%) had an incident MI and 178 women (48.2%) had an incident stroke. Those who had an incident MI or stroke during the follow-up period had, at baseline, slightly higher triglycerides and systolic blood pressure, and lower HDL cholesterol, renal function, and health status. Cases were more likely to have angina, hypertension, and prior stroke at baseline, and were less likely to have complete covariate data (**table 2**). No association was noted between case status and either total hip BMD or clodronate treatment.

Among the 732 women with VFA images evaluable for AAC, there was a statistically significant linear trend for increasing risk of incident MI or stroke with increasing tertile of AAC-24 (p= 0.004) and with increasing tertile of AAC-8 (p=0.002) using multiple imputation for missing covariate data. Those in the third tertiles of AAC-24 (score >6) and AAC-8 (score>3), respectively, had multivariable-adjusted excess odds of 74% and 77% for incident MI or stroke compared to those in the first tertiles of AAC score (**table 3**). No statistically significant differences in odds ratio were observed comparing the second tertile to the first or third tertiles. Results were very similar when analyses were limited to those with complete covariate data.

When the associations of AAC with incident MI and incident stroke were analyzed separately, a statistically significant linear trend with increasing tertile of both AAC-24 (p=0.003) and AAC-8 (p<0.001) was noted for incident MI, but not for incident stroke. Those in the third tertiles of AAC-24 and AAC-8, respectively, had excess odds of 106% and 114% for incident MI compared to the first tertiles. Those in the third tertiles of AAC-24 and AAC-8, respectively, had apparent excess odds of 49% and 51% for incident stroke compared to the first tertiles (**table 4**). Those in the second tertile of AAC-8 also had a 105% excess odds of incident MI compared to the first tertile. Otherwise, no differences in the odds of either incident MI or incident stroke were noted between the third and second or between the second and first tertiles of AAC using either scale. Again, no associations were found between incident stroke and MI analyzed as separate outcomes and baseline total hip BMD or clodronate treatment.

Those in the third tertile of Framingham Point Score (FPS > 23) had an odds ratio of 1.74 (95% C.I. 1.18 – 2.55) and those in the second FPS tertile (FPS equal to 21 or 22) had an odds ratio of 1.06 (95% C.I. 0.68 – 1.66) for incident MI or stroke compared to the first tertile (FPS < 16 to 20). When stratified by FPS tertiles, AAC tertiles remain statistically significant predictors of increased risk of MI or stroke (p-value for trend = 0.001 for both AAC-24 and AAC-8). Among those in the second tertile of FPS, those in the third tertile of AAC-24 or AAC-8 score, respectively, had odds ratios of 2.95 (95% C.I. 1.45 – 6.03) and 2.53 (95% C.I. 1.29 – 4.98) for incident MI or stroke compared to those in the lowest tertiles of both AAC and FPS (**figure 3**)..

Discussion

Radiographic abdominal aortic calcification has been shown to be a strong predictor of incident coronary heart disease,[13,18] stroke,[19] heart failure,[37] and intermittent claudication(38) independent of traditional clinical CVD risk factors, and assessments of AAC on VFA images and standard radiographs have been shown to be highly correlated. In this study, a high level of AAC (score of $\geq$ 6 on the 24 point scale or score of $\geq$ 3 on the 8-point scale) on VFA images with either a previously validated 24-point scale or a simpler 8-point scale was predictive of incident MI or stroke among elderly women age 75 and older, after adjustment for traditional clinical CVD risk factors. These results are consistent with previous studies documenting the association between CVD and AAC, most of which scored AAC with the same 24-point scale also used in this study. Supine lateral and lateral decubitus imaging yield spine images of similar quality, and on both the aorta can be visualized sufficiently on VFA for AAC to be scored in 90% of post-menopausal women.[(29)]

The association between a high level of AAC and incident MI or stroke appeared to be as strong as the association between a high Framingham Point Score (corresponding to an absolute 10 year risk of incident coronary heart disease of 20% or more) and incident MI or stroke. Moreover, VFA may identify a subset of elderly women at high risk for incident MI or stroke that do not appear to be at high risk based on traditional clinical risk factors. Many women within the intermediate risk of coronary heart disease based on the FPS (10 year coronary disease risk of 11-20%) may benefit the most from the detection of AAC on VFA images, in that if a VFA shows an AAC-8 score of 3 or higher or an AAC-24 score of 6 or higher, then the 10-year probability of incident coronary disease for them may exceed 20%. Current National Cholesterol Education Program guidelines recommend more aggressive treatment goals for those with a 10 year risk greater than 20% compared to those at lower risk.[(36)]

Low bone density itself has been shown to be associated both with vascular calcification[(39,40)] and with incident cardiovascular disease.[(41)] Unlike these prior reports, we found no association between total hip or femoral neck BMD and incident MI or stroke. However, our study population was much older (mean age 80) than the populations of those prior studies (mean ages ranging from 54 years to 64 years of age), and was not selected to have low bone density (only 21% of cases and 23% of controls had a femoral neck T-score < -2.5). If the association between BMD and incident cardiovascular disease weakens with increasing age (as has been demonstrated between BMD and incident hip fracture with increasing age),[42] or if the association between BMD and incident CVD is stronger at lower ranges compared to higher ranges of BMD, this may at least in part explain this discrepancy. Further research is required to address these issues.

One prior study has found that etidronate reduced carotid intimal medial thickness, a risk factor for stroke,[43] while another small study found no effect of alendronate on progression of coronary artery calcification.[44] Neither our analysis nor that of the parent study found any association between clodronate treatment and incident cardiovascular disease. Our study was not designed to specifically test the hypothesis that clodronate may reduce incident stroke or MI. Moreover, while animal studies suggest that oral bisphosphonates may *prevent* vascular calcification,[45] our study population consisted of very elderly women of whom a substantial proportion had *established* vascular calcification. Finally, unstable atherosclerotic plaques, thought to be important in the pathogenesis of acute vascular events such as stroke and MI, may actually contain *less* calcium than stable plaques,[46] and hence the association between vascular calcification and cardiovascular disease events may be due to the fact that vascular calcification is strongly associated with the simultaneous presence of unstable plaques.[47] Therefore, reduction of myocardial infarction or stroke with bone active agents may require mechanisms of action other than simply preventing vascular calcification.

Bone densitometry is now recommended for all women age 65 and older to assess incident fracture risk,[23,24,48,49] and VFA is indicated for the detection of vertebral fracture in such women.[50] This may allow identification of a significant CVD risk factor among the majority of the female population age 65 and older at minimal additional cost or radiation exposure. Based on identification of prevalent vertebral fracture alone, this procedure is cost-effective for that subset of post-menopausal women who in the absence of prevalent vertebral fracture would not be candidates for fracture prevention therapy.[51] Simultaneous assessment for AAC on VFA images in this population may increase the utility of the procedure even further. Although AAC is not as predictive of coronary events as coronary calcium,[52] VFA imaging has the advantage over other imaging modalities of lower cost and greater convenience, and in comparison to CT imaging, much lower radiation exposure.

However, as is true for other candidate tests to detect those at high risk of CVD that are not identified by traditional clinical CVD risk factors (such as c-reactive protein, homocysteinemia, carotid IMT, and coronary calcium score), the precise role that imaging for AAC may play in strategies to prevent clinical cardiovascular disease remains undefined.[3] Future studies of VFA imaging with larger populations including younger post-menopausal women and men, with more complete covariate data collection, and with the specific *pre hoc* intention to assess the association between AAC and multiple cardiovascular disease endpoints (including mortality) are needed. These will greatly help define the role that VFA imaging may play in strategies to prevent incident clinical cardiovascular disease within the broader population.

Our study has several important strengths. This is the first study to show that AAC scored on VFA images is predictive of a form of incident cardiovascular disease, and the first to demonstrate the predictive validity of the AAC-8 scale, that is practical for use in clinical practice. Assessments of AAC were done completely blinded to case status and covariate data. Although the parent study population was recruited to participate in a randomized controlled trial, the parent study had very few exclusion criteria, such that our results are generalizable to elderly female Caucasian populations. Records of all hospitalizations and deaths were obtained during the study follow-up period for all participants, such that ascertainment of fatal and non-fatal MI and stroke sufficient to cause death or hospitalization is highly likely to be accurate. To the extent that misclassification of cardiovascular disease outcomes occurred, our results would be biased toward the null.

This study, however, has important limitations. This is an *ad hoc* analysis of a randomized clinical trial done for purposes unrelated to cardiovascular disease. Significant proportions of the study cohort had missing cholesterol and triglyceride levels, and missing data regarding smoking status. This is mitigated, however, by the similarity of the results whether the multivariable analyses were restricted to those with complete covariate data or done with multiple imputation. This study did not have adequate power to assess the association of AAC with incident MI and stroke separately, or to assess the association between AAC and cardiovascular mortality or other CVD endpoints. These results are strictly applicable only to Caucasian women age 75 and older, and additional studies may be required to confirm the applicability to men, younger post-menopausal women, and those of other ethnic backgrounds. However, since radiographically detected AAC has been confirmed as a CVD risk factor in men and younger women[13,18] and good agreement has been demonstrated between radiographic and VFA detected AAC,[28,29] results using VFA in these populations to detect AAC may be similar to radiographically detected AAC.

In conclusion, a high level of abdominal aortic calcification detected on VFA images is predictive of incident myocardial infarction or stroke among elderly Caucasian women, independent of other clinical CVD risk factors. VFA imaging performed at the time of bone densitometry offers an opportunity to simultaneously assess for prevalent vertebral fracture and AAC at minimal additional cost. Our data strongly suggest that

AAC incidentally detected on images obtained for the purpose of vertebral fracture assessment should not be ignored, and the provider responsible for care of the patient should be notified of its presence and significance. Further studies in larger and more diverse populations will be required to better define how VFA can be best incorporated into strategies to prevent incident cardiovascular disease.

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Figure 1 – Study Participant Selection and AAC Evaluation

Figure 2 – Examples of Abdominal Aortic Calcification on VFA Images (White Arrows)

Figure 3 – Association of AAC-8 and AAC-24 Scores with Incident MI or Stroke within Three Levels of Framingham Point Score (FPS)

Table 1 – Characteristics of Those With VFA Images Evaluable for AAC Different from those with VFA Images Unevaluable for AAC

Parameter (Number of Participants with Data)	Unevaluable for Baseline AAC (n=75)	Evaluable for Baseline AAC (n=732)	P-value
Proportion with Incident Stroke or MI (Cases)	45.3%	50.4%	0.40*
BMI (n=730), kg/m^2	32.4	26.6	<0.001**
Total Cholesterol (n=627), mg/dl (SD)	228.5 (60.2)	244.1 (53.84)	0.02**
LDL Cholesterol (n=612), mg/dl (SD)	147.6 (48.4)	159.7 (43.0)	0.02**
Triglycerides (n=627), mg/dl (SD)	132.2	149.8	0.04**
Creatinine Clearance (n=732), MDRD^ (SD)	49.3	46.8	0.03**

*Chi-square statistic
**Cochrane t-test statistic

Table 2 – Baseline Characteristics of Cases and Controls

Parameter (Number of Participants with Data)	Cases (n=369, 50%)	Controls (n=363, 50%)	P-value
AAC-24 Score (n=732) 0-1 2-5 ≥ 6	 27% 34% 39%	 35% 38% 27%	0.002*
AAC-8 Score (n=732) 0-1 2 ≥ 3	 34% 30% 36%	 47% 28% 26%	0.001*
Age (n=732), years (SD)	80.1 (4.1)	79.7 (3.9)	0.185**
BMI (n=730), kg/m^2 (SD)	26.6 (4.5)	26.5 (4.3)	0.917**
Systolic BP (n=730), mm Hg (SD)	151.9 (22.7)	149.2 (22.7)	0.109**
Diastolic BP (n=730), mm Hg (SD)	79.0 (11.8)	79.0 (12.3)	0.956**
Total Cholesterol (n=627), mg/dl (SD)	244.7 (60.2)	243.5 (53.84)	0.796**
LDL Cholesterol (n=612), mg/dl (SD)	159.3 (48.4)	160.0 (43.0)	0.854**
HDL Cholesterol (n=627), mg/dl (SD)	52.8 (17.6)	55.6 (16.5)	0.041**
Triglycerides (n=627), mg/dl (SD)	160.5 (111.1)	139.3 (66.8)	0.001**
Creatinine Clearance (n=732), MDRD^ (SD)	45.7 (9.1)	47.8 (8.4)	0.001**
Smoking status (n=512) Current	9	7	0.364*
Diabetes Mellitus (n=732), %	9%	6%	0.146*
Angina (n=732), %	36%	27%	0.007*
Prior CVA (n=732), %	6%	2%	0.004*
Diagnosis of Hypertension (n=732), %	45%	39%	0.078*
Diagnosis of Heart Failure (n=732), %	3%	3%	0.801*
Health Status (n= 709) EuroQol VAS	64.6 (19.4)	71.2 (17.6)	<0.001**
Total Hip BMD (n=732)	0.749 (0.132)	0.752 (0.144)	0.802
Treatment Assignment (n=732), % on Clodronate	54%	49%	0.162*
Complete Covariate Data (n=420), %	48%	67%	<0.001*

*Chi-square statistic p-value **Cochrane t-test statistic p-value
^Estimated creatinine clearance by

Table 3 – Association of AAC with Incident Myocardial Infarction or Stroke (Primary Analyses)

AAC Scale	Tertile	Odds Ratio (95% C.I.)		
		Age-Adjusted (n=732)	Multivariable-Adjusted** (n=732)	Multivariable-Adjusted* (n=420)
AAC-24	First	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
	Second	1.15 (0.80 – 1.65)	1.14 (0.79 – 1.66)	0.88 (0.53 -1.45)
	Third	1.84 (1.27 - 2.68)	1.74 (1.19 – 2.56)	1.67 (1.00 – 2.79)
AAC-8	First	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
	Second	1.48 (1.04 – 2.12)	1.42 (0.98 – 2.05)	1.38 (0.85 – 2.25)
	Third	1.88 (1.32 – 2.67)	1.77 (1.22 – 2.55	1.80 (1.09 – 2.95)

*Analysis restricted to those with complete covariate data, adjusted for age, systolic BP, LDL and HDL cholesterol, triglycerides, smoking status, renal function (MDRD), health status as measured by the EuroQol VAS, and diagnoses of diabetes mellitus, hypertension, angina, and/or prior stroke.

**Analysis done with multiple imputation for missing covariate data

Table 4 – Multivariable-Adjusted (with Multiple Imputation) Association of AAC with Incident Myocardial Infarction and Stroke as Separate Outcomes

AAC Scale	Tertile	Odds Ratio (95% C.I.)	
		Myocardial Infarction	Stroke
AAC-24	First	1.0 (Reference)	1.0 (Reference)
	Second	1.35 (0.85-2.16)	1.00 (0.63 – 1.60)
	Third	2.06 (1.28 – 3.31)	1.49 (0.92 – 2.40)
AAC-8	First	1.0 (Reference)	1.0 (Reference)
	Second	2.05 (1.30 – 3.24)	0.99 (0.62 – 1.58)
	Third	2.14 (1.35 – 3.39)	1.51 (0.96 – 2.37)

Figure 1 – Study Participant Selection and AAC Evaluation

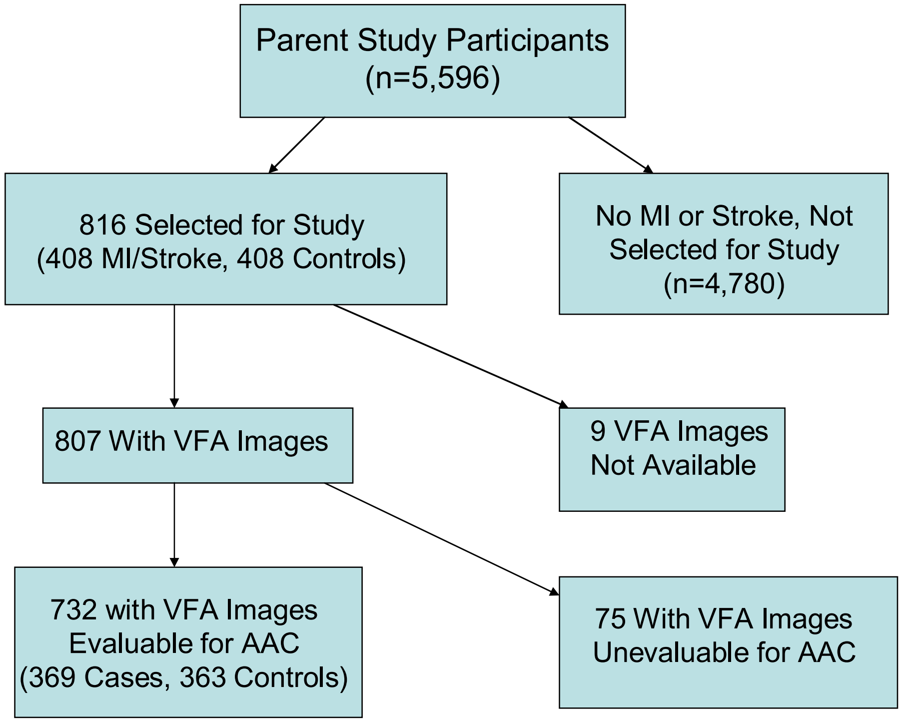


Figure 2 – Examples of Abdominal Aortic Calcification on VFA Images (Indicated by White Arrows)

a) No AAC **b) AAC-24 =4, AAC-8 =2** **c)AAC-24 =12, AAC-8 =4**

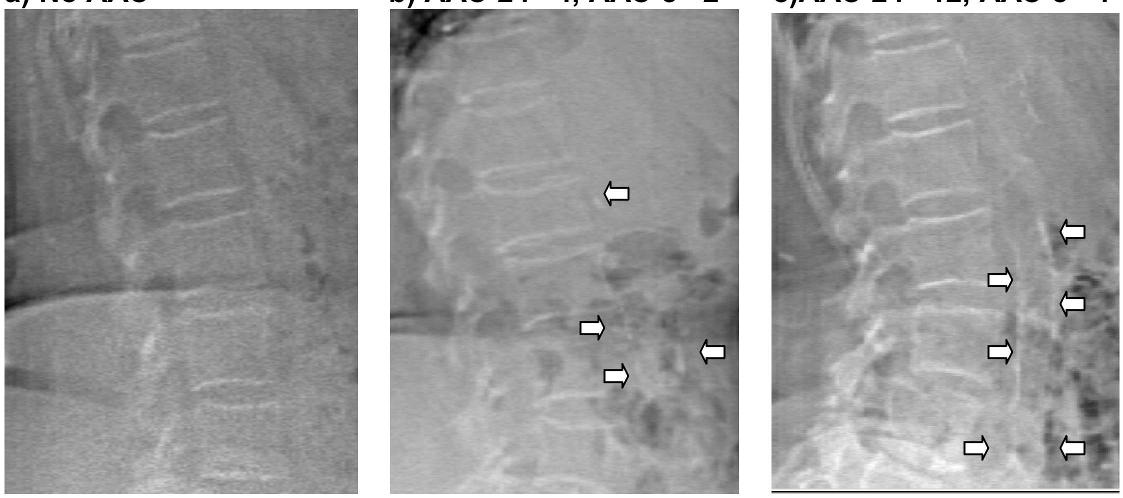
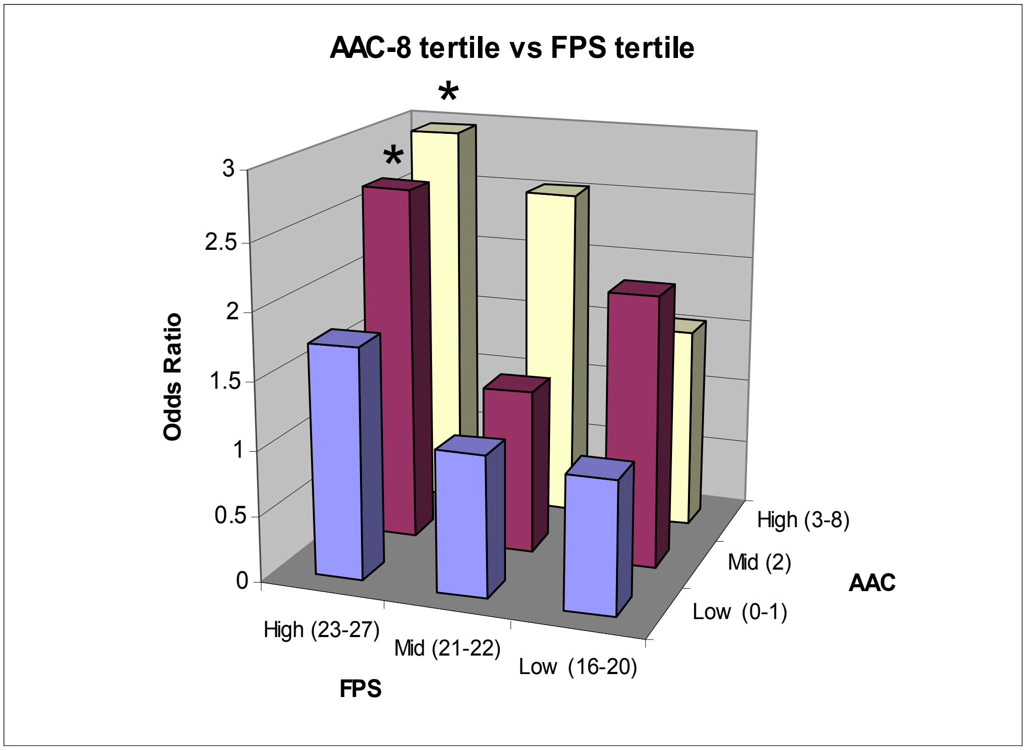
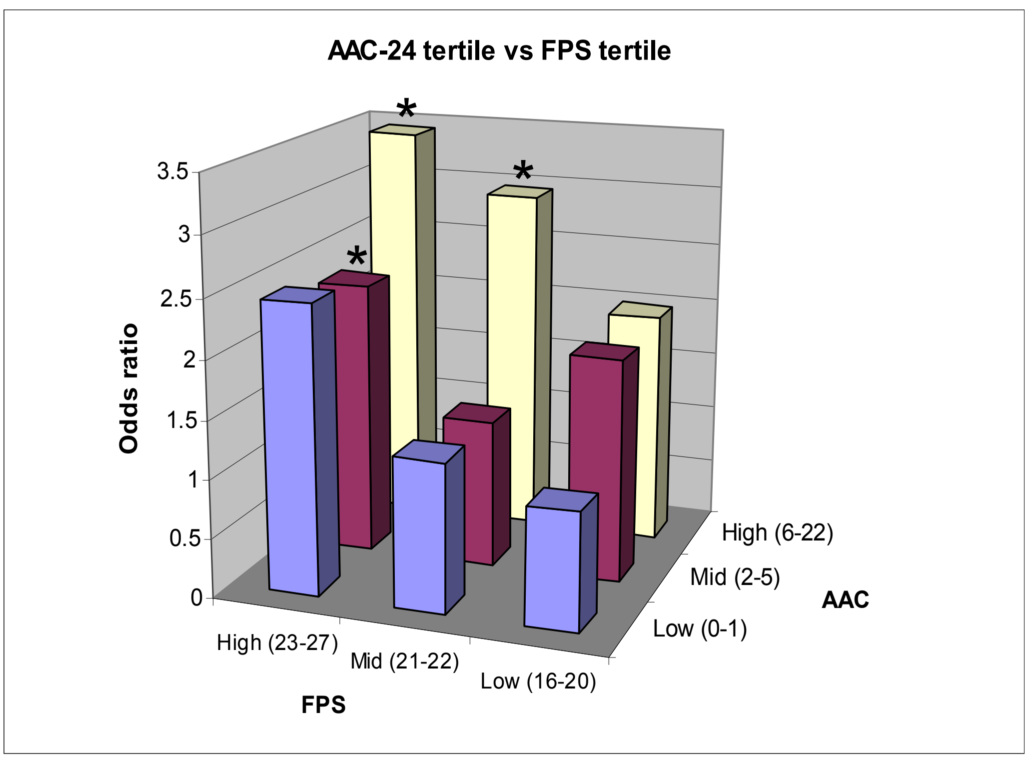


Figure 3 – Association of AAC-8 and AAC-24 Scores with Incident MI or Stroke Within Three Levels of Framingham Point Score





* Lower Bound of 95% Confidence Interval is Greater than 1.0

Figure

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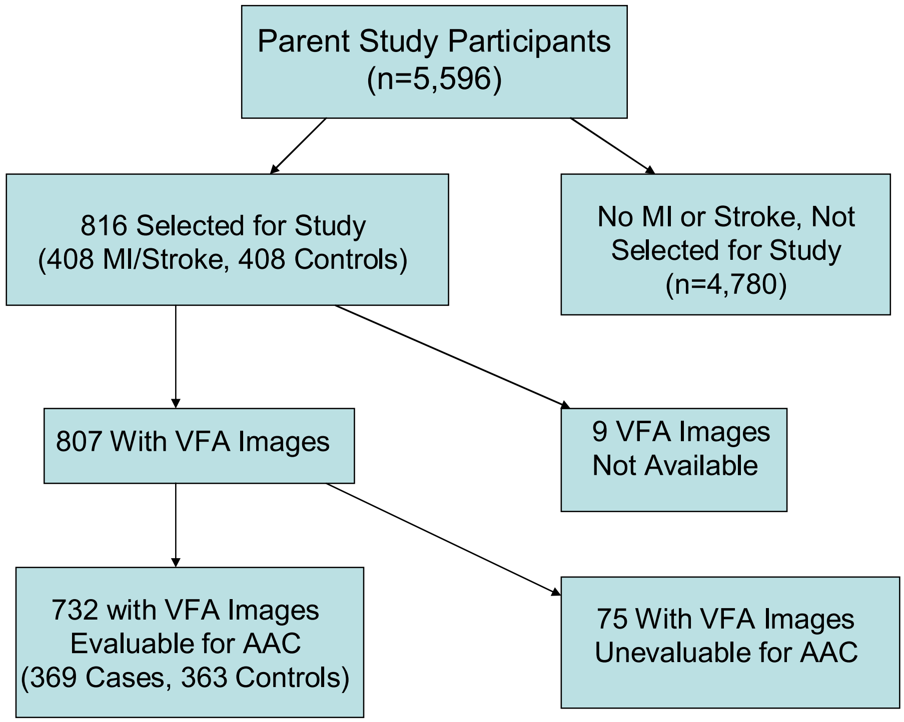

Figure

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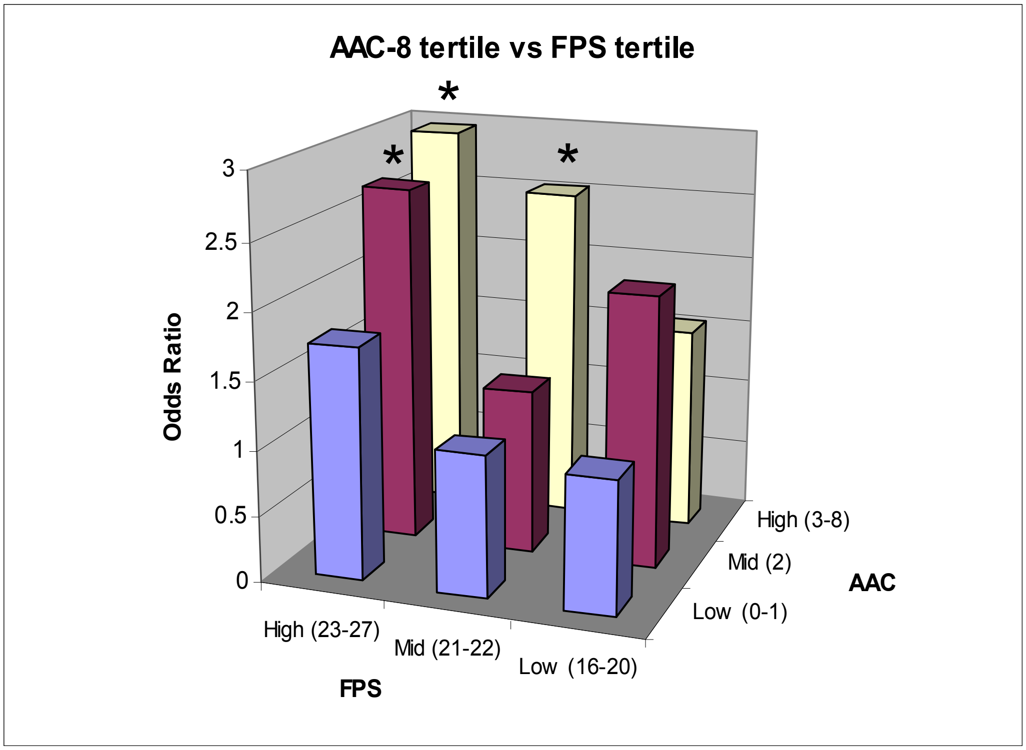

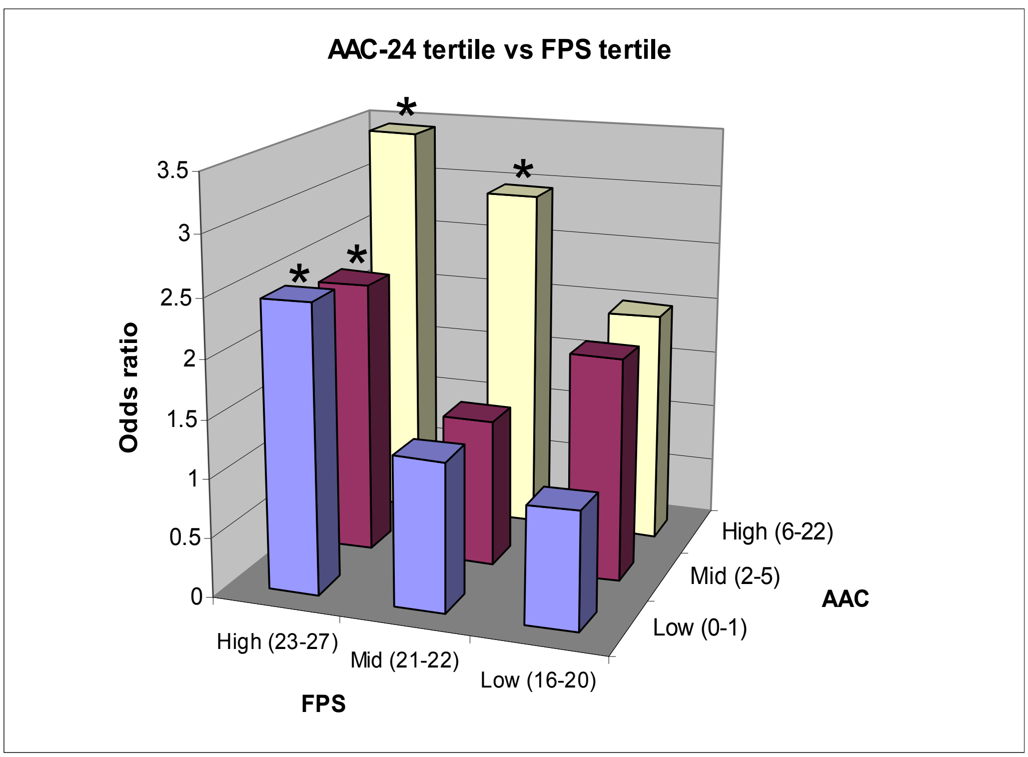

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Figure

Figure 2 – Examples of Abdominal Aortic Calcification on VFA Images (Indicated by White Arrows)

a) No AAC **b) AAC-24 =4, AAC-8 =2** **c)AAC-24 =12, AAC-8 =4**