

Coronary Artery Calcium, Carotid Artery Wall Thickness, and Cardiovascular Disease Outcomes in Adults 70 to 99 Years Old

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Few population studies have evaluated the associations of both coronary artery calcium (CAC) and carotid ultrasound with cardiovascular events, especially in adults >70 years of age. At the Pittsburgh Field Center of the Cardiovascular Health Study, 559 men and women, mean age 80.2 (SD 4.1) years had CAC score assessed by electron beam computerized tomographic scan and common and internal carotid artery intimal medial wall thickness (CCA-IMT and ICA-IMT) by carotid ultrasound between 1998 and 2000 and were followed for total and incident cardiovascular disease events through June 2003. Crude rates and hazard ratios for total and incident events were examined with and without adjustment for cardiovascular risk factors. After 5 years, there were 127 cardiovascular disease events, 48 myocardial infarctions or cardiovascular disease deaths, and 28 strokes or stroke deaths. Total and incident cardiovascular disease event rates were higher in each quartile of CAC and CCA-IMT, but not of ICA-IMT. For total cardiovascular disease, the adjusted hazard ratio for the fourth versus first quartile of CAC was 2.1 (95% confidence interval 1.2 to 3.9) and for CCA-IMT was 2.3 (95% confidence interval 1.3 to 4.1). The CCA-IMT was more strongly related to stroke risk than was CAC, although CAC was also an important predictor of stroke. No significant gender differences were found, although relative risks appeared to be stronger in women, especially for stroke. In conclusion, in adults >70 years of age, CAC and CCA-IMT had similar hazard ratios for total cardiovascular disease and coronary heart disease. The CCA-IMT was more strongly related to stroke than CAC, but CAC was also a predictor of stroke. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101:186–192)

In the Cardiovascular Health Study, coronary artery calcium (CAC) scanning was performed concurrently with carotid ultrasound at 1 of the 4 field centers. We evaluated total cardiovascular disease event rates, myocardial infarction, and stroke by the level of CAC and by internal carotid artery intimal medial wall thickness (ICA-IMT) and common carotid artery intimal medial wall thickness (CCA-IMT) individually and together. We hypothesized that these measures would provide similar prediction of total cardiovascular disease events but that CAC level may be more predictive of myocardial infarction and that carotid wall thickness may be more predictive of stroke.

Methods

The Cardiovascular Health Study is an ongoing investigation of risk factors for cardiovascular disease in older adults in 4 communities in the United States.¹ Both CAC and carotid wall thickness were measured in 559 men and women between the years 1998 and 2000 in the Cardiovascular Health Study in Pittsburgh, Pennsylvania. The CAC scans were scheduled separately from the annual visit when the carotid ultrasound was performed beginning 6 months before the annual visit and were completed up to 6 months after. All participants gave informed consent for testing procedures and follow-up as approved by the Institutional Review Board of the University of Pittsburgh.

Electron-beam computerized tomography (Imatron C-150 scanner, San Francisco, California) was used to assess CAC using a base value region of interest computer program extracts all pixels that 130 Hounsfield units within an operator-defined region of interest in each 3-mm-thick image of the coronary arteries (26 cm² field of view). All pixels >130 Hounsfield units and >1 mm (≥2 contiguous pixels) within the coronary arteries were considered to be calcium. The calcium score was calculated for each region by multiplying the area of significant pixels by a grade number (1, 2, 3, or 4) indicative of the peak computed tomographic number (Hounsfield units). The individual region of interest scores were then summed for a total CAC (Agatston) score.²

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Carotid high-resolution B-mode ultrasonography was used to assess the average maximal thickness of the common and internal carotid arteries.³ The maximal intimal medial thickness of the common carotid artery and of the internal carotid artery was defined as the mean of the maximal intimal medial thickness of the near and far wall on both the left and right sides. The number of measurements that were available for averaging ranged from 1 to 4 for the common carotid artery and 1 to 12 for the internal carotid artery.⁴

Prevalent clinical cardiovascular disease was defined at enrollment as a history of cardiovascular disease, including myocardial infarction, angina, coronary artery bypass, angioplasty or stent placement, heart failure, stroke, transient ischemic attack, endarterectomy, or history of peripheral artery disease defined by self report and confirmed by medication use and with medical records. This was updated by recoding incident events after enrollment and before the time of the second of the 2 scans as prevalent disease.

Over the course of the Cardiovascular Health Study, participants were interviewed by telephone or during an annual in-person clinical examination every 6 months to ascertain new cardiovascular events. The related medical records, death certificates, and informant interviews were reviewed by a central morbidity and mortality committee to confirm fatal and nonfatal cardiovascular disease events including myocardial infarction, angina (symptomatic coronary artery disease), stroke, transient ischemic attack, or hospitalized peripheral artery disease in the legs.^{5,6} All events were symptomatic; no procedures without symptoms were classified as study outcomes. Reviewers of outcomes were blinded to test results. Furthermore, each event record was re-evaluated for the potential that any coronary or peripheral arterial procedure was conducted as a consequence of reporting the coronary calcium scores or the carotid ultrasound results to participants. All events were new symptomatic events; there were no procedures consequent to test reporting.

In the first analyses, the first event after the 2 scans (incident or recurrent disease) was examined for total cardiovascular disease events, including fatal or nonfatal myocardial infarction or coronary heart disease death, angina, stroke, transient ischemic attack, heart failure, or peripheral artery disease. For analysis of incident events only, those with history of that event were excluded. Follow-up was completed through June 2003 with a mean duration of 5 years and was virtually complete for mortality and 94% complete for cardiovascular events.

Age and cardiovascular risk factors were assessed at the 1998 or 1999 clinical examination when the carotid artery scan was performed. Age was updated from baseline reported date of birth. Hypertension was defined as seated average systolic blood pressure >140 mm Hg or diastolic >90 mm Hg or as a history of self-reported hypertension confirmed with use of antihypertensive medication. Diabetes was defined as present if the participant used insulin or oral hypoglycemic medication or if the fasting glucose level was >126 mg/dl (7.0 mmol/L). Cigarette smoking was analyzed as ever (past and current use) versus never; there were few current smokers (8.0%), and total smoking exposure was assessed by pack-years.⁷ Total cholesterol and glucose were assayed from blood samples that were collected at the time of the ultrasound examination and analyzed according to lab methods previously described, except

for low-density lipoprotein cholesterol, which was assessed in 1992 to 1993.⁸

Continuous data were summarized as means and SDs, categorical variables as counts or percentages. Person-years of follow-up were calculated and used to compare unadjusted event rates of total cardiovascular disease events, myocardial infarction or stroke across coronary artery, or carotid artery intimal medial thickness quartiles. Cox proportional hazard models were used to examine relative risks for each quartile of CAC score or the carotid artery wall thickness. Death from noncardiovascular disease causes was considered a censored nonevent. Initial adjusted models considered age, gender, race, and prevalent cardiovascular disease with subsequent adjustment for other cardiovascular risk factors. Models were examined for incident events, excluding those with cardiovascular disease, myocardial infarction or stroke, respectively, from baseline or before the scan date. Interactions between each measure of disease and gender were tested and were not significant. Hazard ratios were expressed as point estimates with their corresponding 95% confidence intervals (CI). All models tested met the assumption of proportional hazards. The predictive accuracy of CAC, CCA-IMT, and ICA-IMT survival models were compared using a global concordance score that is the weighted average of the area under time-specific receiver-operating characteristic curves^{9,10}. The comparisons were between models adjusted for all covariates. The time-varying areas under the curves were nearly constant throughout the 5 years of follow-up, so global concordance was used as the summary measure.

Results

The study included 559 men and women (Table 1). Those in the lower quartiles of CAC were more likely to be women, black, or to have no history of cardiovascular disease. Ages ranged from 70 to 99 years. Other cardiovascular risk factors did not vary substantially across CAC quartiles except for smoking history.

CAC scores ranged from 0 to 5,459 with a median of 333, and 8.9% had scores of 0.0. The average CCA-IMT was 1.1 mm and the ICA-IMT was 1.7 mm. CCA-IMT and ICA-IMT measurements were significantly greater in each higher CAC quartile. Spearman's correlations were 0.19 between the CCA-IMT and CAC score and 0.33 between the ICA-IMT and the CAC score.

After 5 years there were 127 first total cardiovascular disease events after the scans, 48 myocardial infarctions or coronary heart disease deaths, and 28 fatal or nonfatal strokes. In order to compare similar relative ranges of the different measures, the levels of CAC and carotid wall thickness were examined by quartiles (Table 2). Total cardiovascular disease event rates were higher across the quartiles for each measure of disease, although the gradient of risk was less pronounced for the ICA-IMT, largely related to the higher absolute event rate in the lowest quartile. Cardiovascular disease event rates were more than twofold higher in the top quartile of the CAC and common carotid artery. After adjustment for age, gender, and prevalent cardiovascular disease, these relations remained statistically significant in the third and fourth quartiles for both CAC and the fourth quartile of CCA-IMT, but not for the

Table 1

Characteristics of study participants by coronary artery calcium (CAC) quartile: the Cardiovascular Health Study, Pittsburgh Field Center, n = 559.

Characteristic	Quartile of CAC				p Value
	1 0–56 (n = 140)	2 57–332 (n = 143)	3 333–916 (n = 143)	4 >917 (n = 133)	
Age (yrs)	79.0 ± 3.9	79.6 ± 3.9	80.4 ± 4.1	81.9 ± 4.1	<0.0001
Men	38 (27.1%)	41 (28.7%)	64 (54.9%)	80 (40.3%)	
Women	102 (72.9%)	102 (71.3%)	78 (45.1%)	54 (59.7%)	<0.0001
White	89 (63.6%)	112 (78.3%)	115 (81.0%)	118 (89.1%)	
Black	51 (36.4%)	31 (21.7%)	27 (19.0%)	16 (11.9%)	<0.0001
Prevalent CVD	32 (22.9%)	33 (23.1%)	45 (31.7%)	76 (56.7%)	<0.0001
Hypertension	43 (30.9%)	50 (35.0%)	42 (29.6%)	46 (65.7%)	0.7271
Diabetes mellitus	21 (15.0%)	20 (14.0%)	13 (9.2%)	20 (14.9%)	0.4167
Smoking status, n (%)					
Ever smoked	69 (52.3%)	62 (47.3%)	80 (64.5%)	84 (67.2%)	
Never smoked	63 (47.7%)	69 (52.7%)	44 (35.5%)	41 (32.8%)	0.0025
Systolic blood pressure (mm Hg)	131.5 ± 19.7	131.9 ± 21.1	135.5 ± 23.1	134.9 ± 20.1	0.2693
Total cholesterol (mg/dl)	203.9 ± 38.8	200.7 ± 36.1	195.7 ± 35.0	191.9 ± 39.9	0.0447
LDL cholesterol (mg/dl)	118.7 ± 32.6	119.4 ± 29.5	121.4 ± 27.7	120.1 ± 34.5	0.9066
CCA-IMT (mm)	1.1 ± 0.2	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.4	<0.0001
ICA-IMT (mm)	1.3 ± 0.6	1.6 ± 0.9	1.9 ± 0.9	2.0 ± 0.9	<0.0001
CAC (Agatston units)	11.8 ± 15.9	172.8 ± 78.4	591.1 ± 163.8	1,912.9 ± 970.5	<0.0001

Tests of significance for categorical variables were chi-square tests and for continuous variables were analysis of variance.

Data are presented as numbers (percent) and mean ± SD.

CVD = cardiovascular disease; LDL = low-density lipoprotein.

Table 2

Total and incident cardiovascular disease (CVD) events, rates, and hazard ratios (HR) for coronary artery calcium (CAC), common carotid artery intimal medial wall thickness (CCA-IMT), and internal carotid artery intimal medial wall thickness (ICA-IMT)

Quartiles	Total CVD Events					Incident CVD Events				
	No. at Risk	No. of Events	Rate per 100 p-y	HR* (95% CI) (n = 559)	Adjusted HR† (95% CI) (n = 559)	No. at Risk	No. of Events	Rate per 100 p-y	HR‡ (95% CI) (n = 373)	Adjusted HR§ (n = 373)
CAC score										
0–56	140	18	3.5	Referent	Referent	108	8	1.9	Referent	Referent
57–332	143	30	5.9	1.62 (0.90–2.91)	1.56 (0.86–2.80)	110	22	5.4	2.72 (1.20–6.20)	2.89 (1.26–6.64)
333–916	143	37	8.0	2.11 (1.19–3.75)	2.04 (1.14–3.64)	98	21	6.3	3.19 (1.39–7.36)	3.27 (1.41–7.60)
>917	133	42	10.6	2.23 (1.23–4.06)	2.12 (1.16–3.85)	57	13	6.9	3.15 (1.24–8.00)	3.07 (1.20–7.84)
CCA-IMT (mm)										
<.95	141	18	3.6	Referent	Referent	109	12	3.0	Referent	Referent
.95–1.06	140	29	5.9	1.42 (0.79–2.57)	1.29 (0.71–2.35)	93	14	4.0	1.23 (0.57–2.68)	1.00 (0.45–2.24)
1.07–1.22	140	33	6.8	1.71 (0.96–3.04)	1.54 (0.86–2.75)	97	18	5.1	1.60 (0.77–3.32)	1.24 (0.58–2.63)
1.23–3.14	138	47	11.7	2.61 (1.49–4.58)	2.30 (1.30–4.08)	74	20	8.2	2.53 (1.22–5.25)	2.02 (0.95–4.32)
ICA-IMT (mm)										
<1.01	139	27	5.4	Referent	Referent	101	15	3.9	Referent	Referent
1.02–1.44	141	27	5.6	0.92 (0.54–1.59)	0.84 (0.49–1.46)	97	13	3.8	0.84 (0.39–1.78)	0.79 (0.36–1.72)
1.45–2.12	140	27	5.5	0.90 (0.52–1.53)	0.75 (0.43–1.30)	94	14	4.1	0.93 (0.44–1.96)	0.79 (0.37–1.69)
>2.13	139	46	11.2	1.64 (1.00–2.68)	1.39 (0.84–2.30)	81	22	8.4	1.93 (0.98–3.80)	1.61 (0.80–3.25)

* Adjusted for age, gender, race, and prevalent CVD.

† Adjusted for age, gender, race, prevalent CVD, hypertension, diabetes, systolic blood pressure, smoking status, cholesterol, and LDL cholesterol.

‡ Adjusted for age, gender, race.

§ Adjusted for age, gender, race, hypertension, diabetes, systolic blood pressure, smoking status, cholesterol, and LDL cholesterol.

p-y = person-years; other abbreviations as in Table 1.

ICA-IMT. Results were similar when only incident cardiovascular disease events were examined.

When considering myocardial infarction or coronary heart disease death as the outcome (Table 3), relative risks were similar for CAC as for the CCA-IMT. Results were also similar when considering only incident myocardial infarction

or coronary heart disease death, but not statistically significant. Risks were not as striking for the internal carotid artery.

The pattern of association of CAC with stroke suggested similar levels of elevated risk for stroke as for myocardial infarction (Table 4). When considering only incident stroke events, risks related to the CAC score

Table 3

Total and incident myocardial infarction or coronary heart disease rates and hazard ratios (HR) for coronary artery calcium (CAC), common carotid artery intimal medial wall thickness (CCA-IMT), and internal carotid artery intimal medial wall thickness (ICA-IMT)

Quartiles	Total Myocardial Infarction or Coronary Heart Disease Death					Incident Myocardial Infarction or Coronary Heart Disease Death				
	No. at Risk	No. of Events	Rate per 100 p-y	HR* (95% CI) (n = 559)	Adjusted HR† (95% CI) (n = 559)	No. at Risk	No. of Events	Rate per 100 p-y	HR‡ (95% CI) (n = 486)	Adjusted HR§ (n = 486)
CAC score										
0–56	140	6	1.1	Referent	Referent	108	5	1.0	Referent	Referent
57–332	143	10	1.8	1.56 (0.56–4.31)	1.53 (0.55–4.26)	110	9	1.8	1.62 (0.54–4.89)	1.62 (0.54–4.91)
333–917	143	13	2.6	2.02 (0.75–5.42)	1.92 (0.71–5.19)	98	11	2.4	2.19 (0.75–6.44)	2.08 (0.71–6.12)
>917	133	19	4.4	2.94 (1.09–7.90)	2.60 (0.99–7.00)	57	12	3.8	3.19 (1.05–9.72)	3.05 (1.00–9.29)
CCA-IMT (mm)										
<.95	141	7	1.3	Referent	Referent	109	7	1.5	Referent	Referent
.95–1.06	140	10	1.9	1.34 (0.51–3.53)	1.10 (0.41–2.94)	93	7	1.5	0.97 (0.33–2.77)	0.78 (0.27–2.29)
1.07–1.22	140	11	2.1	1.48 (0.57–3.81)	1.25 (0.48–3.26)	97	9	2.0	1.31 (0.49–3.52)	1.05 (0.38–2.90)
1.23–3.14	138	20	4.4	2.99 (1.23–7.26)	2.38 (0.95–5.97)	74	14	3.7	2.52 (0.99–6.43)	1.94 (0.73–5.14)
ICA-IMT (mm)										
<1.01	139	10	1.9	Referent	Referent	101	8	1.6	Referent	Referent
1.02–1.44	141	9	1.8	0.85 (0.35–2.11)	0.80 (0.32–2.00)	97	9	2.2	1.14 (0.44–2.99)	0.99 (0.37–2.64)
1.45–2.12	140	11	2.1	1.05 (0.44–2.49)	0.84 (0.34–2.04)	94	8	1.8	1.01 (0.37–2.72)	0.80 (0.29–2.19)
>2.13	139	18	3.9	1.83 (0.82–4.07)	1.49 (0.65–3.40)	81	12	3.1	1.80 (0.72–4.52)	1.41 (0.55–3.63)

* Adjusted for age, gender, race, and prevalent CVD.

† Adjusted for age, gender, race, prevalent CVD, hypertension, diabetes, systolic blood pressure, smoking status, cholesterol, and LDL cholesterol.

‡ Adjusted for age, gender, race.

§ Adjusted for age, gender, race, hypertension, diabetes, systolic blood pressure, smoking status, cholesterol, and LDL cholesterol.

Abbreviations as in Table 1.

Table 4

Total and incident stroke rates and hazard ratios (HR) for coronary artery calcium (CAC), common carotid artery intimal medial wall thickness (CCA-IMT), and internal carotid artery intimal medial wall thickness (ICA-IMT)

Quartiles	Total Stroke					Incident Stroke				
	No. at Risk	No. of Events	Rate per 100 p-y	HR* (95% CI) (n = 559)	Adjusted HR† (95% CI) (n = 559)	No. at Risk	No. of Events	Rate per 100 p-y	HR‡ (95% CI) (n = 538)	Adjusted HR§ (n = 538)
CAC score										
0–56	140	3	0.6	Referent	Referent	108	3	0.6	Referent	Referent
57–332	143	7	1.3	2.29 (0.59–8.94)	2.51 (0.63–9.91)	110	6	1.1	1.84 (0.46–7.44)	1.93 (0.47–7.85)
333–917	143	11	2.2	4.14 (1.13–15.23)	4.09 (1.09–15.31)	98	9	1.8	3.52 (0.93–13.26)	3.35 (0.88–12.74)
>917	133	7	1.6	3.51 (0.85–14.56)	3.29 (0.79–13.80)	57	6	1.4	2.85 (0.67–12.07)	2.59 (0.60–11.10)
CCA-IMT (mm)										
<.95	141	2	0.4	Referent	Referent	109	2	0.4	Referent	Referent
.95–1.06	140	4	0.8	1.95 (0.36–10.68)	1.64 (0.29–9.14)	93	3	0.6	1.48 (0.25–8.86)	1.26 (0.21–7.69)
1.07–1.22	140	7	1.4	3.48 (0.72–16.76)	3.64 (0.75–17.75)	97	6	1.2	3.07 (0.62–15.24)	2.85 (0.57–14.38)
1.23–3.14	138	15	3.3	8.80 (1.98–39.10)	8.54 (1.90–38.48)	74	13	3.0	8.70 (1.93–39.23)	7.34 (1.57–34.27)
ICA-IMT (mm)										
<1.01	139	5	0.9	Referent	Referent	101	5	1.0	Referent	Referent
1.02–1.44	141	8	1.6	1.60 (0.52–4.93)	1.71 (0.54–5.45)	97	5	1.0	0.97 (0.28–3.39)	1.06 (0.30–3.83)
1.45–2.12	140	3	0.6	0.58 (0.14–2.43)	0.57 (0.13–2.46)	94	3	0.6	0.52 (0.12–2.18)	0.45 (0.10–1.96)
>2.13	139	12	2.6	2.34 (0.81–6.80)	2.48 (0.84–7.29)	81	11	2.5	2.24 (0.76–6.63)	2.07 (0.68–6.30)

* Adjusted for age, gender, race, and prevalent CVD.

† Adjusted for age, gender, race, prevalent CVD, hypertension, diabetes, systolic blood pressure, smoking status, cholesterol, and LDL cholesterol.

‡ Adjusted for age, gender, race.

§ Adjusted for age, gender, race, hypertension, diabetes, systolic blood pressure, smoking status, cholesterol, and LDL cholesterol.

Abbreviations as in Tables 1 and 2.

were higher and statistically significant. The CCA-IMT appeared to be more strongly related to stroke than coronary calcium level, with an adjusted hazard ratio of 8.5 (95% CI 1.9 to 38.5) for the highest quartile of CCA-IMT. When considering only incident stroke, risk esti-

mates were similar and remained statistically significant for the fourth quartile of CCA-IMT. Findings for the ICA-IMT were not statistically significant.

In order to compare the relative contribution of each of these measures with cardiovascular disease risk, we considered

Table 5

Cardiovascular disease (CVD) event rates and hazard ratios(HR); models include coronary artery calcium (CAC), common carotid artery intimal medial wall thickness (CCA-IMT), and internal carotid artery intimal medial wall thickness (ICA-IMT) together with cardiovascular risk factors

Variables	Total CVD Events	Total MI	Total Stroke
	Adjusted HR* (n = 559)	Adjusted HR* (n = 559)	Adjusted HR* (n = 559)
Age (yrs)	1.03 (0.99–1.08)	1.00 (0.92–1.07)	1.04 (0.94–1.16)
Men	0.73 (0.49–1.09)	1.10 (0.58–2.07)	0.24 (0.10–0.61)
Race (Black)	0.86 (0.54–1.37)	0.54 (0.23–1.28)	1.03 (0.37–2.84)
CAC score			
0–56	Referent	Referent	Referent
57–332	1.54 (0.85–2.79)	1.46 (0.52–4.11)	2.53 (0.60–10.67)
333–917	2.10 (1.16–3.81)	1.91 (0.69–5.31)	4.61 (1.14–18.70)
>917	2.37 (1.27–4.45)	2.66 (0.94–7.49)	3.73 (0.81–17.11)
CCA-IMT (mm)			
<.95	Referent	Referent	Referent
.95–1.06	1.36 (0.74–2.50)	1.13 (0.41–3.09)	1.80 (0.32–10.19)
1.07–1.22	1.61 (0.88–2.95)	1.30 (0.48–3.51)	4.22 (0.84–21.20)
1.23–3.14	2.35 (1.28–4.32)	2.31 (0.86–6.22)	11.25 (2.28–55.61)
ICA-IMT (mm)			
<1.01	Referent	Referent	Referent
1.02–1.44	0.76 (0.44–1.32)	0.78 (0.30–1.99)	1.34 (0.40–4.47)
1.45–2.12	0.50 (0.28–0.91)	0.59 (0.23–1.50)	0.20 (0.04–0.95)
>2.13	0.90 (0.52–1.56)	0.97 (0.39–2.39)	0.75 (0.22–2.52)
Prevalent CVD	1.80 (1.24–2.62)	—	—
Prevalent MI	—	1.68 (0.81–3.47)	—
Prevalent stroke	—	—	4.67 (1.51–14.43)
Hypertension	1.44 (0.99–2.11)	1.55 (0.84–2.86)	0.64 (0.27–1.53)
Diabetes	1.66 (1.03–2.69)	2.01 (0.95–4.28)	1.78 (0.56–5.67)
Systolic blood pressure (mm Hg)	1.00 (0.99–1.01)	1.01 (0.99–1.02)	1.01 (0.99–1.03)
Smoking status (ever)	1.39 (0.95–2.00)	1.37 (0.74–2.54)	1.27 (0.56–2.85)
Cholesterol (mg/dl)	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (0.99–1.01)
LDL cholesterol (mg/dl)	1.00 (0.99–1.01)	1.00 (0.99–1.01)	0.99 (0.98–1.00)

MI = myocardial infarction; other abbreviations as in Table 1.

models for each outcome that included all 3 measures at once with other cardiovascular risk factors (Table 5). In these models, the hazard ratios remained similar to hazard ratios seen when examining each measure separately, and there was no substantial attenuation of the CAC by the CCA-IMT or vice versa. When considering total cardiovascular disease events as the outcome, both the CAC score and the CCA-IMT were independently predictive of cardiovascular disease events to a similar degree. The CAC level and CCA-IMT were independently and similarly predictive of myocardial infarction, although CI overlapped by 1.0. When considering stroke as the outcome, there seemed to be a stronger association with the CCA-IMT (Table 5); however, CI were wide and overlapping. The ICA-IMT was not related to any of these outcomes in the multivariate models. When only incident events were considered the risks of total cardiovascular disease and myocardial infarction were higher for CAC than for CCA-IMT, but because of the smaller sample size and wider CI, many of the estimates were not statistically significant (data not shown).

All analyses were further stratified by gender. Results suggested that the CAC and CCA-IMT appeared to be more strongly predictive of cardiovascular disease events, myocardial infarction, and stroke in women than in men, although tests for interaction were not significant. However, the number of events in men was too small to interpret interactions meaningfully. Of note, women with low levels of either CAC or CCA-IMT had markedly low rates of myocardial infarction

and stroke (Figure 1), and absolute event rates for total cardiovascular disease and stroke were higher in women than men in the same quartile regardless of disease measure. We further examined the data using a CAC score of 0.0 as a referent group and did not find a difference in rates between CAC of 0.0 versus 1 to 53.

Analysis of time-varying receiver-operator curves for total cardiovascular disease showed that the weighted average areas under the curve (wAUC) or concordance >5 years adjusted for all covariates were similar for each measure: CAC wAUC = 0.67, CCA wAUC = 0.68, ICA wAUC = 0.67. When considering incident cardiovascular disease, wAUC were slightly higher for CAC with adjusted wAUC = 0.68 (CCA-IMT wAUC = 0.65 and ICA-IMT wAUC = 0.66).

Discussion

In this group of older, community-dwelling men and women with a mean age of 80 years, the CCA-IMT and the CAC score had a similar ability to predict total cardiovascular disease events, myocardial infarction, and stroke. Rates of cardiovascular disease events were high— $\geq 3\%$ per year in the lowest quartile of CAC and CCA-IMT. The poorer discrimination of the ICA-IMT was in part due to the higher event rate in the lowest internal carotid artery quartile. There was a tendency for

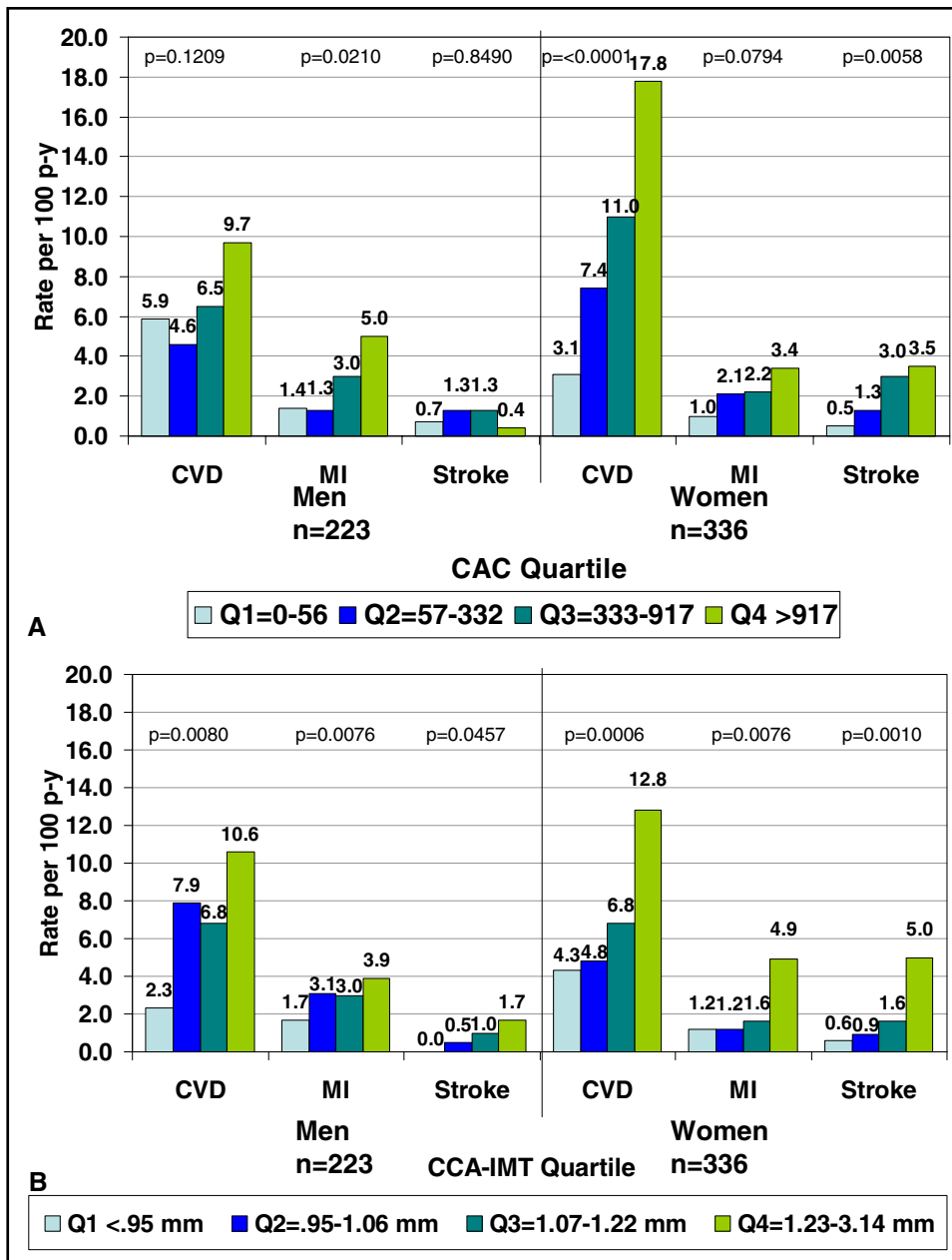


Figure 1. Rates of cardiovascular events in men and women subsequent to CAC scan and CCA-IMT ultrasound. CVD = cardiovascular disease; MI = myocardial infarction; p-y = patient-year.

the CCA-IMT to be more specific for stroke and a slight tendency for CAC to be more predictive of myocardial infarction. Additional follow-up with a larger number of events is needed to determine if there is a substantial advantage for these measures for predicting event type.

There has been little published work comparing these measures as predictors of outcome. However, reports of CAC shows risks of four- to 20-fold, depending on the referent group and population.¹¹⁻¹⁶ This is far in excess of risks previously reported for carotid wall thickness, which range from two- to fivefold, again depending on the population and referent category.^{3,17} This suggests that in those populations reported, the CAC will have better discrimination when compared within a popula-

tion,¹¹⁻¹⁶ as is planned in the Multi-Ethnic Study of Atherosclerosis study.¹⁸ This does not appear to be the case in this older Cardiovascular Health Study cohort; thus it is possible that the high risks being reported for CAC will prove to be age dependent. Our finding of a similar risk prediction for CAC versus CCA-IMT for total cardiovascular disease events is important because stroke is a common aspect of total cardiovascular disease risk in the elderly. Risk assessment methods that consider total cardiovascular disease are highly relevant for preserving quality of life and prevention of disability; therefore, carotid artery screening may have particular utility in advanced old age.

The relative risks shown here are somewhat lower than studies have reported in middle-aged and younger old

adults.^{11–16} This may be in part due to the referent group for our population having substantial disease with levels of CAC and carotid wall thickness that far exceed those seen at younger ages. Our lowest quartile included <10% with calcium scores of 0.0. The predictive power of traditional risk factors is known to decline with increasing age, partly due to selective survival and partly due to the effects of failing health on risk factor levels. This may also hold true for these measures of subclinical atherosclerosis. Both CAC and carotid wall thickness have been shown to predict cardiovascular disease events in older adults, but there are few studies on individuals over age 80 as described here. The absolute event rate for this age group exceeds the 20% event rate in 10 years that is considered to be high risk. Because overall risk is so high, these tests may have greater utility in identifying elderly people with exceptionally low risk.

The CCA-IMT and the CAC levels did not substantially attenuate each other. This finding might have been expected given the modest correlations. This illustrates that there is heterogeneity of disease severity across vascular beds¹⁹ and suggests that these measures should be considered complementary in describing the overall burden of vascular disease in older adults. The lack of significant hazard ratios for ICA-IMT appeared to be due to a higher risk of events in the referent category, suggesting that a low ICA-IMT is less specific for identifying low-risk patients.

Strengths of this study include the long-term detailed characterization of clinical and subclinical cardiovascular disease through advanced old age. The advanced age of the cohort is also a limitation as few men remain. This is likely to result in substantial survival bias for risk prediction. We had limited ability to explore gender differences in risk prediction with these measures as a result of the small sample size of men, which limited power. However, in the women relative risks tended to be higher, and CAC was found to be a strong predictor of stroke risk in women. Consistent with autopsy studies,²⁰ we have previously reported that the CAC and carotid wall thickness is more closely correlated in women than in men.²¹ There is a stronger cross-sectional relation between coronary heart disease and CAC in women than in men.²² Thus, our data support the contention that CAC may better indicate a high overall atherosclerotic burden in women than it does in men, who are more often found to have coronary disease when peripheral disease is limited. There are also potential differences in risk prediction by race.²³ We did not have adequate power to determine this with the number of events in this study. Further follow-up may reveal important differences in risk prediction by both race and gender.¹⁸

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