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Cardiovascular Imaging for Assessing Cardiovascular Risk in Asymptomatic Men Versus Women:

The Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Background—Coronary artery calcium (CAC), carotid intima-media thickness, and left ventricular (LV) mass and geometry offer the potential to characterize incident cardiovascular disease (CVD) risk in clinically asymptomatic individuals. The objective of the study was to compare these cardiovascular imaging measures for their overall and sex-specific ability to predict CVD.

Methods and Results—The study sample consisted of 4965 Multi-Ethnic Study of Atherosclerosis participants (48% men; mean age, 62±10 years). They were free of CVD at baseline and were followed for a median of 5.8 years. There were 297 CVD events, including 187 coronary heart disease (CHD) events, 65 strokes, and 91 heart failure (HF) events. CAC was most strongly associated with CHD (hazard ratio [HR], 2.3 per 1 SD; 95% CI, 1.9 to 2.8) and all CVD events (HR, 1.7; 95% CI, 1.5 to 1.9). Most strongly associated with stroke were LV mass (HR, 1.3; 95% CI, 1.1 to 1.7) and LV mass/volume ratio (HR, 1.3; 95% CI, 1.1 to 1.6). LV mass showed the strongest association with HF (HR, 1.8; 95% CI, 1.6 to 2.1). There were no significant interactions for imaging measures with sex and ethnicity for any CVD outcome. Compared with traditional risk factors alone, overall risk prediction (C statistic) for future CHD, HF, and all CVD was significantly improved by adding CAC, LV mass, and CAC, respectively (all $P<0.05$).

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Conclusions—There was no evidence that imaging measures differed in association with incident CVD by sex. CAC was most strongly associated with CHD and CVD; LV mass and LV concentric remodeling best predicted stroke; and LV mass best predicted HF.

Keywords

imaging; cardiovascular diseases; sex

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in both men and women. Sex differences in the prevalence, presentation, and prognosis of CVD as well as in the role of traditional risk factors in determining CVD risk have been increasingly recognized, which necessitates accrual of sex-specific information for the optimal prevention and management of CVD.[1,2]

Cardiovascular imaging is a well-validated form of noninvasive diagnostic and prognostic testing, and coronary artery calcium (CAC),[3] carotid intima-media thickness (IMT),[4] and left ventricular (LV) mass[5] and geometry[6] offer the potential to characterize increased subsequent CVD risk in clinically asymptomatic individuals. However, there is limited population-based evidence specific to women on the independent and incremental utility of these imaging tests in CVD risk assessment.[7]

Previous studies have evaluated CAC and carotid IMT for their relative performance in predicting incident CVD,[8,9] but CAC, carotid IMT, and LV mass and geometry together have not been assessed in relation to one another with respect to CVD risk estimation. The purpose of this study was to compare these noninvasive imaging tests for their overall and sex-specific predictive value of incident CVD in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods

Study Sample

The MESA is a prospective longitudinal study initiated in July 2000 in a population-based multiethnic cohort of 6814 men and women (age 45 to 84 years, 3601 women) free of clinically recognized CVD at enrollment. The study objectives and design have been previously reported.[10] The study was approved by the institutional review boards of each of the 6 participating US field sites, and all participants gave written informed consent.

Traditional Risk Factor Measurements

Standardized baseline questionnaires were used to obtain information about age, sex, race/ethnicity, cigarette smoking, and medication use for high blood pressure or high cholesterol. Race and ethnicity were characterized on the basis of participants' responses to questions modeled on the year 2000 US census. Cigarette smoking was defined as current, former, or never. Weight was measured with a balance scale to the nearest pound and height to the nearest 0.1 cm with the participants in light clothing and stockings. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Resting blood pressure was measured 3 times in the seated position with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon; Tampa, FL). The average of the last 2 measurements was used in the analysis. Total and high-density lipoprotein (HDL) cholesterol and glucose levels were measured from blood samples obtained after a 12-hour fast. Fasting glucose was obtained by a thin-film adaptation of the glucose oxidase method (Johnson & Johnson Clinical Diagnostics, Inc; Rochester, NY). Diabetes was defined as a fasting glucose of ≥126 mg/dL or use of hypoglycemic medication.

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CAC Measurement

CAC was measured by chest CT imaging with either a cardiac-gated electron-beam CT scanner at 3 sites or a multidetector CT system at the other 3 sites. A radiologist or cardiologist read all CT scans at a central reading center (Los Angeles Biomedical Research Institute at Harbor-UCLA; Torrance, CA) using an interactive scoring system that has been documented previously.[11] The amount of calcium was quantified by using the Agatston scoring method.[12] Details of CT scanning and interpretation methods in MESA have been reported before.[13]

Carotid IMT Measurement

The carotid arteries were evaluated with high-resolution B-mode ultrasonography. Readings were performed centrally at the Department of Radiology, New England Medical Center (Boston, MA). Internal carotid IMT was measured at the level of the carotid bifurcation (common carotid artery bulb and proximal internal carotid artery), and common carotid IMT was measured over a distance of 10 mm proximal to the common carotid bulb. IMT measurement included plaque thickness. Maximal IMT of the internal and common carotid sites was measured as the mean of the maximum IMT of the near and far walls of the right and left sides. A composite *z* score for overall maximal IMT was created by summing the 2 carotid IMT sites (if both were measured) after standardization (subtraction of the mean and division by the SD of each measure) and then dividing by the SD of the sum. If only 1 of the 2 measures was available, it was used. The *z* score maximum IMT has a mean of 0 and an SD of 1.[8]

LV Mass and Volume Measurement

LV mass and volume determination was performed by cardiac MRI using 1.5-T magnets. The endocardial and epicardial myocardial borders were contoured using a semiautomated method (MASS 4.2; Medis; Leiden, The Netherlands). The difference between the epicardial and endocardial areas for all slices was multiplied by the slice thickness and section gap and then multiplied by the specific gravity of myocardium (1.04 g/mL) to determine the ventricular mass. Papillary muscle mass was included in the LV cavity and excluded from the LV mass. The cardiac MRI protocol, image analysis, and inter- and intrareader reproducibility in MESA have been described previously.[14,15]

LV Mass Indexation

Preliminary evaluation in MESA showed that commonly used LV mass indices such as body surface area, height$^{2.7}$, or height$^{1.9}$ do not fully remove the correlation of LV mass with weight, height, or both. We adjusted LV mass for body size by dividing 100×LV mass by predicted LV mass. LV mass was predicted using the following allometric height-, weight-, and sex-adjusted equations previously derived from a separate reference MESA subpopulation of 822 men and women without traditional cardiovascular risk factors, using a multiplicative model estimated by regressing log (LV mass) on log (height), log (weight), and sex: predicted LV mass=a×height$^{0.561}$×weight$^{0.608}$, where a=6.82 for women and 8.17 for men with LV mass in grams, height in meters, and weight in kilograms.[14]

CVD Events

MESA criteria for events were adapted from the Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, and the Women's Health Initiative. A detailed description has been published on adjudication of events as well as follow-up procedures in MESA.[14] The following symptomatic CVD events were considered separately: (1) all coronary heart disease (CHD) (myocardial infarction [definite/probable], resuscitated cardiac arrest, definite angina, probable angina [if followed by revascularization], and CHD

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death [definite/probable]), (2) stroke (fatal or nonfatal, excluding transient ischemic attacks), (3) heart failure (HF) (definite/probable), and (4) all CVD (CHD, stroke, stroke death, HF, other atherosclerotic death, and other CVD death).

Statistical Methods—All analyses were performed using STATA version 9.0 (StataCorp; College Station, TX) statistical software. A 2-sided *P* value of <0.05 was considered statistically significant, unless specified otherwise.

Univariate summary statistics were used to calculate baseline demographic characteristics of the study population by sex. All continuous characteristics are reported as mean±SD and compared using Student unpaired *t* test. Categorical characteristics are reported as frequency (%) and compared using Pearson x^2 test. We used either (1) continuous values of CAC score, carotid IMT, LV mass, and LV mass/volume ratio (CAC values were natural log-transformed after adding 1 before transformation to accommodate zeroes and very small values) or (2) categorical values of imaging measures after dividing them into 3 groups based on quartiles. We combined the first 2 quartiles of each imaging measure in anticipation that first and second quartiles of CAC score would be mostly 0 as based on previous report.[16]

We used multivariate Cox proportional hazards models to calculate overall and sex-specific hazard ratios (HRs) for different incident CVD events in relation to imaging measures of subclinical disease. Sex-specific estimates, wherever necessary, were derived using subgroup analysis. Two different models were used: Model 1 was adjusted for traditional cardiovascular risk factors (age, sex, BMI, ethnicity, cigarette smoking, systolic blood pressure, diabetes, total and HDL cholesterol levels, and hypertension or lipid-lowering medication use), and model 2 was adjusted for traditional cardiovascular risk factors and all 4 imaging measures of subclinical disease (CAC, carotid IMT, LV mass, and LV mass/volume ratio) together. HRs were expressed per 1-SD increment in continuous measures or in relation to the first 2 quartiles as the reference for categorical measures. We tested for 2-way interactions of imaging measures with sex and with ethnicity to assess whether the association of imaging with CVD risk varied with sex and ethnicity; for this, significance was declared at $P<0.006$ after Bonferroni correction due to a total of 8 interaction tests (both sex and ethnicity interactions for each of the 4 imaging measures) per CVD outcome.

Receiver operating characteristic areas under the curve (AUCs) also were used for an overall and sex-specific evaluation and comparison of the imaging measures for their incremental risk predictive ability for each CVD outcome type beyond traditional risk factors. AUCs were computed based on the 5-year predicted risk from the Cox hazards modeling and compared using a parametric method. The 5-year follow-up is almost complete for the study population. In addition to the AUC analysis, we assessed imaging measures for net reclassification improvement (NRI) in CHD risk prediction.[17]

Results

Participant Characteristics

Table 1 shows the characteristics of the study sample, which consisted of 4965 participants (2365 [48%] men; mean age, 62±10 years; race/ethnicity, 39% white, 13% Chinese, 26% black, 22% Hispanic) who had available measures of CAC, carotid IMT, and LV mass and volume. Men had a significantly higher burden of subclinical disease at baseline than women based on imaging measures (all $P<0.001$). Over a median follow-up of 5.8 years, there were 297 incident CVD events (187 CHD, 65 stroke, and 91 HF) observed. Men experienced a significantly higher incidence of CHD, HF, and CVD than women (all $P<0.05$).

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Association of Imaging Measures With Incident CVD

Table 2 summarizes HRs (95% CIs) associated with imaging measures treated as continuous variables. In model 2 (traditional risk factors and all imaging measures together), log CAC score showed the highest HR for incident CHD (2.3; 1.9 to 2.8) and CVD (1.7; 1.5 to 1.9) in the overall study population as well as in men (CHD, 2.4; 1.9 to 2.9; CVD, 1.9; 1.6 to 2.3) and women (CHD, 2.2; 1.5 to 3.1; CVD, 1.5; 1.2 to 1.8) separately. Although both LV mass and LV mass/volume ratio were associated with the highest hazard for incident stroke in the overall study cohort (1.3 [1.1 to 1.7] and 1.3 [1.1 to 1.6], respectively), LV mass/volume ratio showed the highest HR among men (1.4; 1.0 to 1.9), and LV mass showed the highest HR among women (1.5; 1.1 to 1.9). LV mass was associated with the highest HR for HF (1.8; 1.6 to 2.1) overall as well as in men (1.9; 1.6 to 2.2) and in women (1.7; 1.3 to 2.2). In models using imaging measures as continuous variables, none of the imaging measures showed a significant 2-way interaction with sex or ethnicity for any of the CVD outcomes (Table 3).

Imaging measures treated as categorical variables (Table 4) revealed similar relationships with CVD events as the continuous analysis. The HRs generally increased with increasing quartiles of the imaging measures in both men and women. The first and second quartiles of LV mass were not associated with incident HF in either sex.

Table 5 shows the AUC statistics for incident CVD prediction. Compared with traditional risk factors alone, AUC values for future CHD, HF, and CVD showed the highest improvement after adding CAC, LV mass, and CAC, respectively, in the overall cohort (0.766 versus 0.815 [$P<0.0001$]; 0.818 versus 0.853 [$P=0.02$]; 0.773 versus 0.797 [$P<0.001$], respectively) and in men (0.714 versus 0.785 [$P<0.0001$]; 0.790 versus 0.845 [$P<0.01$]; 0.738 versus 0.777 [$P<0.01$], respectively). For women, CAC added most to AUC for CHD prediction (0.805 versus 0.835; $P=0.04$).

With regard to the supplemental NRI analysis, addition of CAC to traditional risk factors resulted in the highest improvement in CHD prediction among all imaging measures (NRI for CAC, 0.24; $P<0.001$; carotid IMT, 0.04; $P=0.27$; LV mass, 0.02; $P=0.58$; LV mass/volume, 0.06; $P=0.06$) (results not shown in tables).

Discussion

The present study did not find significant sex differences in the ability of a range of imaging measures to predict CVD overall and CHD, stroke, and HF separately despite the clinically relevant differences between men and women with respect to CVD. In addition, CAC was most strongly associated with CHD and CVD; LV mass and LV concentric remodeling were most strongly associated with stroke; and LV mass showed the strongest association with HF after adjustment for traditional risk factors in the overall MESA sample and in men and women separately. Imaging measures showed these associations with incident CVD independently of one another. According to the AUC analysis, CAC provided the highest incremental CHD prediction in both men and women, and LV mass added the most to HF prediction beyond traditional risk factors in men compared with the other imaging measures.

A number of prior studies have reported a strong positive association between CAC score and incident CHD after inclusion of conventional coronary risk factors.[3] A prospective analysis in MESA has addressed the potential utility of CAC versus IMT for CVD risk prediction and found that CAC better predicted CHD and total CVD than did IMT.[8] Similarly, CAC has been shown in detail to significantly improve CHD risk classification in MESA using the NRI statistic.[18] Previous ECG- and echocardiography-based studies have demonstrated LV hypertrophy and abnormal LV geometry to confer an independent,

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increased risk of stroke.[19,20] Although the highest quartile of IMT was linked to an increased risk of CHD independent of traditional risk factors as well as of other imaging tests, IMT did not show an independent association with stroke, in contrast to prior reports.[4,8] This finding could be variously attributable to methodological differences among these studies with respect to population demographics, carotid segment definition, ultrasound protocols, adjustment for confounding covariates, and definition and number of clinical end points.

Sex and Ethnic Considerations

Imaging measures of subclinical CVD are associated similarly with incident CVD in men and women as indicated by the lack of any effect modification by sex. This finding is despite the multifactorial influence of female reproductive hormones on the cardiovascular system and lower sensitivity and specificity of imaging modalities for disease detection in women due to smaller vessels and heart size,[15,21] and the resulting potential for larger errors in measurements. Our study offered an important advantage over previous studies by calculating and comparing hazards in relation to standardized increments in CAC score used as a continuous measurement, ensuring a greater degree of comparability between the 2 sexes. Furthermore, other studies were based on specialized study samples consisting of largely white patients selected by primary care physicians for screening, thereby limiting the applicability of their findings to population-based settings.

Past studies have demonstrated racial differences in the prevalence and severity of many of these imaging risk measures, favoring the due consideration of ethnicity in any cardiac risk prediction tool. Whites have been reported to have a higher prevalence and extent of CAC than blacks and other racial/ethnic groups[22] but lower LV mass and lower prevalence of concentric LV hypertrophy than blacks.[23] In our multiethnic cohort, absence of ethnicity interactions in the prognostic value of imaging measures implies that imaging tests may have a similar ability of risk stratification across different ethnicities to sex. Further research is needed to determine whether the same levels of these imaging measures (eg, CAC) translate to differences in prognosis depending on race/ethnicity, which may result in improved characterization of CVD risk across different ethnic groups.

Strengths and Limitations

Strengths of this study include its large, ethnically diverse cohort free of symptomatic CVD at baseline, standardized imaging protocols and risk factor assessments, and reliance on systematically defined symptomatic end points. We assessed imaging measures as both continuous and categorical variables, which enabled more complete assessment of their relationship to CVD outcomes.

Several limitations exist. First, our study had limited power to detect stroke and HF associations, particularly incremental risk prediction, and to assess sex and ethnicity interactions. Women showed relatively fewer cardiovascular events. Coronary artery disease is known to lag by approximately a decade in women compared to men, with an observed increase in coronary calcification in women after the sixth decade.[3] The cardiovascular risk and event rates should predictably increase in women with the aging of this population on longer-term follow-up. For the same reason, the relationship between imaging measures and cardiovascular risk could not be evaluated by specific sex and ethnic subgroups. Second, carotid plaque area (CPA) is known to be an independent predictor of coronary artery disease and future cardiovascular risk and is believed to be a more direct measure of the global atherosclerotic process and stronger predictor of cardiovascular risk than carotid IMT.[24–26] CPA >0 emerged to be moderately more sensitive in detecting underlying coronary artery plaque stenosis than CAC >0. This finding is potentially attributable to the

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reliance of CAC testing on the presence of calcium in the plaque, which may not characterize early lesions because of the correlation of calcification with disease evolution over time.[25] Although this prior evidence could underlie the scope of a direct comparative assessment of CAC and CPA for their predictive ability of CHD and CVD, it could not be accomplished in the present study because of the nonavailability of measures of plaque area. Third, we could not compare imaging measures for their NRI for prediction of events other than CHD. Reclassification measures depend on particular risk categories used. However, unlike CHD, there are no clearly defined clinical risk categories for stroke, HF, and all CVD, rendering any choice of categorization as arbitrary and movement among categories not clearly meaningful. This issue was compounded by the limited number of strokes and HF events in MESA. Finally, the cardiovascular events considered were an admixture of both hard (myocardial infarction, resuscitated cardiac arrest, stroke, CHD death, stroke death) and soft end points (angina, HF, other atherosclerotic death, other CVD death) to maximize statistical power.

Conclusion

Bioimaging tests differ in their association with incident CVD. Their ability to predict cardiovascular events does not seem to differ by sex and ethnicity.

CLINICAL PERSPECTIVE

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in both men and women. We found that (1) coronary artery calcium (CAC) was most strongly associated with coronary heart disease and total CVD, (2) left ventricular (LV) mass and concentric remodeling best predicted stroke, and (3) LV mass best predicted heart failure. Refining the role of potentially competing bioimaging tests in CVD risk assessment can guide the selection of the optimal screening test for a given population. Although CAC best predicted overall incident CVD events, it may be more relevant in populations where coronary heart disease is common, and LV mass and concentric remodeling may be more suitable if demographics and risk factor profile favor an increased likelihood of subsequent heart failure or stroke. Practical considerations such as cost, availability, patient preference, local expertise, and technological limitations are important factors that also may dictate the potential choice among these imaging measures. Although the number of events in women was limited, our results provide population-based evidence that the independent prognostic utility of CAC, LV mass, and LV concentric remodeling in women is similar to men and suggest that CAC offers incremental risk prediction beyond traditional risk factors in women as in men. Like sex, imaging tests also may have a similar ability of risk stratification across different ethnicities.

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References

1. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Roger VL, Thom T, Wasserthiel-Smoller

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S, Wong ND, Wylie-Rosett J, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. Circulation 2010;121:e46–e215. [PubMed: 20019324]

2. Pilote L, Dasgupta K, Guru V, Humphries KH, McGrath J, Norris C, Rabi D, Tremblay J, Alamian A, Barnett T, Cox J, Ghali WA, Grace S, Hamet P, Ho T, Kirkland S, Lambert M, Libersan D, O'Loughlin J, Paradis G, Petrovich M, Tagalakis V. A comprehensive view of sex-specific issues related to cardiovascular disease. CMAJ 2007;176:S1–S44. [PubMed: 17353516]
3. Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, Lauer MS, Post WS, Raggi P, Redberg RF, Rodgers GP, Shaw LJ, Taylor AJ, Weintraub WS, Harrington RA, Abrams J, Anderson JL, Bates ER, Grines CL, Hlatky MA, Lichtenberg RC, Lindner JR, Pohost GM, Schofield RS, Shubrooks SJ Jr, Stein JH, Tracy CM, Vogel RA, Wesley DJ, American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography); Society of Atherosclerosis Imaging and Prevention; Society of Cardiovascular Computed Tomography. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). Circulation 2007;115:402–426. [PubMed: 17220398]
4. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007;115:459–467. [PubMed: 17242284]
5. Gardin JM, Lauer MS. Left ventricular hypertrophy: the next treatable, silent killer? JAMA 2004;292:2396–2398. [PubMed: 15547168]
6. Pierdomenico SD, Lapenna D, Bucci A, Manente BM, Cuccurullo F, Mezzetti A. Prognostic value of left ventricular concentric remodeling in uncomplicated mild hypertension. Am J Hypertens 2004;17:1035–1039. [PubMed: 15533730]
7. Mieres JH, Shaw LJ, Arai A, Budoff MJ, Flamm SD, Hundley WG, Marwick TH, Mosca L, Patel AR, Quinones MA, Redberg RF, Taubert KA, Taylor AJ, Thomas GS, Wenger NK, Cardiac Imaging Committee, Council on Clinical Cardiology; Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. Circulation 2005;111:682–696. [PubMed: 15687114]
8. Folsom AR, Kronmal RA, Detrano RC, O'Leary DH, Bild DE, Bluemke DA, Budoff MJ, Liu K, Shea S, Szklo M, Tracy RP, Watson KE, Burke GL. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med 2008;168:1333–1339. [PubMed: 18574091]
9. Newman AB, Naydeck BL, Ives DG, Boudreau RM, Sutton-Tyrrell K, O'Leary DH, Kuller LH. Coronary artery calcium, carotid artery wall thickness, and cardiovascular disease outcomes in adults 70 to 99 years old. Am J Cardiol 2008;101:186–192. [PubMed: 18178404]
10. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–881. [PubMed: 12397006]
11. Yaghoubi S, Tang W, Wang S, Reed J, Hsiai J, Detrano R, Brundage B. Offline assessment of atherosclerotic coronary calcium from electron beam tomograms. Am J Card Imaging 1995;9:231–236. [PubMed: 8680138]
12. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–832. [PubMed: 2407762]

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13. Carr JJ, Nelson JC, Wong ND, McNitt-Gray M, Arad Y, Jacobs DR Jr, Sidney S, Bild DE, Williams OD, Detrano RC. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. Radiology 2005;234:35–43. [PubMed: 15618373]

14. Bluemke DA, Kronmal RA, Lima JA, Liu K, Olson J, Burke GL, Folsom AR. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. J Am Coll Cardiol 2008;52:2148–2155. [PubMed: 19095132]

15. Natori S, Lai S, Finn JP, Gomes AS, Hundley WG, Jerosch-Herold M, Pearson G, Sinha S, Arai A, Lima JA, Bluemke DA. Cardiovascular function in Multi-Ethnic Study of Atherosclerosis: normal values by age, sex, and ethnicity. Am J Roentgenol 2006;186:S357–S365. [PubMed: 16714609]

16. Bild DE, Detrano R, Peterson D, Guerci A, Liu K, Shahar E, Ouyang P, Jackson S, Saad MF. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2005;111:1313–1320. [PubMed: 15769774]

17. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new biomarker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–172. [PubMed: 17569110]

18. Polonsky TS, McClelland RL, Jorgensen NW, Bild DE, Burke GL, Guerci AD, Greenland P. Coronary artery calcium score and risk classification for coronary heart disease prediction. JAMA 2010;303:1610–1616. [PubMed: 20424251]

19. Di Tullio MR, Zwas DR, Sacco RL, Sciacca RR, Homma S. Left ventricular mass and geometry and the risk of ischemic stroke. Stroke 2003;34:2380–2384. [PubMed: 12958319]

20. Kohsaka S, Sciacca RR, Sugioka K, Sacco RL, Homma S, Di Tullio MR. Additional impact of electrocardiographic over echocardiographic diagnosis of left ventricular hypertrophy for predicting the risk of ischemic stroke. Am Heart J 2005;149:181–186. [PubMed: 15660051]

21. Sheifer SE, Canos MR, Weinfurt KP, Arora UK, Mendelsohn FO, Gersh BJ, Weissman NJ. Sex differences in coronary artery size assessed by intravascular ultrasound. Am Heart J 2000;139:649–653. [PubMed: 10740147]

22. Orakzai SH, Orakzai RH, Nasir K, Santos RD, Edmundowicz D, Budoff MJ, Blumenthal RS. Subclinical coronary atherosclerosis: racial profiling is necessary! Am Heart J 2006;152:819–827. [PubMed: 17070140]

23. Kamath S, Markham D, Drazner MH. Increased prevalence of concentric left ventricular hypertrophy in African-Americans: will an epidemic of heart failure follow? Heart Fail Rev 2006;11:271–277. [PubMed: 17131073]

24. Finn AV, Kolodgie FD, Virmani R. Correlation between carotid intimal/medial thickness and atherosclerosis: a point of view from pathology. Arterioscler Thromb Vasc Biol 2010;30:177–181. [PubMed: 19679833]

25. Brook RD, Bard RL, Patel S, Rubenfire M, Clarke NS, Kazerooni EA, Wakefield TW, Henke PK, Eagle KA. A negative carotid plaque area test is superior to other noninvasive atherosclerosis studies for reducing the likelihood of having underlying significant coronary artery disease. Arterioscler Thromb Vasc Biol 2006;26:656–662. [PubMed: 16357319]

26. Johnsen SH, Mathiesen EB, Joakimsen O, Stensland E, Wilsgaard T, Lochen ML, Njolstad I, Arnesen E. Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than in men: a 6-year follow-up study of 6226 persons: the Tromso study. Stroke 2007;38:2873–2880. [PubMed: 17901390]

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Table 1
Demographics of the Study Population by Sex

Characteristic	Overall (n=4965)	Men (n=2365)	Women (n=2600)	*P**
Traditional risk factors				
Age, y	61.5±10.1	61.6±10.1	61.5±10.1	0.68
Ethnicity				0.11
White	1944 (39.2)	919 (38.9)	1025 (39.4)	
Chinese	652 (13.1)	318 (13.4)	334 (12.8)	
Black	1272 (25.6)	577 (24.4)	695 (26.7)	
Hispanic	1097 (22.1)	551 (23.3)	546 (21.0)	
BMI, kg/m^2	27.7±4.9	27.4±4.1	28±5.6	<0.001
Systolic blood pressure, mm Hg	125.4±21.3	125±19.3	126±22.9	0.49
Total cholesterol, mg/dL	194.2±35.4	188±34.1	200±35.7	<0.001
HDL cholesterol, mg/dL	51.2±14.9	45.1±11.6	56.8±15.5	<0.001
Diabetes	578 (11.6)	271 (10.4)	307 (13.0)	<0.01
Cigarette smoking				<0.001
Never	2552 (51.6)	993 (42.1)	1559 (60.2)	
Former	1773 (35.8)	1028 (43.6)	745 (28.7)	
Current	626 (12.6)	338 (14.3)	288 (11.1)	
Hypertension medication	1748 (35.2)	798 (33.7)	950 (36.6)	<0.05
Lipid-lowering medication	790 (15.9)	365 (15.4)	425 (16.4)	0.37
Imaging-derived subclinical risk measures				
CAC score, median (IQR)	0 (0, 75)	13.6 (0, 154.9)	0 (0, 26.6)	<0.001
Maximal common carotid IMT, mm	0.9±0.2	1.1±0.6	0.9±0.6	<0.001
Maximal internal carotid IMT, mm	1.1±0.6	0.9±0.2	0.8±0.2	<0.001
LV mass, g	145.3±39.6	169±37.3	124±27.4	<0.001
LV mass/volume, g/mL	1.2±0.2	1.2±0.3	1.1±0.2	<0.001
Incident CVD events				
CHD	187 (3.8)	134 (5.7)	53 (2.0)	<0.001
Stroke	65 (1.3)	27 (1.1)	38 (1.5)	0.32
HF	91 (1.8)	58 (2.5)	33 (1.3)	<0.01
All CVD	297 (5.9)	190 (8.0)	107 (4.1)	<0.001

Data are presented as no. (%) or mean±SD, unless otherwise indicated. IQR indicates interquartile range.

*The *P* value is for difference between men and women.

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Table 2

HRs and 95% CIs for Incident CVD by Imaging Measures of Subclinical Disease Treated as Continuous Variables

	Model 1*			Model 2†		
Measure	**Overall (n=4965)**	**Men (n=2365)**	**Women (n=2600)**	**Overall (n=4965)**	**Men (n=2365)**	**Women (n=2600)**
CHD (n=187)						
CAC score	**2.4 (1.9–2.8)‡**	**2.4 (1.9–3.0)‡**	**2.3 (1.7–3.3)‡**	**2.3 (1.9–2.8)‡**	**2.4 (1.9–2.9)‡**	**2.2 (1.5–3.1)‡**
Carotid IMT	1.3 (1.1–1.5)‡	1.2 (1.0–1.4)§	1.5 (1.1–1.9)//	1.1 (0.9–1.3)	1.0 (0.9–1.2)	1.3 (1.0–1.7)
LV mass	1.1 (1.0–1.3)§	1.2 (1.0–1.4)§	1.1 (0.8–1.4)	1.1 (0.9–1.2)	1.1 (0.9–1.3)	1.0 (0.8–1.3)
LV mass/volume	1.2 (1.0–1.4)//	1.2 (1.0–1.4)§	1.2 (0.9–1.6)	1.1 (0.9–1.3)	1.2 (0.9–1.3)	1.1 (0.8–1.5)
Stroke (n=65)						
CAC score	1.1 (0.8–1.4)	1.4 (0.9–2.2)	0.9 (0.6–1.3)	1.0 (0.8–1.4)	1.3 (0.8–2.1)	0.9 (0.6–1.3)
Carotid IMT	1.1 (0.8–1.3)	1.2 (0.9–1.7)	0.9 (0.6–1.3)	1.0 (0.8–1.3)	1.1 (0.8–1.6)	0.9 (0.6–1.3)
LV mass	**1.3 (1.1–1.7)//**	1.2 (0.9–1.7)	**1.4 (1.1–1.9)§**	**1.3 (1.1–1.7)//**	1.2 (0.8–1.6)	**1.5 (1.1–1.9)//**
LV mass/volume	**1.3 (1.1–1.6)//**	**1.4 (1.1–1.9)§**	1.3 (0.9–1.7)	**1.3 (1.1–1.6)//**	**1.4 (1.0–1.9)§**	1.3 (0.9–1.7)
Heart failure (n=91)						
CAC score	1.4 (1.1–1.8)//	1.4 (0.9–1.8)	1.6 (1.1–2.4)§	1.4 (1.1–1.7)§	1.4 (0.9–1.9)	1.4 (0.9–2.2)
Carotid IMT	1.0 (0.9–1.3)	0.9 (0.8–1.3)	1.1 (0.8–1.6)	0.9 (0.7–1.1)	0.8 (0.6–1.1)	1.0 (0.7–1.5)
LV mass	**1.8 (1.6–2.1)‡**	**1.9 (1.6–2.1)‡**	**1.8 (1.4–2.4)‡**	**1.8 (1.6–2.1)‡**	**1.9 (1.6–2.2)‡**	**1.7 (1.3–2.2)‡**
LV mass/volume	1.1 (0.9–1.4)	1.1 (0.8–1.3)	1.3 (0.9–1.7)	1.1 (0.9–1.3)	1.1 (0.8–1.3)	1.2 (0.9–1.7)
All CVD (n=297)						
CAC score	**1.7 (1.5–2.0)‡**	**1.9 (1.6–2.3)‡**	**1.5 (1.2–1.9)‡**	**1.7 (1.5–1.9)‡**	1.9 (1.6–2.3)‡	1.5 (1.2–1.8)‡
Carotid IMT	1.2 (1.0–1.3)//	1.2 (1.0–1.3)§	1.2 (0.9–1.4)	1.0 (0.9–1.1)	0.9 (0.8–1.1)	1.1 (0.9–1.3)
LV mass	1.4 (1.2–1.5)‡	1.4 (1.2–1.5)‡	1.3 (1.1–1.5)//	1.3 (1.2–1.5)‡	1.4 (1.2–1.5)‡	1.2 (1.0–1.5)
LV mass/volume	1.1 (1.0–1.3)//	1.2 (1.0–1.3)§	1.1 (0.9–1.3)	1.1 (1.0–1.2)§	1.1 (1.0–1.3)§	1.1 (0.9–1.3)

CAC score refers to the natural logarithm of (CAC+1) values. Carotid IMT refers to a composite *z* score for overall maximal IMT. LV mass was adjusted for body size when implied as a separate imaging measure but not in LV mass/volume ratio. HR expresses hazard in relation to 1-SD increment of the respective imaging measure. Boldface indicates imaging measures showing the highest HR for each event type.

*Adjusted for traditional risk factors (age, sex, ethnicity, BMI, systolic blood pressure, total and HDL cholesterol, diabetes, cigarette smoking, hypertension, and lipid medication).

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† Adjusted for traditional risk factors as well as imaging-derived measures (CAC, IMT, LV mass, and LV mass/volume) in the same model.

‡ $P \leq 0.001$.

§ $P < 0.05$.

‖ $P \leq 0.01$.

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Table 3

***P* Values* of Two-Way Interactions of Imaging Measures With Sex and Ethnicity for Each CVD Outcome**

	Sex				Ethnicity			
Measure	**CHD**	**Stroke**	**Heart Failure**	**All CVD**	**CHD**	**Stroke**	**HF**	**All CVD**
CAC score	0.89	0.32	0.52	0.43	0.11	0.60	0.90	0.58
Carotid IMT	0.13	0.26	0.45	0.53	0.63	0.05	0.71	0.65
LV mass	0.30	0.84	0.80	0.31	0.49	0.88	0.09	0.21
LV mass/volume	0.97	0.53	0.23	0.65	0.55	0.03	0.25	0.12

CAC score refers to the natural logarithm of (CAC+1) values. Carotid IMT refers to a composite *z* score for overall maximal IMT. LV mass was adjusted for body size when implied as a separate imaging measure but not in LV mass/volume ratio.

*Significance at $P<0.006$ after Bonferroni adjustment for multiple testing.

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Table 4

HRs and 95% CIs for Incident CVD by Imaging Measures of Subclinical Disease Treated as Categorical Variables

		3rd Quartile			4th Quartile		
Measure	**<50th Percentile**	**Overall (n=4965)**	**Men (n=2365)**	**Women (n=2600)**	**Overall (n=4965)**	**Men (n=2365)**	**Women (n=2600)**
CHD (n=187)							
CAC score	Ref	**3.2 (1.9–5.4)***	**3.4 (1.7–6.9)***	**2.6 (1.1–6.1)**†	**6.6 (3.9–10.9)***	**7.6 (3.9–14.8)***	**5.2 (2.2–12.1)***
Carotid IMT	Ref	1.5 (0.9–2.4)	1.3 (0.8–2.1)	2.7 (1.1–6.6)†	2.0 (1.3–3.1)*	1.7 (1.0–2.7)†	3.7 (1.5–9.0)‡
LV mass	Ref	0.8 (0.5–1.2)	0.7 (0.5–1.2)	1.1 (0.5–2.2)	1.2 (0.9–1.7)	1.2 (0.8–1.8)	1.4 (0.7–2.8)
LV mass/volume	Ref	0.8 (0.6–1.3)	1.1 (0.6–1.8)	0.5 (0.2–1.1)	1.5 (1.0–2.1)†	1.8 (1.1–2.8)†	1.1 (0.6–2.1)
Stroke (n=65)							
CAC score	Ref	0.9 (0.4–1.7)	1.1 (0.3–4.4)	0.8 (0.4–1.9)	1.1 (0.5–2.1)	2.1 (0.6–7.0)	0.7 (0.3–1.8)
Carotid IMT	Ref	0.6 (0.3–1.1)	0.8 (0.3–2.4)	0.4 (0.2–1.2)	0.7 (0.4–1.4)	0.7 (0.3–2.0)	0.8 (0.4–1.8)
LV mass	Ref	**2.5 (1.3–4.8)**‡	**2.9 (1.1–8.3)**†	2.0 (0.8–4.9)	**2.3 (1.2–4.4)**†	1.8 (0.6–5.4)	**2.6 (1.1–6.1)**†
LV mass/volume	Ref	**2.2 (1.0–4.4)**†	1.8 (0.5–6.6)	2.1 (0.8–5.0)	**2.9 (1.4–5.7)**‡	2.3 (0.7–7.3)	**3.1 (1.3–7.4)**‡
Heart failure (n=91)							
CAC score	Ref	0.8 (0.4–1.6)	0.6 (0.3–1.5)	1.1 (0.4–3.2)	1.6 (0.9–2.8)	1.1 (0.5–2.4)	2.7 (1.1–6.9)†
Carotid IMT	Ref	0.9 (0.5–1.6)	0.7 (0.3–1.5)	1.1 (0.4–3.2)	0.9 (0.6–1.7)	0.8 (0.4–1.5)	1.4 (0.5–3.8)
LV mass	Ref	1.5 (0.8–2.8)	1.1 (0.4–2.6)	2.3 (0.9–6.3)	**3.9 (2.3–6.7)***	**4.9 (2.6–9.5)***	**3.0 (1.2–7.7)**†
LV mass/volume	Ref	0.6 (0.3–1.1)	0.4 (0.2–0.9)†	0.9 (0.4–2.5)	0.9 (0.5–1.5)	0.7 (0.4–1.2)	1.4 (0.6–3.3)
All CVD (n=297)							
CAC score	Ref	**1.5 (1.0–2.1)**†	1.6 (0.9–2.7)	1.2 (0.7–2.2)	**2.9 (2.0–4.0)***	**3.6 (2.3–5.8)***	**2.2 (1.3–3.7)**‡
Carotid IMT	Ref	1.2 (0.8–1.6)	1.2 (0.8–1.8)	1.1 (0.6–1.9)	1.3 (0.9–1.8)	1.3 (0.9–1.9)	1.4 (0.8–2.4)
LV mass	Ref	1.0 (0.8–1.4)	0.9 (0.6–1.4)	1.4 (0.8–2.2)	1.7 (1.3–2.2)*	1.8 (1.2–2.5)*	1.6 (0.9–2.6)
LV mass/volume	Ref	0.9 (0.7–1.3)	0.9 (0.6–1.3)	0.9 (0.6–1.6)	1.4 (1.0–1.8)†	1.4 (0.9–2.0)	1.2 (0.7–1.9)

CAC score refers to the natural logarithm of (CAC+1) values. Carotid IMT refers to a composite *z* score for overall maximal IMT. LV mass was adjusted for body size when implied as a separate imaging measure but not in LV mass/volume ratio. HR expresses hazard in relation to the first 2 quartiles as reference. Boldface indicates imaging measures showing the highest HR for each event type.

The results presented are based on the model adjusted for both traditional risk factors as well as imaging-derived measures.

* $P \leq 0.001$.

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† $P<0.05$.

‡ $P\leq0.01$.

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Table 5
AUC for Incident CVD by Imaging Measures of Subclinical Disease

Measure	Overall (n=4965)	Men (n=2365)	Women (n=2600)
CHD (n=187)			
Base model*	0.766	0.714	0.805
Base model+CAC	**0.815**†	**0.785**†	**0.835**‡
Base model+carotid IMT	0.777‡	0.720	0.820
Base model+LV mass	0.768	0.722	0.805
Base model+LV mass/volume	0.772‡	0.725	0.809
Base model+CAC+IMT+LV mass	**0.817**†	**0.787**†	0.837
Stroke (n=65)			
Base model	0.835	0.834	0.858
Base model+CAC	0.836	0.838	0.857
Base model+carotid IMT	0.835	0.833	0.856
Base model+LV mass	0.843	0.839	0.869
Base model+LV mass/volume	0.843	0.841	0.864
Base model+CAC+IMT+LV mass	0.844	0.840	0.867
Heart failure (n=91)			
Base model	0.818	0.790	0.851
Base model+CAC	0.826	0.794	0.862
Base model+carotid IMT	0.818	0.791	0.851
Base model+LV mass	**0.853**‡	**0.845**§	0.868
Base model+LV mass/volume	0.818	0.790	0.858
Base model+CAC+IMT+LV mass	**0.856**‡	**0.849**§	0.881
All CVD (n=297)			
Base model	0.773	0.738	0.806
Base model+CAC	**0.797**‖	**0.777**§	0.819
Base model+carotid IMT	0.775	0.739	0.810
Base model+LV mass	0.785‡	0.757‡	0.811
Base model+LV mass/volume	0.777	0.745	0.806
Base model+CAC+IMT+LV mass	**0.806**†	**0.790**†	**0.824**‡

P values stand for comparison with the respective base model. CAC score refers to the natural logarithm of (CAC+1) values. Carotid IMT refers to a composite *z* score for overall maximal IMT. LV mass was adjusted for body size when implied as a separate imaging measure but not in LV mass/volume ratio. Boldface indicates to imaging measures leading to the highest increment in AUC when added to the base model.

* Consists of traditional risk factors only.

† $P \leq 0.0001$.

‡ $P < 0.05$.

§ $P < 0.01$.

‖ $P < 0.001$.