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VASCULAR BIOMARKERS IN THE PREDICTION OF CLINICAL CARDIOVASCULAR DISEASE: THE STRONG HEART STUDY

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Abstract

We compared the ability of separately measured intimal-medial thickness and atherosclerotic plaque to predict incident cardiovascular disease. American Indian men and women from the Strong Heart Study who were free of cardiovascular disease were evaluated with carotid ultrasound and cardiovascular disease risk factor assessment. End-diastolic intimal-medial thickness of the common carotid arteries was measured and averaged. Arterial mass (cross-sectional area) was calculated from intimal-medial thickness and end-diastolic diameter. Atherosclerosis was defined by focal plaque (discrete thickening >50% relative to the adjacent wall) and the number of carotid segments containing plaque (plaque score). 2441 participants (age 63±8 years) were followed for a mean of 7.7±2.8 years during which time 495 experienced incident cardiovascular disease events. Time to event analyses were performed in groups stratified according to diabetes and hypertension status. cardiovascular disease events were predicted by presence and extent of atherosclerosis in all groups; intimal-medial thickness and arterial mass were only associated with outcomes when neither hypertension nor diabetes were present. Unequivocal evidence of atherosclerosis (plaque) and its extent (plaque score) are independently associated with incident cardiovascular disease events in individuals without preexisting cardiovascular disease regardless of diabetes and hypertension status. Hypertension-related increases in IMT and arterial mass appear to limit their use as measures of early or diffuse atherosclerosis and hence association with cardiovascular disease outcomes. These findings support the utility of separate assessment of focal atherosclerosis and intimal-medial thickness in epidemiologic studies, trials, and risk stratification protocols.

Keywords

carotid arteries; epidemiologic methods; cardiovascular disease prognosis

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INTRODUCTION

Duplex carotid ultrasonography has traditionally been used as a clinical tool to evaluate the presence of significant stenosis in the setting of asymptomatic carotid bruit or clinical cerebrovascular disease. More recently, the technique has been utilized in epidemiologic studies to detect subclinical vascular disease (intimal-medial thickness [IMT] and non-obstructive plaque) and assess its relation to cardiovascular disease (CVD) risk factors and prevalent and incident cardiovascular disease (1). Studies examining the prognostic value of carotid ultrasonography have varied in methodology. Importantly, IMT and plaque have not always been separately evaluated. Focal plaque is a direct manifestation of atherosclerosis whereas IMT has been considered a measure of diffuse or early atherosclerosis. However, IMT is increased by hypertension due to medial hypertrophy unrelated to atherosclerosis (2) and is not increased in chronic inflammatory diseases despite markedly premature subclinical (and clinical) atherosclerosis manifest by focal plaque (3–5). Thus protocols reporting wall thicknesses that incorporate focal plaque thickness conflate the two entities and thereby potentially overstate the prognostic importance of 'IMT.'

Although a number of studies have separately examined IMT and plaque in relation to CVD outcomes, several limitations are noteworthy. Multivariable analyses including standard CVD risk factors have not always been performed to examine the independent or additive associations of carotid ultrasound findings (6–8). Some studies have limited CVD events to either myocardial infarction (6,9,10) or stroke (11,12). Other studies have examined combined carotid and femoral artery IMTs (7,8) or have used study-specific internal reference values of multiple averaged IMT segments (13). Thus, the present study was designed to evaluate the separate prognostic associations of definite carotid atherosclerosis (presence and extent of plaque) and common carotid artery wall thickness (IMT) and cross-sectional area in a population with high prevalences of hypertension and diabetes.

METHODS

Study Population

The Strong Heart Study (SHS) is a population-based, longitudinal study of prevalent and incident CVD and its risk factors in American Indians that began in 1989. Details of the study design have been previously published (14,15). At the 3rd examination in 1997–1999, carotid ultrasonography was added to the study protocol.

Blood was drawn following a 12-hour fast to determine lipids, plasma glucose, and creatinine. Diabetes was defined by the American Diabetes Association criteria (16) as fasting plasma glucose ≥7.0 mmol/L (126 mg/dl) or by use of hypoglycemic treatment. Blood pressures were obtained in the seated position from the right brachial artery after 5 minutes of rest by trained personnel using an Omron 907 device (OMRON Healthcare, Inc., Kyoto, Japan). The mean of the second and third of three consecutive readings was recorded. Hypertension was defined by Joint National Committee 7 criteria (17) as systolic pressure ≥140 mmHg, diastolic pressure ≥90 mmHg or current use of antihypertensive medication. Renal function was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (18).

Participants free of clinically overt CVD, including atrial fibrillation, at the 3rd SHS exam were included in analyses. The occurrence of fatal and non-fatal CVD events (myocardial infarction, coronary heart disease, sudden death, congestive heart failure, and ischemic stroke) was tabulated during follow-up, as previously described (19,20). Events were reviewed based on a range of ICD-9 codes (390–448, 250, 518.4, 585, 798); medical charts, autopsy reports, death certificates and informant interviews about causes of death were

independently reviewed by physician members of the SHS morbidity and mortality committees using standard criteria. The study was approved by the participating tribes and institutional review boards of the Indian Health Service and the participating institutions; informed consent was obtained from all participants.

Carotid Ultrasonography

The extracranial carotid arteries were examined using a standardized protocol (2,21). Imaging was performed by field sonographers following central training using Acuson 128 systems equipped with a 7.5-MHz imaging transducer. With the subject in the supine position with slight hyperextension of the neck, the common carotid artery, carotid bulb, and extracranial internal and external carotid arteries were identified. Two-dimensionally guided M-mode tracings of the distal common carotid artery approximately 1 cm proximal to the carotid bulb were obtained with simultaneous ECG and recorded on super VHS videotape. Videotapes were sent to the Reading Center at Weill Cornell Medical Center to be reviewed by an experienced cardiologist (MJR). Suitable frames for measurement were obtained in real time by use of a frame grabber (Imaging Technology, Inc., Woburn, Mass.) interfaced with a high-resolution (640 × 640-pixel) video monitor and stored on diskettes.

All carotid measurements were performed on stored images by use of a mouse-driven computer program (ARTSS, Cornell University). The simultaneous ECG was used to time carotid artery measurements at end diastole. Carotid measurements included IMT of the far wall and end-diastolic diameter. All measurements were performed on several cycles and averaged. Carotid cross-sectional area, a measure of vascular volume or mass, was calculated as previously described (21). Wall thickness and diameter measurements of the left and right common carotid arteries were averaged; averaged values were used in all analyses. Plaques are uncommon in the common carotid artery (22,23), and wall thickness and diameter measurements were never obtained at the level of a discrete plaque. Carotid arteries were also scanned for evidence of atherosclerosis, defined as the presence of wall thickening at least 50% greater than that of the surrounding wall (24). Plaque score, a semi-quantitative measure of the extent of atherosclerosis (11,25,26), was calculated by the number of left and right segments (common carotid, bulb, internal carotid, external carotid) containing plaque; thus plaque score ranged from 0 to 8.

Statistical Analyses

Data are presented as means±standard deviation or percents. For continuous variables, trends across categories defined by hypertension and diabetes status were assessed with analysis of variance using linear contrasts, with post hoc testing for multiple comparisons. Categorical variables were evaluated using chi-square analysis. Relations of carotid ultrasound findings to cardiovascular events were determined in Cox regression analyses adjusting for age, sex, body mass index, waist circumference, current smoking, non-HDL cholesterol, HDL cholesterol, triglycerides, and estimated glomerular filtration rate. The non-hypertensive groups are additionally adjusted for systolic blood pressure and the non-diabetic groups are additionally adjusted for fasting glucose. Two-tailed $p<0.05$ was considered significant.

We tested for multiplicative interactions between vascular measures and sex, diabetes and hypertension by including appropriate cross-product terms in Cox models. There was no significant effect-measure modification by sex for any of the four vascular measures (IMT, arterial mass, plaque and plaque score) in relation to outcomes, but there was evidence of multiplicative interaction of diabetes status with both IMT ($p=0.021$) and vascular mass ($p=0.001$) and of hypertension status with both IMT ($p=0.001$) and vascular mass ($p=0.001$). Although similar effect-modification by diabetes or hypertension status was not observed for

the presence (p=0.424 and p=0.714, respectively) or extent of atherosclerosis (p=0.554 and p=0.425, respectively), all analyses were stratified by diabetes status and by hypertension status. The C-statistic, which is equivalent to the area under the receiver-operating characteristic curve, was calculated as a measure of model discrimination. All analyses were performed with SPSS, version 19 (Chicago, IL) or STATA, version 11 (College Station, TX).

RESULTS

Population Characteristics and CVD Outcomes

A total of 2441 participants were free of prevalent clinical CVD at the time of examination. Mean age was 63±8 years (range 51 to 84 years); 65% were women; body mass index was 31.3±6.6 kg/m^2. Hypertension was present in 52.2% of the population, of whom 69% were taking antihypertensive medications. Use of lipid-lowering therapy was very uncommon at the time of examination (2.4%). Diabetes was present in 47.6% of the population, and 27.4% were active smokers. Among the 2441 participants, 495 (20.3%) suffered initial fatal and non-fatal CVD events (101 myocardial infarction, 204 definite coronary heart disease, 92 stroke, 98 congestive heart failure) during a mean follow-up of 7.7±2.8 years; 21.4% of initial events were fatal.

Traditional CVD risk factors, vascular biomarkers and CVD outcomes are compared in Tables 1 and 2, stratified according to diabetes and hypertension status. Ages were higher and renal function was lower in the two groups with hypertension compared to the other two groups. Body mass index and waist circumference were higher and rates of smoking were lower in the groups with hypertension and/or diabetes compared to the normal group. Body mass index and waist circumference were also significantly higher in the two groups with diabetes compared to the group with hypertension alone. The proportion of men was lowest in those with both hypertension or diabetes. The four groups were comparable in levels of non-HDL cholesterol, however the two groups with diabetes had significantly lower HDL cholesterol levels and significantly higher triglyceride levels than the normal group and the group with hypertension alone. As expected, systolic blood pressure was significantly higher in the hypertensive groups and fasting glucose was significantly higher in the diabetic groups.

Values of IMT, arterial mass, plaque prevalence and plaque score were comparable in the groups with hypertension and/or diabetes and significantly higher compared to the normal group. (Table 2). Incident CVD was substantially higher in the groups with hypertension and/or diabetes compared to the normal group and substantially higher in the two groups with diabetes compared to the group with hypertension alone.

Relation of Vascular Biomarkers to Cardiovascular Disease Events

Results from the Cox models are presented in Table 3. All four vascular imaging biomarkers were strongly associated with incident CVD in both age- and sex-adjusted and broadly adjusted models in the group with neither hypertension nor diabetes. However, neither IMT nor arterial mass was associated with outcomes in either model in the groups with hypertension and/or diabetes. In contrast, atherosclerotic plaque and plaque score were associated with outcomes in all four groups. In secondary analyses adding use of anti-hypertensive or glucose-lowering medications to multivariable analyses did not substantially alter results (data not shown).

In the entire population, the C statistic for prediction of events by risk factors alone (0.700 [95% CI, 0.674–0.726]) was significantly increased by addition of either plaque (C statistic=0.714 [95% CI, 0.688–0.739], p=0.011) or plaque score (C statistic=0.719 [95% CI,

0.694–0.744], p=0.001) to the model. In view of the significant effect modification observed for carotid IMT by hypertension and diabetes status, wherein carotid IMT was only predictive of outcome in the normal group, ROC curve analyses using IMT were restricted to this group. Although addition of IMT substantially increased the magnitude of the C statistic compared to the risk factor model alone (from 0.735 [95% CI, 0.678–0.791] to 0.748 [95% CI, 0.690–0.806), the change was not statistically significant (p=0.198).

To determine whether carotid IMT might be more predictive of incident stroke or coronary artery disease than plaque, we performed additional analyses in the entire group because of the relatively small number of separate events in the four subgroups. Multivariable analyses adjusting for the covariates listed in Table 3 as well as for the presence or absence of diabetes and hypertension indicated that IMT was not an independent predictor of either coronary heart disease or of stroke whereas atherosclerotic plaque was a strong independent predictor of coronary heart disease (HR=1.88 [1.35–2.61], p<0.001) and plaque score was an independent predictor of stroke (HR=1.19 [1.04–1.35], p=0.012).

DISCUSSION

Our study shows that the presence and extent of carotid plaque, direct manifestations of atherosclerosis, are strong predictors of incident CVD, independent of the effects of diabetes, hypertension and other established risk factors. Importantly, our findings are adjusted for both traditional CVD risk factors as well as estimated glomerular filtration rate, itself a potent predictor of CVD risk. In contrast, common carotid artery IMT and arterial mass (cross-sectional area) were only predictive of CVD outcome in SHS participants without diabetes and, particularly, hypertension. Our findings suggest that, in the absence of hypertension, these two vascular biomarkers may represent arterial wall thickening associated with atherosclerosis. In contrast, hypertension-associated medial hypertrophy (2,21) is not independently related to CVD outcomes.

Studies that have analyzed IMT and plaque separately generally show the greatest risk of future CVD events to be conferred by the presence of focal plaque. In one of the first such studies (7), 2000 healthy subjects aged 30–70 years were followed for 6 years after baseline carotid and femoral ultrasound examination. Cardiovascular events occurred in 5.5% of those with increased IMT (diffuse thickening > 1 mm) and in 18.4% of those with plaque (focal thickening of IMT >2 mm). Similarly, in 10,000 healthy individuals followed for 10 years in the Cafes-Caves Study, incident CVD occurred in 8.6% of those with increased IMT and in 39.3% of those with plaque (8). However, neither of these studies adjusted for CVD risk factors. In the Kuopio Ischemic Heart Disease Risk Factor Study of 2,181 middle-aged Finnish men, the four-year risk of acute myocardial infarction was increased 2.1-fold in those with increased IMT (>1.0 mm) and 3.4-fold in those with non-obstructive plaque in comparison to those with normal carotid ultrasound studies (6); again, results were not adjusted for CVD risk factors.

Three recent analyses in population-based studies separately examined IMT and plaque in relation to outcomes and adjusted for CVD risk factors. Among 1249 participants aged 18 to 99 years in the San Daniele Study, a town in northeastern Italy, the relative risk of ischemic cerebrovascular events (ischemic stroke or transient ischemic attack) was 5.6 (95% CI, 3.2–10.1) for common carotid artery IMT >1 mm and 10.4 (95% CI, 6.4–17.1) for ≥1 plaque compared to those with normal IMT and no plaque at baseline exam approximately 12 years earlier (12). The analyses included those with prevalent CVD at baseline, and data were not available from the baseline evaluation to examine IMT as a continuous measure.

In the Atherosclerosis Risk in Communities (ARIC) Study, categories (<25th percentile, 25th to 75th percentile, >75th percentile) of averaged common carotid artery, bifurcation and internal carotid artery IMT and plaque were added to the ARIC 10-year coronary risk score in 13,145 participants without prevalent CVD at baseline (13). The area under the receiver-operating characteristic curve (AUC) significantly improved when plaque, but not IMT, was added to traditional risk factors in women. Although both plaque and IMT increased the AUC in men, the increase was greater for IMT than plaque. Since this study evaluated averaged IMTs measured from areas that might include plaque in the IMT measurement, it is possible that the significance of IMT in relation to outcomes is overstated. The extent of atherosclerosis, i.e., the presence of plaques in multiple segments, was not examined in relation to outcome.

In 2965 members of the Framingham Offspring Study cohort followed for 7.2 years, mean IMT of the common carotid artery, maximum IMT of the internal carotid artery and plaque within the internal carotid artery (defined as IMT>1.5 mm) were all associated with incident cardiovascular events (27). Only the internal carotid artery IMT and plaque resulted in an increase in the C statistic generated by consideration of the Framingham risk score. The present study confirms this observation for both the presence as well as the extent of atherosclerosis. Similarly to the Framingham Offspring Study, the C statistic was not significantly improved by addition of common carotid IMT in our study. However, our group of normal participants (no hypertension or diabetes) is relatively small, and lacks sufficient power for assessment of the incremental discriminatory value of this measure. Larger studies of healthy individuals will be necessary to determine whether the increased magnitude of the C statistic achieved by carotid IMT suggested here in fact represents genuine improvement in risk prediction.

An indirect validation of the superiority of carotid plaque over carotid IMT is provided by the substantially stronger relation of carotid plaque area to significant underlying coronary artery disease as evidenced by computed tomography angiogram (28). Similarly, right carotid artery plaque area were more strongly related to incident myocardial infarction (10) and ischemic stroke (29) than carotid IMT in the Tromsø Study. These results are of particular interest since IMT measurement could incorporate plaque thickness if plaque was present in the pre-defined area where IMT measurements were performed. Although plaque area derived from a two-dimensional ultrasound study may not be a precise measure of atherosclerosis burden, these findings are similar to those using the semi-quantitative plaque score in the present study. The Rotterdam Study found IMT and plaque (evaluated as none vs. at least three plaques using a plaque score) to be equally predictive of myocardial infarction independent of traditional risk factors (9); the authors comment on the ease of plaque assessment compared to the precision required for IMT measurement. Furthermore, in the Rotterdam Study, increasing plaque score (0–6) increased the risk of stroke (11) and, in a separate population of elderly men, plaque score independently predicted all-cause and cardiovascular mortality (30).

There is emerging interest in the concept of ‘vascular’ as opposed to biological age (31,32) as well as the optimal ‘vascular biomarker’ to use as an adjunct to traditional risk stratification techniques (33). Although a recent review (34) and a meta-analysis of published data (35) indicated that carotid IMT is a predictor of cardiovascular events, the authors conceded that IMT measurements were not uniformly made in plaque-free area and that focal plaque may have been included in IMT measurement as a consequence of study protocol dictating site of measurement or requiring ‘maximum IMT.’ The present study indicates that, of vascular structural parameters, the presence and extent of direct evidence of atherosclerosis are more strongly associated with future risk of clinical CVD than is IMT. Interestingly, although carotid artery atherosclerosis is a manifestation of cerebrovascular

disease, the majority of events predicted are due to coronary heart disease, underscoring both the systemic nature of atherosclerosis as well as the greater frequency of cardiac compared to cerebral manifestations.

There are several potential limitations to our study. In the Strong Heart Study, IMT was only measured in the distal common carotid artery. Data from the Cardiovascular Health Study (36) and the British Regional Heart Study (37) suggest a stronger association of common carotid artery (CCA) IMT with prevalent stroke whereas bifurcation or internal carotid artery (ICA) IMT were more strongly related to prevalent myocardial infarction. However, adjusted relative risks for prediction of incident events were only marginally different between the CCA and ICA IMTs in the Cardiovascular Health Study (38). A major advantage of CCA IMT is its higher measurement yield compared to other segments. In the ARIC Study, IMT measurements were obtainable from the CCA in 91.4%, from the bifurcation in 77.3%, and from the ICA in 48.6% of participants (39). A report on 1881 Rotterdam Study participants showed a similar trend in measurement yield: 96% in the CCA, 64% in the bifurcation, and 31% in the ICA (40). Measurement yield of CCA IMT in the current study was comparable to that in these earlier studies (96%). The present findings derive from a cohort of American Indians at high cardiometabolic risk, such that generalizability to other populations cannot be assumed. However stratification and adjustment showed that the presence and extent of atherosclerosis were associated with incident CVD independent of diabetes and hypertension and other risk factors. Furthermore the same traditional risk factors for cardiovascular disease in the general U.S. population have been shown to be operative in the SHS population (20). While one cannot necessarily extrapolate results from this generally obese and insulin resistant population to non-obese, non-insulin resistant populations, our findings will be applicable to a greater proprotion of the broader population if current trends in the rising prevalences of obesity and diabetes continue unabated.

Perspectives

The present study shows that unequivocal evidence of atherosclerosis (plaque) and its extent (plaque score) are independently associated with first incident CVD events in individuals regardless of diabetes and hypertension status. In contrast, IMT and arterial mass were only found to be associated with CVD outcome in the absence of diabetes and hypertension, likely due to hypertension-mediated vascular hypertrophy lessening the likelihood that diffuse vessel wall thickening and lumen dilatation are manifestations of atherosclerosis (41). These findings highlight the value of plaque as a vascular biomarker, and support the utility of separate assessment of focal atherosclerosis and IMT in epidemiologic studies as well as risk assessment protocols. Whether these direct measures of atherosclerosis afford improved risk prediction in selected subgroups warrants further study in larger samples.

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REFERENCES

1. Roman MJ, Naqvi TZ, Gardin JM, Gerhard-Herman M, Jaff M, Mohler E. Clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification: a report from the American Society of Echocardiography and the Society of Vascular Medicine and Biology. J Am Soc Echocardiogr. 2006; 19:943–954. [PubMed: 16880089]

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2. Roman MJ, Saba PS, Pini R, Spitzer M, Pickering TG, Alderman MA, Rosen S, Devereux RB. Parallel cardiac and vascular adaptation in hypertension. Circulation. 1992; 86:1909–1918. [PubMed: 1451262]
3. Manzi S, Selzer F, Sutton-Tyrrell, Fitzgerald SG, Rairie J, Tracy RP, Kuller LH. Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus. Arthritis Rheum. 1999; 42:51–60. [PubMed: 9920014]
4. Roman MJ, Shanker B-A, Davis A, Lockshin MD, Sammaritano L, Simantov R, Crow MK, Schwartz JE, Paget SA, Devereux RB, Salmon JE. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. N Engl J Med. 2003; 349:2399–2406. [PubMed: 14681505]
5. Roman MJ, Moeller E, Davis A, Paget SA, Crow MK, Lockshin MD, Sammaritano L, Devereux RB, Schwartz JE, Levine DM, Salmon JE. Preclinical carotid atherosclerosis in patients with rheumatoid arthritis: prevalence and associated factors. Ann Intern Med. 2006; 144:249–256. [PubMed: 16490910]
6. Salonen, JT.; Salonen, R. Arterial wall thickness, carotid atherosclerosis and the risk of myocardial infarction and cerebrovascular stroke. In: Touboul, PJ.; Crouse, JR., III, editors. Intima. Media Thickness and Atherosclerosis: Predicting the Risk. Parthenon Publishing Group; 1997. p. 97-104.
7. Belcaro G, Nicolaides AN, Laurora G, Cesarone MR, De Sanctis M, Incandela L, Barsotti A. Ultrasound morphology classification of the arterial wall and cardiovascular events in a 6-year follow-up study. Arterioscler Thromb Vasc Biol. 1996; 16:851–856. [PubMed: 8673559]
8. Belcaro G, Nicolaides AN, Ramaswami G, Cesarone MR, De Sanctis M, Incandela L, Ferrari P, Geroulakos G, Barsotti A, Griffin M, Dhanjil S, Sabetai M, Bucci M, Martines G. Carotid and femoral ultrasound morphology screening and cardiovascular events in low risk subjects: a 10-year follow-up study (the CAFES-CAVES study). Atherosclerosis. 2001; 156:379–387. [PubMed: 11395035]
9. van der Meer IM, Bots ML, Hofman A, Iglesias del Sol A, van der Kuip DAM, Witteman JCM. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: The Rotterdam Study. Circulation. 2004; 109:1089–1094. [PubMed: 14993130]
10. Johnsen SH, Mathiesen EB, Joakimsen O, Stensland E, Wilsgaard T, Løchen M-L, Njølstad I, Arnesen E. Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than men. A 6-year follow-up study of 6226 persons: The Tromsø Study. Stroke. 2007; 38:2873–2880. [PubMed: 17901390]
11. Hollander M, Bots ML, Iglesias del Sol A, Koudstaal PJ, Witteman HCM, Grobbee DE, Hofman A, Breteler MMB. Carotid plaques increase the risk of strokes and subtypes of cerebral infarction in Asymptomatic elderly: The Rotterdam Study. Circulation. 2002; 105:2872–2877. [PubMed: 12070116]
12. Prati P, Tosetto A, Vanuzzo D, Bader G, Casaroli M, Canciani L, Castellani S, Touboul P-J. Carotid intima media thickness and plaques can predict the occurrence of ischemic cerebrovascular events. Stroke. 2008; 39:2470–2476. [PubMed: 18617662]
13. Nambi V, Chmabless L, Folsom AR, He M, Hu Y, Mosley T, Volcik K, Boerwinkle E, Ballantyne CM. Carotid intima-media thickness and presence or absence of plaque improves the prediction of coronary heart disease risk. J Am Coll Cardiol. 2010; 55:1600–1607. [PubMed: 20378078]
14. Lee ET, Welty TK, Fabsitz RR, Cowan LD, Lee N-A, Oopik AJ, Cucchiara AJ, Savage PJ, Howard BV. The Strong Heart Study: a study of cardiovascular disease in American Indians: design and methods. Am J Epidemiol. 1990; 132:1141–1155. [PubMed: 2260546]
15. Stoddart ML, Jarvis B, Blake B, Fabsitz RR, Howard BV, Lee ET, Welty TK. Recruitment of American Indians in epidemiologic research: the Strong Heart Study. Am Indian Alsk Native Ment Health Res. 2000; 9:20–37. [PubMed: 11279560]
16. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: follow-up report on the diagnosis of diabetes mellitus. Diabetes Care. 2003; 26:3160–3167. [PubMed: 14578255]
17. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. the National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003; 42:1206–1252. [PubMed: 14656957]

18. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF III, Feldman HI, Kursek JW, Eggers P, Van Lente F, Greene T, Coresh J. for the CKD-EPI Collaboration. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150:604–612. [PubMed: 19414839]
19. Lee ET, Cowan LD, Welty TK, Sievers M, Howard WJ, Oopik A, Wang W, Yeh J, Devereux RB, Rhoades ER, Fabsitz RR, Go O, Howard BV. All-cause mortality and cardiovascular disease mortality in three American Indian populations, aged 45–74 years, 1984–1988: The Strong Heart Study. Am J Epidemiol. 1998; 147:995–1008. [PubMed: 9620042]
20. Howard BV, Lee ET, Cowan LD, Devereux RB, Galloway JM, Go OT, Howard WJ, Rhoades ER, Robbins DC, Sievers ML, Welty TK. Rising tide of cardiovascular disease in American Indians: The Strong Heart Study. Circulation. 1999; 99:2389–2395. [PubMed: 10318659]
21. Roman MJ, Pickering TG, Schwartz JE, Pini R, Devereux RB. Relation of arterial structure and function to left ventricular geometric patterns in hypertensive adults. J Am Coll Cardiol. 1996; 28:751–756. [PubMed: 8772767]
22. Finn AV, Kologie 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]
23. O'Leary DH, Bots ML. Imaging of atherosclerosis: carotid intima-media thickness. Eur Heart J. 2010; 31:1682–1689. [PubMed: 20542989]
24. Salonen R, Seppanen K, Ravramara R, Salonen JT. Prevalence of carotid atherosclerosis and serum cholesterol levels in Eastern Finland. Arteriosclerosis. 1988; 8:788–792. [PubMed: 3196222]
25. Roman MJ, Crow MK, Lockshin MD, Devereux RB, Paget SA, Sammaritano L, Levine DM, Davis A, Salmon JE. Rate and determinants of progression of atherosclerosis in systemic lupus erythematosus. Arthritis Rheum. 2007; 56:3412–3419. [PubMed: 17907140]
26. Howard BV, Roman MJ, Devereux RB, Fleg JL, Galloway JM, Henderson JA, Howard WJ, Lee ET, Mete M, Poolaw B, Ratner RE, Russell M, Silverman A, Stylianou M, Umans JG, Wang W, Weir MR, Weissman NJ, Wilson C, Yeh F, Zhu J. Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: the SANDS randomized trial. JAMA. 2008; 299:1678–1689. [PubMed: 18398080]
27. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB. Carotid-wall intima-media thickness and cardiovascular events. N Engl J Med. 2011; 365:213–221. [PubMed: 21774709]
28. Brook RD, Bard RL, Patel S, Rubenfire M, Clarje NS, Kazerooni EA, Wakefield TW, Henke PK, Eagle KA. A negative carotid plaque area 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]
29. Mathiesen EB, Johnsen SH, Wilsgaard T, Bønaa KH, Løchen M-L, Njølstad I. Carotid plaque area and intima-media thickness in prediction of first-ever ischemic stroke. A 10- year follow-up of 6584 men and women: The Tromsø Study. Stroke. 2011; 42:972–978. [PubMed: 21311059]
30. Störk S, van den Beld AW, von Schacky C, Angermann CE, Lamberts SWJ, Grobbee DE, Bots ML. Carotid artery plaque burden, stiffness and mortality risk in elderly men: a prospective, population-based cohort study. Circulation. 2004; 110:344–348. [PubMed: 15238459]
31. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General Cardiovascular risk profile for use in primary care: The Framingham Heart Study. Circulation. 2008; 117:743–753. [PubMed: 18212285]
32. Cuende JI, Cuende N, Calaveras-Lagartos J. How to calculate vascular age with the SCORE project scales: a new method of cardiovascular risk evaluation. Eur Heart J. 2010; 31:2351–2358. [PubMed: 20584778]
33. Nilsson PM, Boutouyrie P, Laurent S. Vascular aging: a tale of EVA and ADAM in cardiovascular risk assessment and prevention. Hypertension. 2009; 54:3–10. [PubMed: 19487587]
34. Simon A, Megnien J-L, Chironi G. The value of carotid intima-media thickness for predicting cardiovascular risk. Arterioscler Thromb Vasc Biol. 2010; 30:182–185. [PubMed: 19948842]

35. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and metaanalysis. Circulation. 2007; 115:459–467. [PubMed: 17242284]

36. O'Leary DH, Polak JF, Kronmal RA, Kittner SJ, Bond MG, Wolfson SK Jr, Bommer W, Price TR, Gardin JM, Savage PJ. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Heath Study. Stroke. 1992; 23:1752–1760. [PubMed: 1448826]

37. Ebrahim S, Papacosta O, Whincup P, Wannamethee G, Walker M, Nicolaides AN, Dhanjil S, Griffin M, Belcaro G, Rumley A, Lowe GDO. Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: The British Regional Heart Study. Stroke. 1999; 30:841–850. [PubMed: 10187889]

38. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med. 1999; 340:14–22. [PubMed: 9878640]

39. Howard G, Sharrett AR, Heiss G, Evans GW, Chambless LE, Riley WA, Burke GW. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. Stroke. 1993; 24:1297–1304. [PubMed: 8362421]

40. del Sol AI, Moons KGM, Hollander M, Hofman A, Koudstaal PJ, Grobbee DE, Breteler MMB, Witteman JCM, Bots ML. Is carotid intima-media thickness useful in cardiovascular disease risk assessment? The Rotterdam Study. Stroke. 2001; 32:1532–1538. [PubMed: 11441197]

41. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. New Engl J Med. 1987; 316:1371–1375. [PubMed: 3574413]

Table 1

Comparison of Demographic Variables and CVD Risk Factors Stratified According to Diabetes and Hypertension Status

Variable	No HTN or DM (n=734)	HTN Alone (n=545)	DM Alone (n=432)	HTN and DM (n=730)
Age (years)	62.1±7.5	64.6±8.4*	61.9±6.9	63.2±7.2†
Male gender (%)	39.2	38.0	32.2	29.5*
Body mass index (kg/m^2)	29.2±6.2	30.7±6.0*	32.1±6.8*	33.4±6.8*
Waist circumference (cm)	100±15	104±14*	108±15*	108±15*
Current smoking (%)	37.9	27.1*	27.3‡	17.2*
Systolic pressure (mmHg)	120±11	143±19*	139±21*	139±21*
Fasting glucose (mg/dl)	99±11	100±11	191±75*	184±67*
Non-HDL cholesterol (mg/dl)	147±39	146±39	146±39	145±39
HDL cholesterol (mg/dl)	45±14	46±15	39±10*	43±13*
Triglycerides (mg/dl)	127±74	140±86	167±132*	171±129*
eGFR (ml/min per 1.73 m^2)	86±16	79±22*	86±21	78±26*

Abbreviations: CVD=cardiovascular disease; HTN=hypertension; DM=diabetes mellitus; HDL=high density lipoprotein; eGFR= estimated glomerular filtration rate

*p<0.001,

†p<0.05,

‡p<0.005 vs. No HTN or DM group.

Table 2

Comparison of Vascular Biomarkers and CVD Outcomes Stratified According to Diabetes and Hypertension Status

Variable	No HTN or DM (n=734)	HTN Alone (n=545)	DM Alone (n=432)	HTN and DM (n=730)
Intimal-medial thickness (mm)	0.72±0.14	0.75±0.15‡	0.75±0.16§	0.76±0.15*
Arterial mass (mm^2)	15.03±4.12	16.14±4.27*	16.10±4.49*	16.59±4.27*
Atherosclerotic plaque (%)	57.2	66.4‡	66.4†	66.2‡
Plaque score	1.2±1.4	1.6±1.7*	1.4±1.4	1.6±1.7*
Incident CVD, n (%)	74 (10.1)	97 (17.8) §	110 (25.5)*	214 (29.3)*

Abbreviations: CVD=cardiovascular disease; HTN=hypertension; DM=diabetes mellitus

*p<0.001,

†p<0.05,

‡p<0.005,

§p<0.01 vs. No HTN or DM group.

Table 3

Multivariable Cox Regression Models* of Relation of Vascular Biomarkers to Cardiovascular Outcome Stratified According to Diabetes and Hypertension Status

Vascular Biomarker	No HTN or DM HR (95% CIs)	p Value	HTN Alone HR (95% CIs)	p Value	DM Alone HR (95% CIs)	p Value	HTN and DM HR(95%CIs)	p Value
IMT, per SD								
Age-sex adjusted model	1.29 (1.05–1.59)	0.017	0.95 (0.78–1.16)	0.616	1.16 (0.98–1.38)	0.087	0.96 (0.84–1.10)	0.576
Multivariable model	1.26 (1.01–1.57)	0.041	0.96 (0.78–1.17)	0.681	1.10 (0.92–1.31)	0.311	0.96 (0.84–1.10)	0.555
Arterial mass, SD								
Age-sex adjusted model	1.42 (1.15–1.74)	0.001	1.16 (0.95–1.42)	0.142	1.16 (0.97–1.39)	0.103	1.06 (0.91–1.22)	0.463
Multivariable model	1.39 (1.11–1.73)	0.004	1.11 (0.90–1.36)	0.331	1.12 (0.92–1.36)	0.270	1.04 (0.90–1.22)	0.558
Atherosclerotic plaque								
Age-sex adjusted model	2.53 (1.39–4.60)	0.002	1.79 (1.07–3.00)	0.026	1.71 (1.08–2.72)	0.023	2.66 (1.87–3.79)	<0.001
Multivariable model	2.26 (1.25–4.10)	0.007	1.74 (1.06–2.86)	0.030	1.26 (0.80–1.99)	0.319	2.14 (1.50–3.01)	<0.001
Plaque score, per segment								
Age-sex adjusted model	1.42 (1.23–1.63)	<0.001	1.21 (1.083–1.36)	<0.001	1.30 (1.14–1.48)	<0.001	1.34 (1.25–1.44)	<0.001
Multivariable model	1.41 (1.23–1.63)	<0.001	1.17 (1.05–1.30)	0.006	1.26 (1.10–1.43)	0.001	1.22 (1.13–1.31)	<0.001

Abbreviations: HR=hazard ratio; CI=confidence interval; HTN=hypertension; DM=diabetes mellitus; IMT=intimal-medial thickness; SD=standard deviation

*Multivariable models are adjusted for age, sex, body mass index, waist circumference, current smoking, non-HDL cholesterol, HDL cholesterol, triglycerides, and estimated glomerular filtration rate. The non-hypertensive groups are additionally adjusted for systolic blood pressure and the non-diabetic groups are additionally adjusted for fasting glucose.