Carotid Arterial Wall Characteristics Are Associated With Incident Ischemic Stroke But Not Coronary Heart Disease in the Atherosclerosis Risk in Communities (ARIC) Study

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Background and Purpose—Ultrasound measurements of arterial stiffness are associated with atherosclerosis risk factors, but limited data exist on their association with incident cardiovascular events. We evaluated the association of carotid ultrasound-derived arterial stiffness measures with incident coronary heart disease (CHD) and ischemic stroke in the Atherosclerosis Risk in Communities (ARIC) study.

Methods—Carotid arterial strain and compliance, distensibility and stiffness indices, pressure–strain, and Young elastic moduli were measured in 10 407 individuals using ultrasound. Hazard ratios for incident CHD (myocardial infarction, fatal CHD, coronary revascularization) and stroke in minimally adjusted (age, sex, center, race) and fully adjusted models (minimally adjusted model + diabetes, height, weight, total cholesterol, high-density lipoprotein cholesterol, tobacco use, systolic blood pressure, antihypertensive medication use, and carotid intima-media thickness) were calculated.

Results—The mean age was 55.3 years. Over a mean follow-up of 13.8 years, 1267 incident CHD and 383 ischemic stroke events occurred. After full adjustment for risk factors and carotid intima-media thickness, all arterial stiffness parameters (carotid arterial strain hazard ratio [HR], 1.14 [95% CI, 1.02–1.28]; arterial distensibility HR, 1.19 [1.02–1.39]; stiffness indices HR, 1.14 [1.04–1.25]; pressure–strain HR, 1.17 [1.06–1.28]; Young elastic moduli HR, 1.13 [1.03–1.24]), except arterial compliance (HR, 1.02 [0.90–1.16], were significantly associated with incident stroke but not with CHD.

Conclusions—After adjusting for cardiovascular risk factors, ultrasound measures of carotid arterial stiffness are associated with incident ischemic stroke but not incident CHD events despite that the 2 outcomes sharing similar risk factors.

Clinical Trial Registration—URL: www.clinicaltrials.gov. Unique identifier: NCT00005131.

Key Words: ARIC ■ arterial stiffness ■ carotid ultrasound ■ coronary heart disease ■ stroke

Aging is associated with progressive stiffening of the arteries, a process that involves the progressive disorganization of elastin lamellae, loss of compliance, and a resultant increase in pressure. These increased pressure loads are then transferred to the heart and other organs such as the brain and kidney and may thereby increase the risk of cardiovascular disease (CVD) events. Arterial stiffness can be noninvasively measured using pulse wave velocity (regional) or ultrasound-based distensibility (local) measurements.

A previous report from the Atherosclerosis Risk in Communities (ARIC) study showed that local measurement of carotid artery stiffness was only weakly associated with carotid intima-media thickness (CIMT), suggesting that arterial stiffening may be a process independent of arterial thickening. Therefore, variations in arterial stiffness may contribute risk of cardiovascular events independent of CIMT.

However, data on the association between ultrasound-based local arterial stiffness and incident CVD are limited. Two studies with limited follow-up (ie, ≤4 years) reported no significant association of common carotid distensibility with incident CVD.

Therefore, we investigated whether carotid ultrasound-derived local arterial wall characteristics are associated with incident CVD events in the ARIC study with almost 14 years of follow-up.

Materials and Methods

Study Population

The design and objectives of the ARIC study, a prospective, biracial study of CVD incidence in 15 792 individuals aged between 45 to 64
Table 1. Calculation of Arterial Stiffness Measures

<table>
<thead>
<tr>
<th>Arterial Stiffness Measure</th>
<th>Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid arterial strain, %</td>
<td>(DS – DD)/DD</td>
</tr>
<tr>
<td>Arterial compliance, mm²/kPa</td>
<td>(\pi (Ds^2 – DD^2)/(4*PP))</td>
</tr>
<tr>
<td>Arterial distensibility, %/kPa</td>
<td>((- (Ds^2 – DD^2)/(PP*DD^2)))</td>
</tr>
<tr>
<td>Stiffness index (dimensionless)</td>
<td>(ln((SBP/DBP)/CAS))</td>
</tr>
<tr>
<td>Pressure–strain modulus, kPa</td>
<td>PP/CAS</td>
</tr>
<tr>
<td>Young elastic modulus, kPa</td>
<td>((0.5*DD/CIMT)*E_p)</td>
</tr>
</tbody>
</table>

DS indicates peak systolic arterial diameter; DD, end diastolic arterial diameter; PP, pulse pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAS, carotid arterial strain; CIMT, carotid intima-media thickness.

years at the time of their initial visit (1987–1989), have been previously described. Our analysis used the first measurement of arterial stiffness, which occurred either at ARIC Visit 1 (1987–1989) or 2 (1990–1992). After applying previously used ARIC exclusions (excluding participants in Minneapolis and Washington County with nonwhite race and participants in Forsyth County with race neither white nor black \(n=103\) altogether), individuals having at least 1 acceptable electrocardiography-gated cardiac cycle from the ultrasound scan were included. Individuals were excluded for missing CIMT values, arterial wall stiffness parameters, and traditional coronary heart disease (CHD) risk factors (smoking status, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, diabetes, systolic blood pressure \(SBP\), antihypertensive medication use) at the time that arterial wall stiffness parameters were measured or missing data on CHD/stroke history or having a history of CHD/stroke at the baseline visit. In all, 10 470 individuals (of 15 792) were eligible for the incident CHD analysis, and 10 407 individuals were eligible for the incident stroke analysis (Supplemental Figure I; http://stroke.ahajournals.org).

Ultrasonic Imaging and Determination of Arterial Wall Characteristics

Methods for the acquisition of B-mode ultrasound scans that were electrocardiography-gated and for the echo tracking of the arterial diameter in the ARIC study have been described. Participants were asked to refrain from smoking, vigorous exercise, and caffeine-containing beverages beginning the night before ultrasound imaging. There was an average of 5.6 cardiac cycles of adequate quality for readers to measure arterial diameter whose changes through the cardiac cycle were used in the determination of the arterial wall characteristics. A description of the measurement of the arterial diameter and its reproducibility is presented in the Supplemental Methods in the Online Supplement (see “Ultrasonic Imaging”).

Indices of arterial wall characteristics were derived from these ultrasound measurements and from supine brachial blood pressure measured during the ultrasound examination (Table 1). Carotid arterial strain (CAS), arterial compliance (AC), and arterial distensibility (AD) are indices inversely proportional to arterial stiffness such that higher values of these indices represent less stiffness; whereas the stiffness index (SI), pressure–strain modulus \(E_p\), and Young’s elastic modulus \(E_Y\) are direct measures of arterial stiffness. Additionally, the calculation of \(E_Y\) includes the CIMT measurement, therefore representing the thickness-adjusted stiffness of the vessel. Additional description of these indices can be also found in the Supplemental Methods in the Online Supplement (see “Description of Carotid Stiffness Parameters”).

Definition and Ascertainment of Outcomes

Outcomes of interest were incident CHD and ischemic stroke occurring before December 31, 2005. Incident CHD events included definite or probable myocardial infarction, silent myocardial infarction between examinations (based on electrocardiographic findings with the last examination occurring during 1996–1998 [ARIC Visit 4]), death due to CHD, or coronary revascularization (percutaneous transluminal angioplasty or coronary arterial bypass graft). Incident ischemic stroke included definite or probable ischemic strokes (embolic or thrombotic). Incident CVD was a composite end point of CHD and ischemic stroke defined as previously. The methods by which these events were ascertained and classified and the details of quality assurance have been published. Additional analyses were also performed excluding nonthrombotic ischemic strokes.

Statistical Analysis

Baseline characteristics (ie, those measured at the time of the ultrasound scan) were compared between individuals with and without incident cardiovascular events. Cox proportional hazard models were used to estimate the hazard ratio (HR) for a 1-SD difference toward greater arterial stiffness for each parameter, specifically for lower values of CAS, AC, and AD and for higher values of SI, \(E_p\), and \(E_Y\). Three models were used to examine the relationship between arterial stiffness parameters and incident events: Model 1 included age, gender, race, and study site; Model 2 included Model 1 variables plus several CHD risk factors (ie, height, weight, diabetic status, total cholesterol, high-density lipoprotein cholesterol, smoking status, SBP taken at the time of the ultrasound examination, and use of antihypertensive medication); and Model 3 included Model 2 variables plus CIMT. The SBP measurements used in Models 2 and 3 were taken supine at the time of the ultrasound examination. Additional hazard models were also examined including aspirin and lipid-lowering therapy use and, for incident strokes, including baseline presence of atrial fibrillation.

Lastly, if adjusted HRs were significant for a given analysis, the area under the receiver operating characteristic curve (ie, probability of classifying an individual with an incident event as greater risk than an individual without an event) was calculated using ARIC risk prediction models with and without the arterial stiffness parameter to assess for model improvement.

Results

In all, 10 470 individuals were eligible for the incident CHD analysis, and 10 407 were eligible for the incident stroke and CVD analysis (Supplemental Figure I). All baseline atherosclerosis risk factors differed in the expected directions between individuals with and without incident CHD/stroke events (Table 2).

Over a mean follow-up of 13.8 years (until December 31, 2005), there were 1267 incident CHD events and 383 incident ischemic strokes.

Arterial Stiffness and Incident CHD

Participants with incident CHD events had lower baseline values for CAS (5.13% versus 5.34%, \(P<0.0001\)), AC (7.71 mm²/kPa versus 7.91 mm²/kPa, \(P=0.03\)), and AD (1.56%/kPa versus 1.76%/kPa, \(P<0.0001\)). SI (0.12 versus 0.11, \(P<0.0001\)) and \(E_p\) (153.38 kPa versus 137.02 kPa, \(P<0.0001\)), both of which can be considered inverses of AD, and \(E_Y\) (895.65 kPa versus 853.16 kPa, \(P=0.0007\)) were higher in individuals with incident CHD events than those without (Table 3). All measures except CAS and \(E_Y\) were significantly associated with CHD in the minimally adjusted model (Figure 1). After full adjustments for CHD risk factors and CIMT, none of the associations were statistically significant (Figure 1). When baseline aspirin and lipid-lowering therapy use was added to the fully adjusted model, arterial stiffness and incident CHD continued not to be associated (CAS HR, 0.995 [95% CI, 0.94–1.06]; AC, 0.96 [0.90–1.02]; AD, 1.01 [0.94–1.09]; SI, 0.97 [0.92; 1.03]; \(E_p\), 0.96 [0.90–1.03]; \(E_Y\), 0.97 [0.90–1.03]).
Arterial Stiffness and Incident Stroke

Individuals with incident stroke also had lower baseline values for CAS (4.95% versus 5.33%, P = 0.0001), AC (7.10 mm²/kPa versus 7.92 mm²/kPa, P = 0.03), and AD (1.41%/kPa versus 1.75%/kPa, P < 0.0001) and higher values for SI (0.13 versus 0.11, P < 0.0001), Ep (157.76 kPa versus 137.54 kPa, P < 0.0001), and YEM (1028.09 kPa versus 851.66 kPa, P < 0.0001; Table 3) when compared with those without incident stroke. All arterial stiffness parameters were significantly associated with incident stroke in the minimally adjusted model. After full adjustments, CAS (HR, 1.13 [95% CI, 1.01–1.27]); AD (HR, 1.19 [1.02–1.39]); SI, 1.14 [1.04–1.24]; Ep, 1.15 [1.05–1.27]; YEM, 1.16 [1.05–1.28]). The addition of atrial fibrillation to the fully adjusted model resulted in no significant change in associations between arterial stiffness parameters and incident ischemic strokes (Supplemental Table II). When a fully adjusted model was examined inclusive of only incident thrombotic stroke subtypes (n = 304), all associations with arterial stiffness parameters maintained their respective significance (Supplemental Table II).

When arterial stiffness parameters were added to the ARIC stroke risk prediction model, the area under the receiver operating characteristic curve increased from 0.625 to 0.665 when Ep was added and to 0.648 when YEM was added.

All baseline atherosclerosis risk factors differed in the expected directions between individuals with and without incident CVD events (Supplemental Table I). The association of arterial stiffness and incident CVD events was also examined and no significant association was found after adjustments for CHD risk factors and CIMT (Supplemental Figure II). Details of the incident CVD analysis is presented in Supplemental Table II.

Table 2. Comparison of Baseline Characteristics for Individuals Having Versus Not Having an Incident Coronary Heart Disease Event or Stroke*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Incident Event</th>
<th>P</th>
<th></th>
<th>Incident Event</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Yes (n = 1267)</td>
<td>56.8 (5.7)</td>
<td>55.13 (5.9)</td>
<td>&lt;0.0001</td>
<td>Yes (n = 383)</td>
</tr>
<tr>
<td>Male, %</td>
<td>No (n = 9203)</td>
<td>63.6</td>
<td>39.5</td>
<td>&lt;0.0001</td>
<td>No (n = 10 024)</td>
</tr>
<tr>
<td>White, %</td>
<td></td>
<td>80.8</td>
<td>75.9</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td></td>
<td>170.4 (9.0)</td>
<td>168.1 (9.3)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Weight, lbs</td>
<td></td>
<td>177.1 (33.4)</td>
<td>168.2 (34.2)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td></td>
<td>125.1 (18.9)</td>
<td>119.0 (17.8)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Hypertensive, %</td>
<td>30.7</td>
<td>20.5</td>
<td>&lt;0.0001</td>
<td></td>
<td>39.4</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>30.4</td>
<td>22.5</td>
<td>&lt;0.0001</td>
<td></td>
<td>29.5</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td></td>
<td>20.6</td>
<td>8.9</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>219.2 (40.6)</td>
<td>209.3 (39.3)</td>
<td>&lt;0.0001</td>
<td></td>
<td>215.1 (43.1)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>44.6 (13.9)</td>
<td>53.0 (17.3)</td>
<td>&lt;0.0001</td>
<td></td>
<td>48.6 (16.3)</td>
</tr>
</tbody>
</table>

*All values are means (SD) or proportions.

Table 3. Comparison of Carotid Arterial Stiffness Parameters for Individuals Having Versus Not Having an Incident Coronary Heart Disease Event or Stroke*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Incident Event</th>
<th>P</th>
<th></th>
<th>Incident Event</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS, %</td>
<td>Yes (n = 1267)</td>
<td>5.13 (1.69)</td>
<td>5.34 (1.73)</td>
<td>&lt;0.0001</td>
<td>Yes (n = 383)</td>
</tr>
<tr>
<td>AC, mm²/kPa</td>
<td>No (n = 9203)</td>
<td>7.71 (2.98)</td>
<td>7.91 (3.12)</td>
<td>0.03</td>
<td>No (n = 10 024)</td>
</tr>
<tr>
<td>AD, %/kPa</td>
<td></td>
<td>1.56 (0.62)</td>
<td>1.76 (0.70)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>SI</td>
<td>0.12 (0.04)</td>
<td>0.11 (0.04)</td>
<td>&lt;0.0001</td>
<td></td>
<td>0.13 (0.05)</td>
</tr>
<tr>
<td>Ep, kPa</td>
<td>153.38 (65.28)</td>
<td>137.02 (61.17)</td>
<td>&lt;0.0001</td>
<td></td>
<td>175.76 (87.63)</td>
</tr>
<tr>
<td>YEM, kPa</td>
<td>895.65 (416.37)</td>
<td>853.16 (432.02)</td>
<td>0.0007</td>
<td></td>
<td>1028.09 (566.26)</td>
</tr>
</tbody>
</table>

*All values are means (SD).
Discussion

Based on our analysis, we now show that several measures of local arterial stiffness, previously shown to be associated with atherosclerotic risk factors, were associated with incident ischemic stroke but not CHD after adjustment for CVD risk factors and CIMT in a middle-aged population followed for approximately 14 years.

There were differences among the arterial stiffness parameters we examined (Table 1). CAS provides the percent arterial diameter change relative to the end diastolic arterial diameter but does not include blood pressure measurements. The remaining parameters relate arterial caliber changes to pulse pressures with a few notable exceptions. First, the calculation of AC does not adjust the arterial diameter change for the end diastolic arterial diameter. Instead of using the pulse pressure, the calculation of SI uses the log ratio of systolic to diastolic blood pressures to adjust for the curvilinear relationship between arterial pressures and diameters. Lastly, the calculation of YEM included CIMT (ie, this parameter is a measure of arterial stiffness adjusted for its thickness). As we noted, we found significant independent associations of all of these parameters, except AC, with incident strokes but not with incident CHD. We are unable to explain the lack of significance for the AC association with stroke. This difference from the associations for other stiffness parameters would certainly need independent confirmation before attempting an interpretation of its potential importance.

Our results are consistent with studies that have examined the association between aortic pulse wave velocity (PWV), a surrogate measure of regional arterial stiffness, and incident stroke and CHD events. These studies reported stronger associations of PWV with stroke than with CHD. Overall, their findings, along with ours, would suggest that arterial stiffness, irrespective of its underlying pathophysiology, may have a more profound effect on outcomes associated with peripheral organs (eg, the brain) than on CHD events.

Atherosclerosis is a process occurring in the arterial intima, whereas arterial stiffening, or arteriosclerosis, is a process involving the arterial media. Arteriosclerosis has been postulated to affect cerebral and coronary perfusion differently. With aging, the structural and functional changes in the artery characteristic of arteriosclerosis lead to marked

in the Supplemental Results in the Online Supplement see “Arterial Stiffness and Incident CVD”).

Figure 1. Hazard ratios for incident composite coronary heart disease events examining a 1-SD difference toward adverse arterial stiffness* for each vascular wall characteristics adjusted for different covariates. Model 1 included age, gender, study site, and race; Model 2 included Model 1 covariates plus height, weight, diabetes, total cholesterol, high-density lipoprotein cholesterol, smoking status, systolic blood pressure, and antihypertensive medication use; and Model 3 included Model 2 covariates plus carotid intima-media thickness. *1-SD decrease for carotid arterial strain (CAS), arterial compliance (AC), and arterial distensibility (AD). 1-SD increase for stiffness index (SI), pressure–strain modulus (Ep), and Young’s elastic modulus (YEM).

Figure 2. Hazard ratios for incident strokes examining a 1-SD difference toward adverse arterial stiffness* for each vascular wall characteristics adjusted for different covariates. Model 1 included age, gender, study site, and race; Model 2 included Model 1 covariates plus height, weight, diabetes, total cholesterol, high-density lipoprotein cholesterol, smoking status, systolic blood pressure, and antihypertensive medication use; and Model 3 included Model 2 covariates plus carotid intima-media thickness. *1-SD decrease for carotid arterial strain (CAS), arterial compliance (AC), and arterial distensibility (AD). 1-SD increase for stiffness index (SI), pressure–strain modulus (Ep), and Young’s elastic modulus (YEM).
increases in SBP, usually slight decreases in diastolic blood pressure, and overall increases in pulse pressures. The marked increase in SBP leads to the transmission of greater systolic pressure loads forward to organs such as the brain and kidney, and backward (through afterload) to the heart (through an increase in end systolic myocardial wall stress leading to increased left ventricular mass). However, the decrease in diastolic pressure (the magnitude of which is less than the increase in SBP) with decreased augmentation of coronary perfusion is thought to be more important in the development of CHD. Therefore, although arteriosclerosis adversely affects both coronary and peripheral circulation, it may, in theory, be expected to have a stronger association with stroke than CHD, a finding borne out in our study in which, despite there being 3 times as many CHD events as strokes, an association was seen with stroke, but not with CHD.

Similar findings have been seen in clinical studies as well. A large meta-analysis conducted by the Prospective Studies Collaboration reported that increased systolic and diastolic blood pressure measurements have stronger associations with stroke than with incident CHD events. Conversely, in the International Verapamil-Trandolapril Study (INVEST), with >22,000 patients, associations were stronger between low diastolic blood pressures and incident myocardial infarction than incident stroke.

Comparison With Other Carotid Stiffness Studies
Two population-based studies have examined the association between carotid stiffness and incident cardiovascular events in populations without prevalent CVD. The Rotterdam Study found no association between carotid distensibility and cardiovascular outcomes in 2265 elderly adults (76 CHD events over mean follow-up 4.1 years, 51 strokes over mean follow-up 3.2 years). An analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, a middle-aged population, also did not find a significant association between carotid YEM and CVD events (n=6523; 313 CVD events; median follow-up 4.6 years). However, these 2 studies had fewer events and shorter duration of follow-up than ours, were not sufficiently powered to examine event subtypes, and thus, did not examine event subtypes separately. Furthermore, they did not examine all measures of arterial stiffness as we have done and did not adjust for arterial thickness or concurrent blood pressures.

Comparison Between Carotid Stiffness Measures and PWV
To date, only the Rotterdam Study has reported association between both carotid distensibility and PWV and outcomes. Although a significant association between PWV and incident CHD was noted (HR, 2.07; 95% CI, 1.08–3.98), no association between carotid distensibility and incident CHD (HR, 1.32; 95% CI, 0.68–2.54) was seen. Similarly (albeit nonsignificant) the association between PWV and incident stroke was stronger (PWV HR, 1.96; 95% CI, 0.94–4.29; carotid distensibility HR, 1.39; 95% CI, 0.55–3.52). Hence, despite a limited sample size, the results of the Rotterdam Study suggest that PWV may be the better measure of general arterial stiffness. However, ultrasound-based CAS measures are still valuable because they assess stiffness in the vessel most relevant to cerebrovascular outcomes and have several advantages discussed next.

Clinical Perspective
We have shown that ultrasound measures of carotid arterial stiffness measures are associated with incident stroke in a general population independent of traditional stroke risk factors and atherosclerosis as measured by CIMT. Arterial stiffness measures can be obtained from standard carotid ultrasound examinations with little addition to the procedure time and could therefore be quickly implemented by centers performing carotid ultrasound imaging. Advances in ultrasound technology may allow for more accurate estimation of the arterial dimensions in multiple planes, thus further improving stiffness measurement. Therefore, arterial stiffness measures on a carotid ultrasound may provide additional information related to the arterial health of an individual. Whether therapeutic interventions benefit patients with increased arterial stiffness remains to be investigated.

Limitations
Exclusion of participants missing data may have introduced selection biases into our analyses. For example, participants may have had ultrasound data missing due to thick necks associated with obesity. However, >10,000 participants remain eligible for the incident CHD and stroke analyses, perhaps more representative of their communities than in many clinical studies. Individuals with atherosclerotic risk factors were more likely to have stiffer arteries and would likely be put on aspirin and lipid-lowering therapies through the course of the study. The use of aspirin and lipid-lowering therapies may bias any associations between arterial stiffness and incident cardiovascular disease toward the null. Despite that, an association with incident strokes still persisted.

Stiffness measurements were estimated using only data from the left distal common carotid artery and reflect the characteristics of only that region of the arterial tree. Only the maximum and minimum distances between the near and far arterial wall borders along a single axis were recorded (ie, distension occurring in other planes were disregarded).

Peripheral brachial blood pressures were used in arterial stiffness calculations instead of central carotid blood pressures. In young healthy individuals, the peripheral pulse pressures tend to be significantly higher than central pulse pressures, whereas in diseased individuals, peripheral and central blood pressures tend to be more comparable to each other. Hence, CAS parameters using peripheral blood pressure measurements may be biased toward overestimating arterial stiffness in younger populations. Central pressures would provide more accurate stiffness values but can be measured in routine clinical practice only indirectly. Hence, although this is a limitation, our analysis tends to more closely mirror clinical practice.

Finally, several of the measures of arterial stiffness include blood pressure in their derivations; however, we adjusted for blood pressure in our final models. Although this could result in overadjustment, we believe that for a clinically useful measure, the measure should show association beyond tradi-
tional, currently available risk factors including blood pressure; and therefore, we opted to show models with and without blood pressure.

Conclusions
We show that ultrasound measures of CAS, which can be obtained from a routine carotid ultrasound, are associated with incident stroke, but not incident CHD over approximately 14 years of follow-up, after adjustments for atherosclerotic risk factors, including blood pressure measured at the time of the stiffness measurement, and CIMT.

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Disclosures
V.N. has research collaborations with GE Healthcare and Tom Tec. He also serves as the editor for “Vascular Ultrasound Today.”

References
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Supplemental List of Abbreviations
ARIC = Atherosclerosis Risk in Communities
CHD = coronary heart disease
CAS = carotid arterial strain
AC = arterial compliance
AD = arterial distensibility
SI = stiffness index
Ep = pressure-strain modulus
YEM = Young's Elastic Modulus
CIMT = carotid intima-media thickness
HR = hazard ratio
CI = confidence interval
CVD = cardiovascular disease
LDL-C = low-density lipoprotein cholesterol
HDL-C = high-density lipoprotein cholesterol
BP = blood pressure
SBP = systolic blood pressure
MI = myocardial infarction
AUC = area under the ROC curve
PWV = pulse wave velocity

Supplemental Methods
Ultrasound imaging
Assessment of arterial diameter variation was conducted using a standardized protocol by readers at the ARIC Ultrasound Reading Center using computer software developed by the Reading Center. The continuous variation of the inter-adventitial arterial diameter throughout the cardiac cycle was measured and recorded from the left common carotid artery using an electronic tracking device designed for ARIC (AUTREC 4881-AWT, Winston-Salem, NC). The inter-adventitial arterial diameter was defined as the distance between the near-wall and far-wall of the longitudinally imaged distal left common carotid artery. The diameter was automatically calculated, digitized, and displayed on a strip-chart for immediate review by the sonographer and stored electronically for off-line reader analysis. The repeatability of this method was conducted in 9 volunteers (each scanned 4 times, two times each by 2 different sonographers) and the between-person reliability coefficient, defined as the ratio of between-person variance to total variance in a random effect analysis of variance model (i.e. the correlation coefficient between measures made at different visits when scanned by different sonographers and read by different readers), was 0.75 for the pressure-adjusted diameter change, 0.67 for carotid arterial strain, 0.77 for arterial compliance, 0.67 for arterial distensibility, and 0.66 for pressure-strain modulus. Of the 10,470 individuals eligible for the incident CHD event analysis, 3,392 had arterial stiffness measurements done at both Visits 1 and 2, with a mean period of 2.9 years (standard deviation 0.2 years) between visits. There was no significant difference in mean stiffness parameter values between the 2 visits for any parameter.
Description of Carotid Stiffness Parameters

Carotid arterial strain (CAS) is the relative change (i.e., distension) in vessel diameter, independent of pressure loads. The other 5 parameters adjust for pressure loads in various ways.

Arterial compliance (AC) and distensibility (AD) examine the absolute and relative change in vessel area (as opposed to diameter) per unit pulse pressure, respectively. In contrast, the other three parameters (stiffness index [SI], pressure-strain modulus [Ep], and Young’s elastic modulus [YEM]) are directly derived from CAS.

The stiffness index (SI) attempts to adjust for the curvilinear relationship between blood pressures and distension. The pressure-strain modulus (Ep) relates the pulse pressure and distension directly. Lastly, Young’s elastic modulus (YEM) adds vessel wall thickness (i.e., intima-medial thickness) to Ep, and can be thought of as accounting for atherosclerosis.
Supplemental Results

Arterial stiffness and incident CVD

All baseline atherosclerosis risk factors differed in the expected directions between individuals with and without incident CHD/stroke events (Supplemental Table). Individuals with incident CVD events had lower baseline values for CAS (5.10% v. 5.35%, p <0.0001), AC (7.62 mm$^3$/kPa v. 7.93 mm$^3$/kPa, p=0.0001), and AD (1.54 %/kPa v. 1.77 %/kPa, p<0.0001) and higher values for SI (0.12 v. 0.11, p <0.0001), $E_p$ (157.33 kPa v. 135.74 kPa, p <0.0001), YEM (921.17 kPa v. 847.15 kPa, p <0.0001) (Supplemental Table 2) when compared with those without incident CVD events. All measures except CAS were significantly associated with CVD in the minimally adjusted model (Supplemental Figure 2). After full adjustments for CHD risk factors and CIMT, none of the observed association between arterial stiffness measures and incident CVD events remained statistically significant (Supplemental Figure 2).
Supplemental Table 1. Comparison of Baseline Characteristics for Individuals Having vs. Not Having an Incident CVD Event

<table>
<thead>
<tr>
<th>Incident Event</th>
<th>Yes (n = 1,547)</th>
<th>No (n = 8,860)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.1 (5.7)</td>
<td>55.0 (5.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>60.8</td>
<td>39.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White (%)</td>
<td>76.9</td>
<td>76.5</td>
<td>0.71</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.2 (9.0)</td>
<td>168.0 (9.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight (lbs.)</td>
<td>176.7 (33.8)</td>
<td>168.0 (34.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>126.1 (19.5)</td>
<td>118.7 (17.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertensive (%)</td>
<td>43.7</td>
<td>27.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anti-hypertensive medication use (%)</td>
<td>31.9</td>
<td>19.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>30.4</td>
<td>22.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>20.9</td>
<td>8.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>218.2 (41.1)</td>
<td>209.2 (39.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>45.4 (14.6)</td>
<td>53.1 (17.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CAS (%)</td>
<td>5.10 (1.70)</td>
<td>5.35 (1.72)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AC (mm³/kPa)</td>
<td>7.62 (3.01)</td>
<td>7.93 (3.12)</td>
<td>0.0001</td>
</tr>
<tr>
<td>AD (%/kPa)</td>
<td>1.54 (0.63)</td>
<td>1.77 (0.70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SI</td>
<td>0.12 (0.05)</td>
<td>0.11 (0.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$E_p$ (kPa)</td>
<td>157.33 (71.15)</td>
<td>135.74 (59.51)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>YEM (kPa)</td>
<td>921.17 (456.99)</td>
<td>847.15 (424.35)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CVD = cardiovascular disease
SBP = systolic blood pressure
HDL-C = high-density lipoprotein cholesterol
CAS = circumferential arterial strain
AD = arterial distensibility
AC = arterial compliance
SI = stiffness index
$E_p$ = pressure-strain elastic modulus
YEM = Young’s elastic modulus
Supplemental Table 2. Hazard ratios (95% confidence intervals) from additional models used to examine associations between arterial stiffness parameters and incident strokes

<table>
<thead>
<tr>
<th>Arterial Stiffness Parameter</th>
<th>Model 3 (thrombotic strokes only)</th>
<th>Model 3 + baseline atrial fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid Arterial Strain</td>
<td>1.18 (1.04, 1.34)</td>
<td>1.14 (1.02, 1.27)</td>
</tr>
<tr>
<td>Arterial Compliance</td>
<td>1.04 (0.90, 1.21)</td>
<td>1.02 (0.90, 1.16)</td>
</tr>
<tr>
<td>Arterial Distensibility</td>
<td>1.22 (1.03, 1.46)</td>
<td>1.19 (1.02, 1.39)</td>
</tr>
<tr>
<td>Stiffness Index</td>
<td>1.14 (1.03, 1.26)</td>
<td>1.14 (1.04, 1.25)</td>
</tr>
<tr>
<td>Pressure-Strain Modulus</td>
<td>1.16 (1.04, 1.29)</td>
<td>1.16 (1.06, 1.28)</td>
</tr>
<tr>
<td>Young’s Elastic Modulus</td>
<td>1.17 (1.04, 1.30)</td>
<td>1.16 (1.06, 1.29)</td>
</tr>
</tbody>
</table>
**Supplemental Figure**
S1. Inclusions and Exclusions of Individuals in the Cohort

Application of exclusions to the ARIC Study Group with data pooled from 1<sup>st</sup> and 2<sup>nd</sup> site visits.

*CHD risk factors include smoking status, low-density lipoprotein cholesterol (LDL-C) levels, high-density lipoprotein cholesterol (HDL-C) levels, diabetes, systolic blood pressure, and antihypertensive medication use.

†CVD risk factors include all CHD risk factors listed above and left ventricular hypertrophy.

CHD = coronary heart disease
CVA = cerebrovascular accident
CVD = cardiovascular disease
CIMT = carotid intima-media thickness
Hazard ratios for incident cardiovascular disease examining a one standard deviation (1-SD) difference toward adverse arterial stiffness* for each vascular wall characteristics adjusted for different covariates. Model 1 included age, gender, study site, and race; Model 2 included Model 1 covariates plus height, weight, diabetes, total cholesterol, high-density lipoprotein cholesterol, smoking status, systolic blood pressure, and antihypertensive medication use; and, Model 3 included Model 2 covariates plus carotid intima-media thickness.

*1-SD decrease for carotid arterial strain (CAS), arterial compliance (AC), and arterial distensibility (AD). 1-SD increase for stiffness index (SI), pressure-strain modulus (Ep), and Young’s elastic modulus (YEM).
Supplemental References

