Carotid arterial wall characteristics are associated with incident ischemic stroke but not coronary heart disease in the ARIC Study

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Abstract

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 ARIC study.

Methods—Carotid arterial strain (CAS) and compliance (AC), distensibility (AD) and stiffness indices (SI), pressure-strain (E_p) and Young's elastic moduli (YEM) were measured in 10,407 individuals using ultrasound. Hazard ratios for incident CHD (myocardial infarction [MI], 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 (CIMT) were calculated.

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Results—The mean age was 55.3 years. Over a mean follow up of 13.8 years, 1,267 incident CHD and 383 ischemic stroke events occurred. After full adjustment for risk factors and CIMT, all arterial stiffness parameters [CAS HR (95% confidence interval [CI]) =1.14 (1.02, 1.28); AD HR=1.19 (1.02, 1.39); SI HR=1.14 (1.04, 1.25); E_p HR=1.17 (1.06, 1.28); YEM 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.

Keywords

arterial stiffness; carotid ultrasound; coronary heart disease; stroke; ARIC

INTRODUCTION

Aging is associated with progressive stiffening of the arteries,[1-4] a process which 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,[2] and may thereby increase the risk of cardiovascular disease (CVD) events.[5, 6] "Arterial stiffness" can be non-invasively measured using pulse wave velocity (regional) or ultrasound-based distensibility (local) measurements.[7]

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.[8] 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 (i.e., 4 years or less) reported no significant association of common carotid distensibility with incident CVD.[9, 10]

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 45-64 years at the time of their initial visit (1987-1989), have been previously described.[11] Our analysis used the first measurement of arterial stiffness, which occurred either at ARIC Visits 1 (1987-1989) or 2 (1990-1992).

After applying previously used ARIC exclusions (excluding participants in Minneapolis and Washington County with non-white race and participants in Forsyth County with race neither white nor black [n=103 altogether]), individuals having at least one acceptable electrocardiography-gated cardiac cycle from the ultrasound scan were included. Individuals were excluded for missing CIMT values, arterial wall stiffness parameters and traditional CHD risk factors (smoking status, low-density lipoprotein (LDL-C) and high-density lipoprotein cholesterol (HDL-C), 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 (out of 15,792) were eligible for the incident CHD analysis, and 10,407 individuals were eligible for the incident stroke analysis (please see http://stroke.ahajournals.org; Figure S1).

Ultrasound imaging and determination of arterial wall characteristics

Methods for the acquisition of B-mode ultrasound scans which were ECG-gated and for the echo tracking of the arterial diameter in the ARIC study have been described.[8, 11-13] 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 (please see http://stroke.ahajournals.org; "Ultrasound Imaging").

Indices of arterial wall characteristics were derived from these ultrasound measurements and from supine brachial blood pressure measured during the ultrasound exam (Table 1).[12] 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 (Ep), and Young's elastic modulus (YEM) are direct measures of arterial stiffness. Additionally, the calculation of YEM 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 (please see http://stroke.ahajournals.org; "Description of Carotid Stiffness Parameters").

Definition and ascertainment of outcomes

Outcomes of interest were incident CHD and ischemic stroke occurring before December 31st, 2005. Incident CHD events included definite or probable MI, silent MI between exams (based on electrocardiogram findings with the last exam 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 endpoint of CHD and ischemic stroke defined as above. The methods by which these events were ascertained and classified and the details of quality assurance have been published.[14, 15] Additional analyses were also performed excluding non-thrombotic ischemic strokes.

Statistical analysis

Baseline characteristics (i.e., 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 one-standard deviation 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 YEM. 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 (i.e., height, weight, diabetic status, total cholesterol, HDL-C, smoking status, SBP taken at the time of the ultrasound exam 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 hazard ratios were significant for a given analysis, the area under the ROC curve (AUC; i.e., 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 S1). 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 1,267 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% v. 5.34%, p<0.0001), AC (7.71 mm^3/kPa v. 7.91 mm^3/kPa, p=0.03), and AD (1.56%/kPa v. 1.76%/kPa, p <0.0001). SI (0.12 v. 0.11, p <0.0001) and E_p (153.38 kPa v. 137.02 kPa, p <0.0001), both of which can be considered inverses of AD, and YEM (895.65 kPa v. 853.16 kPa, p=0.0007) were higher in individuals with incident CHD events than those without (Table 3). All measures except CAS and YEM 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], Ep 0.96 [0.90, 1.03], YEM 0.97 [0.90, 1.03]).

Arterial stiffness and incident stroke

Individuals with incident stroke also had lower baseline values for CAS (4.95% v. 5.33%, p=0.0001), AC (7.10 mm^3/kPa v. 7.92 mm^3/kPa, p=0.03), and AD (1.41 %/kPa v. 1.75 %/kPa, p <0.0001), and higher values for SI (0.13 v. 0.11, p <0.0001), E_p (175.76 kPa v. 137.54 kPa, p <0.0001), and YEM (1028.09 kPa v. 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 (95% confidence interval (CI=1.13 (1.01, 1.27)], AD [HR=1.19 (1.02, 1.38)], SI [HR=1.14 (1.04, 1.25)], E_p [HR=1.15 (1.05, 1.27)], and YEM [HR=1.15 (1.05, 1.28)] continued to have a significant association with incident stroke (Figure 2). However, the association between arterial compliance and incident stroke was no longer significant [HR=1.02 (0.89, 1.16)].

When baseline aspirin and lipid lowering therapy use was added to the fully adjusted model, the trend observed with the fully adjusted model persisted (CAS HR 1.13 [95% CI 1.01, 1.27], AC 1.01 [0.89, 1.16], AD 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 2). 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 2).

When arterial stiffness parameters were added to the ARIC stroke risk prediction model,[16] the AUC 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). 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 S2). Details of the incident CVD analysis is presented in the Supplemental Results in the Online Supplement (please see http://stroke.ahajournals.org; "Arterial stiffness and incident CVD").

DISCUSSION

Based on our analysis, we now show that several measures of local arterial stiffness, previously shown to be associated with atherosclerotic risk factors,[7, 12, 13, 17-22] were associated with incident ischemic stroke but not CHD after adjustment for CVD risk factors and CIMT in a middle-aged population followed for ~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 (i.e. this parameter is a measure of arterial stiffness adjusted for its thickness).[23] 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,[24] and incident stroke and CHD events. These studies reported stronger associations of PWV with stroke than with CHD.[9, 10, 25] Overall, their findings, along with ours, would suggest that arterial stiffness, irrespective of its underlying pathophysiology, may have a more profound adverse effect on outcomes associated with peripheral organs (e.g., the brain) than on CHD events.

Atherosclerosis is a process occurring in the arterial intima, while arterial stiffening, or arteriosclerosis, is a process involving the arterial media.[5, 6] Arteriosclerosis has been postulated to affect cerebral and coronary perfusion differently.[5] With aging, the structural and functional changes in the artery characteristic of arteriosclerosis lead to marked 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[26, 27] and backwards (through afterload) to the heart (via an increase in end-systolic myocardial wall stress leading to increased left ventricular mass).[28] However, the decrease in diastolic pressure (the magnitude of which is less than the increase in systolic pressure) with decreased augmentation of coronary perfusion is thought to be more important in the development of

CHD.[5] 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 where, despite there being three 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.[29] Conversely, in the International Verapamil-Trandolapril Study (INVEST), with over 22,000 patients, associations were stronger between low diastolic blood pressures and incident MI than incident stroke.[30]

Comparison with other carotid stiffness studies

Two population-based studies have examined the association between carotid stiffness and incident CV events in populations without prevalent CVD.[9, 10] The Rotterdam Study found no association between carotid distensibility and CV outcomes in 2,265 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 = 6,523; 313 CVD events; median follow-up 4.6 years). However, these two studies had fewer events and shorter duration of follow-up than ours, were not sufficiently powered to examine event sub-types, and thus, did not examine event sub-types 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 pulse wave velocity

To date, only the Rotterdam Study has reported association between both carotid distensibility and pulse wave velocity (PWV) and outcomes.[31] Although a significant association between PWV and incident CHD was noted [HR 2.07, 95% C.I (1.08-3.98)], no association between carotid distensibility and incident CHD [HR (95% CI) 1.32 (0.68-2.54)] was seen. Similarly (albeit non-significant) the association between PWV and incident stroke was stronger [PWV; HR (95% CI) 1.96 (0.94-4.29), carotid distensibility HR (95% CI) 1.39 (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 carotid arterial stiffness measures are still valuable as 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, over 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 was recorded (i.e. distension occurring in other planes were disregarded).

Peripheral brachial blood pressures were used in arterial stiffness calculations instead of central carotid BPs. In young healthy individuals, the peripheral pulse pressures tend to be significantly higher than central pulse pressures, while in diseased individuals, peripheral and central BPs tend to be more comparable to each other.[5] Hence, carotid arterial stiffness 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 BP in their derivations; however, we adjusted for BP in our final models. Although this could result in over-adjustment, we believe that for a clinically useful measure, the measure should show association beyond traditional, currently available risk factors including BP; and therefore, we opted to show models with and without BP.

SUMMARY

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF, et al. Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. Circulation. 1985; 71:202–210. [PubMed: 3965165]

2. O'rourke MF. Arterial aging: pathophysiological principles. Vasc Med. 2007; 12:329–341. [PubMed: 18048471]

3. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension. 2004; 43:1239–1245. [PubMed: 15123572]

4. O'rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. J Am Coll Cardiol. 2007; 50:1–13. [PubMed: 17601538]

5. Safar ME. Arterial stiffness: a simplified overview in vascular medicine. Adv Cardiol. 2007; 44:1–18. [PubMed: 17075196]

6. Mitchell GF. Pulse pressure, arterial compliance and cardiovascular morbidity and mortality. Curr Opin Nephrol Hypertens. 1999; 8:335–342. [PubMed: 10456265]

7. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006; 27:2588–2605. [PubMed: 17000623]

8. Riley WA, Evans GW, Sharrett AR, Burke GL, Barnes RW. Variation of common carotid artery elasticity with intimal-medial thickness: the ARIC Study. Atherosclerosis Risk in Communities. Ultrasound Med Biol. 1997; 23:157–164. [PubMed: 9140173]

9. Mattace-Raso FU, Van Der Cammen TJ, Hofman A, Van Popele NM, Bos ML, Schalekamp MA, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation. 2006; 113:657–663. [PubMed: 16461838]

10. Duprez DA, Jacobs DR, Lutsey PL, Bluemke DA, Brumback LC, Polak J, et al. Small artery elasticity, but neither carotid artery elasticity nor aorta distensibility, predicts cardiovascular events in an asymptomatic - Results of the Multi-Ethnic Study of Atherosclerosis. J Am Coll Cardiol. 2010; 55 A133.E1252.

11. The ARIC investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. Am J Epidemiol. 1989; 129:687–702. [PubMed: 2646917]

12. Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR, The ARIC Study; Atherosclerosis Risk in Communities Study. Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. Circulation. 1995; 91:1432–1443. [PubMed: 7867184]

13. Arnett DK, Boland LL, Evans GW, Riley W, Barnes R, Tyroler HA, et al. ARIC Investigators. Hypertension and arterial stiffness: the Atherosclerosis Risk in Communities Study. Am J Hypertens. 2000; 13:317–323. [PubMed: 10821330]

14. White AD, Folsom AR, Chambless LE, Sharret AR, Yang K, Conwill D, et al. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. J Clin Epidemiol. 1996; 49:223–233. [PubMed: 8606324]

15. Rosamond WD, Folsom AR, Chambless LE, Wang CH, Mcgovern PG, Howard G, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke. 1999; 30:736–743. [PubMed: 10187871]

16. Chambless LE, Heiss G, Shahar E, Earp MJ, Toole J. Prediction of ischemic stroke risk in the Atherosclerosis Risk in Communities Study. Am J Epidemiol. 2004; 160:259–269. [PubMed: 15257999]

17. Simon A, Chironi G, Levenson J. Comparative performance of subclinical atherosclerosis tests in predicting coronary heart disease in asymptomatic individuals. Eur Heart J. 2007; 28:2967–2971. [PubMed: 17967818]

18. Arnett DK, Evans GW, Riley WA. Arterial stiffness: a new cardiovascular risk factor? Am J Epidemiol. 1994; 140:669–682. [PubMed: 7942769]

19. Simons PC, Algra A, Bots ML, Grobbee DE, Van Der Graaf Y, The SMART Study. Common carotid intima-media thickness and arterial stiffness: indicators of cardiovascular risk in high-risk patients. Circulation. 1999; 100:951–957. Second Manifestations of ARTerial disease. [PubMed: 10468526]

20. Urbina EM, Srinivasan SR, Kieltyka RL, Tang R, Bond MG, Chen W, et al. Correlates of carotid artery stiffness in young adults: The Bogalusa Heart Study. Atherosclerosis. 2004; 176:157–164. [PubMed: 15306189]

21. Malayeri AA, Natori S, Bahrami H, Bertoni AG, Kronmal R, Lima JA, et al. Relation of aortic wall thickness and distensibility to cardiovascular risk factors (from the Multi-Ethnic Study of Atherosclerosis [MESA]). Am J Cardiol. 2008; 102:491–496. [PubMed: 18678312]

22. Koskinen J, Magnussen CG, Taittonen L, Rasanen L, Mikkila V, Laitinen T, et al. Arterial structure and function after recovery from the metabolic syndrome: the cardiovascular risk in Young Finns Study. Circulation. 2010; 121:392–400. [PubMed: 20065161]

23. Nambi V, Chambless L, Folsom A, He M, Hu Y, Mosley T, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. J Am Coll Cardiol. 2010; 55:1600–1607. [PubMed: 20378078]

24. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. Eur Heart J. 2010; 31:2338–2350. [PubMed: 20530030]

25. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, et al. Elevated Aortic Pulse Wave Velocity, a Marker of Arterial Stiffness, Predicts Cardiovascular Events in Well-Functioning Older Adults. Circulation. 2005; 111:3384–3390. [PubMed: 15967850]

26. Schaeffner ES, Kurth T, Bowman TS, Gelber RP, Gaziano JM. Blood pressure measures and risk of chronic kidney disease in men. Nephrol Dial Transplant. 2008; 23:1246–1251. [PubMed: 17984108]

27. Perry HM Jr. Davis BR, Price TR, Applegate WB, Fields WS, Guralnik JM, et al. Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke: the Systolic Hypertension in the Elderly Program (SHEP). JAMA. 2000; 284:465–471. [PubMed: 10904510]

28. Verdecchia P, Angeli F, Gattobigio R, Guerrieri M, Benemio G, Porcellati C. Does the reduction in systolic blood pressure alone explain the regression of left ventricular hypertrophy? J Hum Hypertens. 2004; 18(Suppl 2):S23–28. [PubMed: 15592569]

29. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360:1903–1913. [PubMed: 12493255]

30. Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? Ann Intern Med. 2006; 144:884–893. [PubMed: 16785477]

31. Paini A, Boutouyrie P, Calvet D, Tropeano AI, Laloux B, Laurent S. Carotid and aortic stiffness: determinants of discrepancies. Hypertension. 2006; 47:371–376. [PubMed: 16446398]
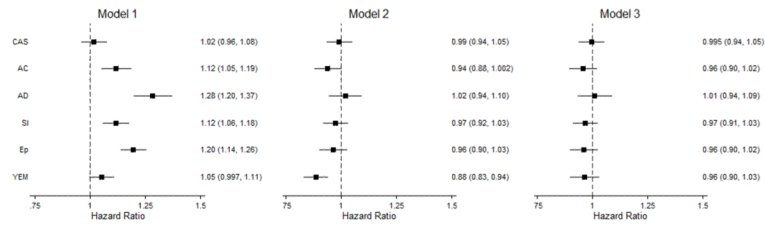
Figure 1. Association of Carotid Arterial Stiffness Parameters and Incident Coronary Heart Disease

Hazard ratios for incident composite coronary heart disease events 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).
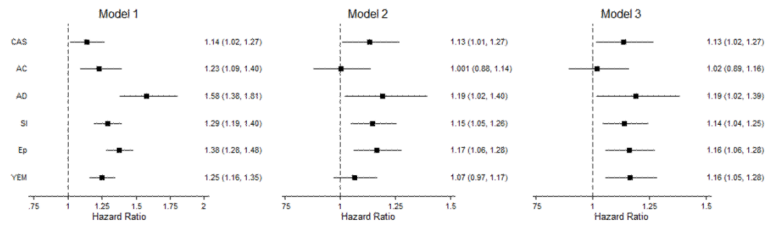
Figure 2. Association of Carotid Arterial Stiffness Parameters and Incident Stroke
Hazard ratios for incident strokes examining a one standard deviation difference (1-SD) difference toward adverse arterial stiffness* for each vascular wall characteristics adjusted for different covariates. Model 1 included 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).

Table 1

Calculation of Arterial Stiffness Measures.

Arterial stiffness Measure	Calculation
Carotid Arterial Strain (CAS) (%)	(DS − DD) / DD
Arterial Compliance (AC) (mm^3/kPa)	π * (DS2 − DD2) / (4 * PP)
Arterial Distensibility (AD) (%/kPa)	100 * (DS^2 − DD^2) / (PP * DD2)
Stiffness Index (SI) (dimensionless)	ln (SBP / DBP) / CAS
Pressure-strain modulus (E$_p$) (kPa)	PP / CAS
Young's elastic modulus (YEM) (kPa)	(0.5 * DD / CIMT) * E$_p$

DS = peak systolic arterial diameter

DD = end diastolic arterial diameter

SBP = systolic blood pressure

DBP = diastolic blood pressure

PP = pulse pressure

Table 2

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

Variable	Incident CHD			Incident Stroke		
Incident Event	Yes (n = 1,267)	No (n = 9,203)	p-value	Yes (n = 383)	No (n = 10,024)	p-value
Age (years)	56.8 (5.7)	55.13 (5.9)	<0.0001	58.0 (5.8)	55.2 (5.9)	<0.0001
Male (%)	63.6	39.5	<0.0001	50.1	42.1	0.002
White (%)	80.8	75.9	0.0001	60.3	77.2	<0.0001
Height (cm)	170.4 (9.0)	168.1 (9.3)	<0.0001	169.3 (8.8)	168.3 (9.3)	0.045
Weight (lbs.)	177.1 (33.4)	168.2 (34.2)	<0.0001	176.3 (35.8)	169.1 (34.2)	<0.0001
SBP (mm Hg)	125.1 (18.9)	119.0 (17.8)	<0.0001	131.1 (21.7)	119.3 (17.8)	<0.0001
Hypertensive (%)	41.6	28.6	<0.0001	54.2	29.3	<0.0001
Anti-hypertensive medication use (%)	30.7	20.5	<0.0001	39.4	21.0	<0.0001
Current smoker (%)	30.4	22.5	<0.0001	29.5	23.2	0.0043
Diabetes (%)	20.6	8.9	<0.0001	26.1	9.7	<0.0001
Total Cholesterol (mg/dL)	219.2 (40.6)	209.3 (39.3)	<0.0001	215.1 (43.1)	210.3 (39.4)	0.03
HDL-C	44.6 (13.9)	53.0 (17.3)	<0.0001	48.6 (16.3)	52.1 (17.1)	<0.0001

CHD = coronary heart disease

SBP = systolic blood pressure

HDL-C = high-density lipoprotein cholesterol

*
All values are means (standard deviation) or proportions

Table 3

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

Variable	Incident CHD			Incident Stroke		
Incident Event	Yes (n = 1,267)	No (n = 9,203)	p-value	Yes (n = 383)	No (n = 10,024)	p-value
CAS (%)	5.13 (1.69)	5.34 (1.73)	<0.0001	4.95 (1.68)	5.33 (1.72)	<0.0001
AC (mm³/kPa)	7.71 (2.98)	7.91 (3.12)	0.03	7.10 (2.99)	7.92 (3.10)	<0.0001
AD (%/kPa)	1.56 (0.62)	1.76 (0.70)	<0.0001	1.41 (0.60)	1.75 (0.69)	<0.0001
SI	0.12 (0.04)	0.11 (0.04)	<0.0001	0.13 (0.05)	0.11 (0.04)	<0.0001
E_p (kPa)	153.38 (65.28)	137.02 (61.17)	<0.0001	175.76 (87.63)	137.54 (60.21)	<0.0001
YEM (kPa)	895.65 (416.37)	853.16 (432.02)	0.0007	1028.09 (566.26)	851.66 (422.74)	<0.0001

CHD = coronary heart disease

CAS = circumferential arterial strain

AD = arterial distensibility

AC = arterial compliance

SI = stiffness index

Ep = pressure-strain elastic modulus

YEM = Young's elastic modulus

*
All values are means (standard deviation)