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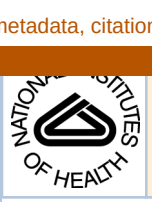

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Stroke. Author manuscript; available in PMC 2012 February 1.

Published in final edited form as:

Stroke. 2011 February ; 42(2): 397–403. doi:10.1161/STROKEAHA.110.592261.

Carotid Artery Wall Thickness and Risk of Stroke Subtypes. The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background and Purpose—Understanding associations of carotid atherosclerosis with stroke subtypes may contribute to more effective prevention of stroke.

Methods—Between 1987 and 1989, 13,560 men and women aged 45 to 64 years and free of clinical stroke, took part in the first examination of the Atherosclerosis Risk in Communities study. Incident strokes were ascertained by hospital surveillance.

Results—During an average follow up of 15.7-years, 82 incident hemorrhagic and 621 incident ischemic strokes (131 lacunar, 358 nonlacunar, and 132 cardioembolic strokes) occurred. The incidence rates of hemorrhagic and ischemic strokes were greater across higher carotid intima-media thickness (IMT) levels. Although this positive association was observed for all stroke subtypes, the age-, sex-, and race-adjusted risk ratios (RR) were higher for cardioembolic and nonlacunar strokes than for hemorrhagic and lacunar strokes. Compared with participants in the lowest quintile (<0.61mm), the adjusted RRs for those in the highest quintile (≥0.85mm) of IMT were 2.55 (95%CI, 1.09 to 5.94) for hemorrhagic, 2.89 (95%CI, 1.50 to 5.54) for lacunar, 3.61 (95%CI, 2.33 to 5.99) for nonlacunar, and 6.12 (95%CI, 2.71 to 13.9) for cardioembolic stroke. The RRs were attenuated by additional adjustment for covariates, but remained statistically significant for nonlacunar and cardioembolic strokes (p for trend <0.001, respectively). The association between carotid IMT and lacunar stroke was somewhat stronger in African Americans than in whites (P for interaction = 0.07).

Conclusions—Carotid atherosclerosis was associated with increased risk of all stroke subtypes, but the association of carotid atherosclerosis with stroke may vary by subtypes.

Keywords

Brain Infarction; Carotid artery; Epidemiology; Intima-media thickness; Stroke subtypes

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Disclosures

None.

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Carotid artery intima-media thickness (IMT) and carotid plaques are markers of subclinical atherosclerosis and help in the early identification of individuals at risk of clinical cardiovascular events. Previous epidemiological studies have documented that carotid IMT predicts future stroke events,[1–4] but few studies have demonstrated associations of IMT with subtypes of stroke [5–7] and these results are inconsistent. Although the associations of carotid IMT with atherothrombotic (nonlacunar) stroke were observed in all three previous studies, an association with lacunar stroke was observed in two of three studies and an association with embolic stroke was shown in only one study. Further, there has been no study to examine the association between carotid IMT and hemorrhagic stroke in a population-based study. [5–8] Since previous studies were cross-sectional, the association of carotid IMT and plaques with risk of stroke subtypes should be confirmed prospectively. The pathogenesis, prognosis, and treatment differ among subtypes; therefore, evaluating the predictive value of IMT for individual subtypes may contribute to more effective primary prevention of stroke.

Previously, the ARIC study reported that African Americans had a 2.4-fold higher age-adjusted relative risk of stroke incidence compared with whites, [9] which could be partially explained by higher prevalences of stroke risk factors such as hypertension, diabetes, and current smoking among African Americans than among whites. [10] In addition, ARIC showed that while African Americans had a 3-fold multivariable-adjusted risk ratio of lacunar stroke compared with whites, there was no racial difference for nonlacunar and cardioembolic strokes after adjustment for traditional and nontraditional cardiovascular risk factors. [11] Mean CCA-IMT was higher among African Americans than among whites [12] and moderate carotid stenosis may have an important role in the development of lacunar stroke as well as non lacunar stroke. [13] Therefore, the association of carotid IMT with the incidence of lacunar stroke may be stronger among African Americans than whites.

To examine the relationships of carotid IMT with the incidence of stroke subtypes, we used data from follow-up of men and women in the ARIC study.

Methods

Study Population

The ARIC cohort comprised 15,792 men and women aged 45 to 64 years between 1987 and 1989 in 4 US communities: Forsyth County, North Carolina; Jackson, Mississippi; 8 northwestern suburbs of Minneapolis, Minnesota; and Washington County, Maryland. [14]

We excluded participants in Forsyth County who were not white or black (n=21) and participants in Minneapolis and Washington County who were not white (n=82), because these participants were scarcely represented in their field centers. We then excluded participants with a history of stroke or transient ischemic attack at baseline (n=282) and participants with missing data for carotid ultrasound measurements (n=928) or cardiovascular risk factors (n=919) at baseline. The remaining 13,560 participants (2,027 black women, 1,266 black men, 5,481 white women, and 4,786 white men) were used in the present analyses of stroke. The study protocol was approved by the institutional review boards of the collaborating institutions and informed written consent was obtained from each participant.

Baseline Measurements

Methods for blood processing in the ARIC study have been described. [15] Participants were asked to fast for 12 hours before their morning clinic appointments. Serum glucose was measured by a hexokinase/glucose-6-phosphate dehydrogenase method. Lipoprotein (Lp)(a)

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was measured as total protein component (apolipoprotein(a) plus apolipoprotein B) with a double-antibody ELISA technique for apo(a) detection. Plasma fibrinogen and von Willebrand factor (vWF) antigen were measured by the thrombin time titration method and ELISA, respectively. Sitting blood pressures were taken using a random-zero sphygmomanometer after 5 minutes of rest. The average of the second and third of three consecutive measurements was used to calculate systolic and diastolic blood pressure (BP) levels. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. The ratio of waist (umbilical level) and hip (maximum buttocks) circumferences (WHR) was calculated as a measure of fat distribution. A 12-lead electrocardiogram (ECG) tracing was obtained, and left ventricular hypertrophy (LVH) was determined by Cornell voltage criteria. [16]

Carotid IMT was measured by high-resolution B-mode ultrasound, based on the technique validated by Pignoli et al., [17] using a Biosound 2000II-SA ultrasound system (Biosound Incorporated, Indianapolis, Indiana). Sonographers who were trained to use standardized procedures in all study centers read the ultrasound measurements. Far-wall IMT was estimated for 1-cm lengths of the carotid bifurcation and the internal and common carotid arteries (right and left) as the mean of as many 1-mm-apart intima-to-media distances as were available. Detailed descriptions of the ultrasound scanning and reading techniques are described elsewhere. [18] The mean IMT values at the six carotid sites were combined to produce an overall mean IMT. Further, sonographers recorded the presence of a plaque if two of the following three characteristics were met: (1) wall shape (protrusion into the lumen, loss of alignment with adjacent arterial boundary, roughness of the arterial boundary), (2) wall texture (brighter echoes than adjacent boundaries), and (3) wall thickness (intima-media thickness ≥1.5mm).

We defined prevalent coronary heart disease (CHD) and stroke at baseline, for exclusion, as a self-reported history of a physician-diagnosed heart attack, prior myocardial infarction (MI) by ECG, prior cardiovascular surgery, prior coronary angioplasty, or prior stroke or transient ischemic attack (TIA) identified by a standardized interview. [19]

Endpoint determination

For the present study, we included stroke events [14] occurring between ARIC visit 1 (1987–1989) and December 31, 2005. TIAs were not ascertained. ARIC participants were contacted annually by phone, and reported hospitalizations and deaths related to possible strokes in the previous year were identified. The annual follow-up retention rate was 93% through 2005, and the rates did not differ appreciably between races. Some additional strokes in those who quit participating in follow-up calls were found through ARIC hospital surveillance. We also surveyed lists of discharges from local hospitals and death certificates from state vital statistics offices for potential cerebrovascular events. Abstractors recorded signs and symptoms and photocopied neuroimaging (CT or MRI) and other diagnostic reports if the list of discharge diagnoses included a cerebrovascular disease code (International Classification of Diseases, 9^{th} Revision, code 430 to 438), if a cerebrovascular condition or procedure was mentioned in the discharge summary, or if a cerebrovascular finding was noted on a CT or MRI report. Of the stroke-eligible hospitalizations, 92% had at least 1 CT scan, 49% had an MRI of the head, 4% had a cerebral angiography, and 3% a lumbar puncture. Each eligible case was classified by computer algorithm and by a physician reviewer, according to criteria adapted from the National Survey of Stroke. [20] Disagreements were adjudicated by another reviewer. Details on quality assurance for ascertainment and classification of stroke are described elsewhere. [9] Qualifying strokes were further classified into definite or probable hospitalized ischemic (cardioembolic or thrombotic), or hemorrhagic stroke on the basis of neuroimaging studies and autopsy, when available.

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A stroke was classified as ischemic if a brain CT or MRI revealed acute infarction or showed no evidence of hemorrhage. All definite ischemic strokes were further classified as either lacunar or nonlacunar on the basis of the recorded neuroimaging results. A stroke was classified as lacunar if two criteria were met: (1) typical location of the infarct (basal ganglia, brain stem, thalamus, internal capsule, or cerebral white matter) and (2) infarct size of ≤2 cm or unstated size. Definite or probable cardioembolic stroke required the same criteria as ischemic infarction, plus either (1) autopsy evidence of an infarcted area in the brain and a source of possible cerebral emboli in a vessel or presence of an embolus in the brain or (2) medical record evidence of a possible source of embolus, such as moderate or greater valvular heart disease, atrial fibrillation, cardiac or arterial procedure, or intracardiac thrombus.

Statistical analysis

Differences among the quintiles of carotid IMT in age-, sex-, and race-adjusted mean values or prevalences of potential confounding factors at baseline were calculated using ANOVA or logistic regression models, and their trends were tested using linear regression for continuous variables and logistic regression for dichotomous variables. Median values of the carotid IMT categories were used in these analyses.

Time at risk (time to event or time to censoring) was calculated from the date of the baseline examination to the earliest of the following: date of hospital admission for incident stroke, date of death, date of last follow-up contact, or December 31, 2005.

The rate ratios (RRs) of incidence of ischemic stroke and its subtypes and 95% confidence intervals (CI) relative to the lowest quintile of carotid IMT were calculated with adjustment for age and other potential confounding factors using the Cox proportional hazards model. We selected covariates based on previous prospective findings for ischemic stroke in ARIC.[11, 21] Covariates included age (years), sex, race-field center, systolic BP (mmHg), antihypertensive medication use (yes, no), diabetes status (yes, no), smoking status (never, former, and current smokers), heavy drinking (≥252 g/week of ethanol), WHR, LDL cholesterol (mg/dl), HDL cholesterol (mg/dl), past history of coronary heart diseases (yes, no), education level (>high school, ≤high school), LVH (yes, no), white blood cell (WBC) count (cells/mm^3), Lp(a) (ug/ml), fibrinogen (mg/dl), and vWF (%).

Results

As table 1 shows, age-, sex-, and race-adjusted mean levels of systolic and diastolic BP, WHR, BMI, LDL cholesterol, Lp(a), fibrinogen, and WBC were positively associated with carotid IMT levels, and HDL cholesterol levels were negatively associated. Higher prevalences of current smoking, diabetes mellitus, heavy drinking, and LVH were also associated with greater carotid IMT levels. Von Willebrand factor was not associated with carotid IMT levels.

Among 13,560 men and women followed for an average 15.7 years, 82 hemorrhagic and 621 ischemic stroke cases occurred, including 131 lacunar, 358 nonlacunar, and 132 cardioembolic strokes. As shown in Table 2, the incidence rates of hemorrhagic and ischemic strokes were greater across successive carotid IMT levels. Compared with the participants in the lowest quintile (IMT<0.61mm), the age-, sex-, and race-adjusted RRs of ischemic stroke for those in the other groups were 1.46 (95%CI, 1.02 to 2.10) for the second quintile (0.61mm≤ IMT <0.67mm), 1.70 (95%CI, 1.20 to 2.42) for the third quintile (0.67mm≤ IMT < 0.74mm), 2.52 (95%CI, 1.80 to 3.52) for the fourth quintile (0.74mm≤ IMT < 0.85mm), and 3.80 (2.73 to 5.28) for the highest quintile (0.85mm≤ IMT) (p for trend < 0.001). The RRs were attenuated by additional adjustment for systolic BP, use of

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antihypertensive medication, diabetes mellitus, smoking status, heavy drinking, LDL cholesterol, HDL cholesterol, past history of coronary heart diseases, education level, WHR, LVH, WBC, fibrinogen, and vWF, but remained statistically significant (p for trend<0.001). The age-, sex-, and race-adjusted RR of hemorrhagic stroke was significantly elevated for those in the highest versus lowest quintile of IMT elevated (RR=2.55, 95%CI, 1.09 to 5.94), but was attenuated after adjustment for the covariates (RR=2.34, 95%CI, 0.99 to 5.58).

Carotid IMT levels were significantly positively associated with risk of each ischemic stroke subtype: lacunar, nonlacunar, and cardioembolic strokes (Table 3). Compared with participants in the lowest quintiles, the age-, sex-, and race-adjusted RRs for those in the highest quintile groups were 2.89 (95%CI, 1.50 to 5.54) for lacunar, 3.61 (95%CI, 2.33 to 5.59) for nonlacunar, and 6.12 (95%CI, 2.70 to 13.9) for cardioembolic stroke. The RRs were attenuated by additional adjustment for covariates, but remained statistically significant for nonlacunar and cardioembolic strokes (p for trend<0.001, respectively). The presence of carotid plaques was also associated with the incidence of each ischemic stroke subtype. Compared with the participants without plaques (n=8,970), the age-, sex-, and race-adjusted RRs for those with plaques (n=4,590) were 1.59 (95%CI, 1.11 to 2.26) for lacunar, 2.00 (95%CI, 1.61 to 2.47) for nonlacunar, and 2.01 (95%CI, 1.46 to 2.94) for cardioembolic stroke. The RRs were attenuated by additional adjustment for covariates, but remained statistically significant for nonlacunar and cardioembolic strokes; the multivariate-adjusted RRs for those with plaques were 1.25 (95%CI, 0.87 to 1.79) for lacunar, 1.68 (95%CI, 1.35 to 2.09) for nonlacunar, and 1.75 (95%CI, 1.22 to 2.51) for cardioembolic stroke, compared with participants without plaques.

As shown in Table 4, the association between carotid IMT and lacunar stroke was somewhat stronger in African Americans than in whites (P for interaction = 0.07), whereas there were no racial differences in the associations of carotid IMT with nonlacunar and cardioembolic strokes (P for interaction >0.15). Compared with the lowest quintile, the age-and sex-adjusted RRs of lacunar stroke for the highest quartile of IMT were 5.81 (95%CI, 1.99 to 17.0, p for trend <0.001) for African Americans and 1.43 (95%CI, 0.58 to 3.48, p for trend=0.29) for whites.

Discussion

Although previous epidemiological studies have documented that carotid IMT predicts future stroke events, [1–4] no prospective study has reported whether the association between carotid IMT and incidence of stroke varies by subtype. [5–8] Our study found that while carotid IMT levels were associated with the incidence of all stroke subtypes, the estimated risk ratios of carotid intima-media thickening for stroke subtypes were higher for cardioembolic and nonlacunar strokes than for hemorrhagic and lacunar strokes. Further, the associations of carotid IMT with stroke subtypes were also observed for analyses using the presence of plaque.

Previously, a few studies have reported associations between carotid IMT and ischemic stroke subtypes. [5–7] Results were inconsistent and limited, because these studies were performed in a clinical setting and used a case-control design. A cross-sectional case-control study of 470 cases and 463 controls in France showed that an increased common carotid artery (CCA)-IMT was associated with all ischemic stroke subtypes, namely atherothrombotic, lacunar, and cardioembolic strokes, even after adjustment for cardiovascular risk factors; the association between CCA-IMT and ischemic stroke was stronger for the atherothrombotic stroke than other subtypes. [5] Another cross-sectional case-control study of 311 cases and 792 controls in Japan observed that CCA-IMT and plaque score were significantly associated with atherothrombotic and lacunar strokes but not

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cardioembolic stroke. [7] Further, a cross-sectional Italian case-control study of 292 cases and 129 controls reported that CCA-IMT values were significantly higher in subjects with nonlacunar stroke versus both those with lacunar stroke and control subjects. [6] In the present study, carotid IMT levels were significantly associated with nonlacunar and cardioembolic strokes, but not hemorrhagic and lacunar strokes, after adjustment for cardiovascular risk factors. This may support the hypothesis, in part, that lacunar and hemorrhagic strokes are different from the other type of ischemic strokes pathophysiologically.

In ARIC, traditional risk factors, such as hypertension, diabetes mellitus, and smoking, were major risk factors for the incidence of ischemic stroke regardless its subtypes. [11] These traditional risk factors were also important factors for progression of carotid artery atherosclerosis. [22, 23] Therefore, carotid intima-media thickening is most certainly associated with the incidence of all stroke subtypes via chronic atherosclerotic change due to hypertension, diabetes, and smoking. On the other hand, in addition to the differences in traditional risk factors between hemorrhagic and ischemic strokes, [24] the estimated impacts of several nontraditional risk factors, such as WHR, Lp(a), HDL cholesterol, and vWF, on the incidence of ischemic stroke likewise varied according to subtype in ARIC. [11] LVH and vWF were independent risk factors for both nonlacunar and cardioembolic stroke; WHR, history of CHD, and Lp(a) for nonlacunar stroke only; white blood cell count for both lacunar and cardioembolic stroke; and education level and HDL cholesterol for lacunar stroke only, suggesting that the etiologic relation of risk factors with ischemic stroke varies by subtype. The present results provide further evidence that carotid intima-media thickening could be related to ischemic stroke not only as a marker of generalized atherosclerosis but also as a source of thromboemboli. A recent study, conducted in 180 patients with ischemic stroke or TIA of undetermined origin, showed that greater carotid IMT was associated with greater cardiovascular sources of emboli identified on transesophageal echocardiography. [25] This may support our results.

In the present study, the association between carotid IMT and lacunar stroke was confined to African Americans, but not whites. Although we have no clear explanation for this ethnic difference, a greater impact of carotid IMT on incidence of lacunar stroke among African Americans may contribute to the difference in the incidence rates of lacunar stroke between African Americans and whites. Previously, we showed that African Americans had a 5.7-fold higher age- and sex-adjusted RR of lacunar stroke compared with whites, and the excess risk for African Americans remained after adjustment for traditional and nontraditional risk factors; the multivariate-adjusted RR was 3.0 (95%CI, 1.9, 4.8). [11] In the present study, however, when we further adjusted for carotid IMT levels, the multivariate-adjusted RR remained statistically significant: the RR was 2.96 (95%CI, 1.95 to 4.49). Therefore, further research is needed to determine factors explaining the difference in the incidence ratio of lacunar stroke between African Americans and whites.

This study had some limitations. First, we had only a single assessment of IMT at baseline, and measurement error may have led to misclassification of carotid IMT in some individuals. Second, to evaluate carotid IMT, we used mean far-wall IMT estimated for 1-cm lengths of the carotid bifurcation and the internal and common carotid arteries, while previous case-control studies used only the common carotid artery. [5–7] This difference may have contributed to different results between the present study and previous studies of the association of carotid IMT with the incidence of stroke subtypes. Third, ischemic stroke subtypes may have been misclassified for some participants, even though neuroimaging reports and clinical features were used to classify ischemic stroke cases into subtypes. [9] For example, some embolic strokes due to cryptogenic sources of emboli such as aortic arch atheroma might be classified into nonlacunar but not cardioembolic stroke. Further, the nonlacunar stroke group could have included some missed lacunar strokes. These may have

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led to an overestimate or underestimate of the impact of carotid IMT on ischemic stroke subtypes. Fourth, although the associations of carotid IMT with nonlacunar and embolic strokes were found to be independent of cardiovascular risk factors, other residual confounders such as duration of hypertension and other coagulation factors may have affected the associations. [26] Fifth, the lack of assessment of TIAs may have biased the observed association between stroke subtypes and carotid IMT, because the association between TIAs and incidence of stroke may vary by its subtypes. [27] Sixth, the associations between carotid plaques and the incidence of stroke subtypes may vary by sonographic characteristics of the plaques, such as surface irregularity, ulceration, or dysmogenic echogenicity, which were not measured in this study. Finally, the number of incident strokes differed among stroke subtypes, potentially decreasing precision of RRs for hemorrhagic, lacunar, and cardioembolic strokes.

In conclusion, carotid atherosclerosis was associated with all stroke subtypes, but the impact of carotid atherosclerosis on the incidence of stroke may vary by subtypes. Further study is needed to confirm the association of carotid IMT with stroke subtypes in additional large multi-ethnic prospective studies.

Acknowledgments

The authors thank the staff and participants in the ARIC study for their important contributions.

Sources of Funding

The ARIC Study was funded by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022.

References

1. 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. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999;340:14–22. [PubMed: 9878640]
2. Chambless LE, Folsom AR, Clegg LX, Sharrett AR, Shahar E, Nieto FJ, Rosamond WD, Evans G. Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol 2000;151:478–487. [PubMed: 10707916]
3. Kitamura A, Iso H, Imano H, Ohira T, Okada T, Sato S, Kiyama M, Tanigawa T, Yamagishi K, Shimamoto T. Carotid intima-media thickness and plaque characteristics as a risk factor for stroke in Japanese elderly men. Stroke 2004;35:2788–2794. [PubMed: 15528460]
4. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007;115:459–467. [PubMed: 17242284]
5. Touboul PJ, Elbaz A, Koller C, Lucas C, Adrai V, Chedru F, Amarenco P. Common carotid artery intima-media thickness and brain infarction: the Etude du Profil Genetique de l'Infarctus Cerebral (GENIC) case-control study. The GENIC Investigators. Circulation 2000;102:313–318. [PubMed: 10899095]
6. Cupini LM, Pasqualetti P, Diomedi M, Vernieri F, Silvestrini M, Rizzato B, Ferrante F, Bernardi G. Carotid artery intima-media thickness and lacunar versus nonlacunar infarcts. Stroke 2002;33:689–694. [PubMed: 11872889]
7. Nagai Y, Kitagawa K, Yamagami H, Kondo K, Hougaku H, Hori M, Matsumoto M. Carotid artery intima-media thickness and plaque score for the risk assessment of stroke subtypes. Ultrasound Med Biol 2002;28:1239–1243. [PubMed: 12467849]
8. Vemmos KN, Tsivgoulis G, Spengos K, Papamichael CM, Zakopoulos N, Daffertshofer M, Lekakis JP, Mavrikakis M. Common carotid artery intima-media thickness in patients with brain infarction and intracerebral haemorrhage. Cerebrovasc Dis 2004;17:280–286.9. [PubMed: 15026610]

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9. Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G, Copper LS, Shahar E. 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]
10. Schreiner PJ, Chambless LE, Brown SA, Watson RL, Toole J, Heiss G. Lipoprotein(a) as a correlate of stroke and transient ischemic attack prevalence in a biracial cohort: the ARIC Study. Atherosclerosis Risk in Communities. Ann Epidemiol 1994;4:351–359. [PubMed: 7981841]
11. Ohira T, Shahar E, Chambless L, Rosamond W, Mosley T Jr, Folsom A. Risk factors for ischemic stroke subtypes. The Atherosclerosis Risk in Communities (ARIC) Study. Stroke 2006;37:2493–2498. [PubMed: 16931783]
12. Ranjit N, Diez-Roux AV, Chambless L, Jacobs DR Jr, Nieto FJ, Szklo M. Socioeconomic differences in progression of carotid intima-media thickness in the Atherosclerosis Risk in Communities study. Arterioscler Thromb Vasc Biol 2006;26:411–416. [PubMed: 16322533]
13. Tejada J, Diez-Tejedor E, Hernandez-Echebarria L, Balboa O. Does a relationship exist between carotid stenosis and lacunar infarction? Stroke 2003;34:1404–1409. [PubMed: 12738897]
14. The ARIC investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. Am J Epidemiol 1989;129:687–702. [PubMed: 2646917]
15. Papp AC, Hatzakis H, Bracey A, Wu KK. ARIC hemostasis study I. Development of a blood collection and processing system suitable for multicenter hemostatic studies. Thromb Haemost 1989;61:15–19. [PubMed: 2526384]
16. Crow RS, Prineas RJ, Rautaharju P, Hannan P, Liebson PR. Relation between electrocardiography and echocardiography for left ventricular mass in mild systemic hypertension (results from Treatment of Mild Hypertension Study). Am J Cardiol 1995;75:1233–1238. [PubMed: 7778546]
17. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation 1986;74:1399–1406. [PubMed: 3536154]
18. The ARIC Study Group. High-resolution B-mode ultrasound scanning methods in the Atherosclerosis Risk in Communities Study (ARIC). The ARIC Study Group. J Neuroimaging 1991;1:68–73. [PubMed: 10149803]
19. Chambless LE, Shahar E, Sharrett AR, Heiss G, Wijnberg L, Paton CC, Sorlie P, Toole JF. Association of transient ischemic attack/stroke symptoms assessed by standardized questionnaire and algorithm with cerebrovascular risk factors and carotid artery wall thickness. The ARIC Study, 1987–1989. Am J Epidemiol 1996;144:857–866. [PubMed: 8890664]
20. The National Survey of Stroke. National Institute of Neurological and Communicative Disorders and Stroke. Stroke 1981;12:I1–91. [PubMed: 7222163]
21. Folsom AR, Rosamond WD, Shahar E, Cooper LS, Aleksic N, Nieto FJ, Rasmussen ML, Wu KK. Prospective study of markers of hemostatic function with risk of ischemic stroke. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. Circulation 1999;100:736–742. [PubMed: 10449696]
22. van der Meer IM, Iglesias del Sol A, Hak AE, Bots ML, Hofman A, Witteman JC. Risk factors for progression of atherosclerosis measured at multiple sites in the arterial tree: the Rotterdam Study. Stroke 2003;34:2374–2379. [PubMed: 12947155]
23. Chambless LE, Folsom AR, Davis V, Sharrett R, Heiss G, Sorlie P, Szklo M, Howard G, Evans GW. Risk factors for progression of common carotid atherosclerosis: the Atherosclerosis Risk in Communities Study, 1987–1998. Am J Epidemiol 2002;155:38–47. [PubMed: 11772783]
24. Sturgeon JD, Folsom AR, Longstreth WT Jr, Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. Stroke 2007;38:2718–2725. [PubMed: 17761915]
25. Ward RP, Lammertin G, Virnich DE, Polonsky TS, Lang RM. Use of carotid intima-media thickness to identify patients with ischemic stroke and transient ischemic attack with low yield of cardiovascular sources of embolus on transesophageal echocardiography. Stroke 2008;39:2969–2974. [PubMed: 18723422]

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26. Su TC, Lee YT, Chou S, Hwang WT, Chen CF, Wang JD. Twenty-four-hour ambulatory blood pressure and duration of hypertension as major determinants for intima-media thickness and atherosclerosis of carotid arteries. Atherosclerosis 2006;184:151–156. [PubMed: 15935357]

27. Purroy F, Montaner J, Molina CA, Delgado P, Ribo M, Alvarez-Sabín J. Patterns and predictors of early risk of recurrence after transient ischemic attack with respect to etiologic subtypes. Stroke 2007;38:3225–3229. [PubMed: 17962602]

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Stroke. Author manuscript; available in PMC 2012 February 1.

Table 1

Age, sex, race-adjusted baseline characteristics (means or prevalences) according to carotid intima-media thickness levels; ARIC, 1987–89.

	Quintiles of carotid intima-media thickness (mm)					
	Q1 (Low)	**Q2**	**Q3**	**Q4**	**Q5 (High)**	**P for trend**
n	2,702	2,716	2,722	2,705	2,715	
Range, mm	<0.61	0.61–0.67	0.67–0.74	0.74–0.85	≥0.85	
Age*, year	51.3	52.9	54.1	55.3	57.1	<0.001
Men**, %	24.1	33.8	45.0	55.0	65.2	<0.001
Blacks***, %	17.3	24.4	26.2	27.0	26.5	<0.001
Body mass index, kg/m^2	26.0	27.0	27.7	28.2	28.1	<0.001
Waist hip ratio	0.90	0.92	0.92	0.93	0.94	<0.001
Current smoking, %	21.6	23.1	23.8	27.2	33.7	<0.001
Systolic blood pressure, mmHg	117	119	120	122	126	<0.001
Diastolic blood pressure, mmHg	72	73	74	74	74	<0.001
Use of antihypertensive medication, %	22.7	25.5	28.4	30.3	36.6	<0.001
History of coronary heart disease (%)	3.0	3.1	3.3	4.1	7.5	<0.001
Diabetes mellitus, %	6.6	7.8	10.2	11.6	15.4	<0.001
Heavy drinking (≥ 252 g/week of ethanol) (%)	3.3	3.7	3.9	4.2	4.9	0.004
Left ventricular hypertrophy (%)	1.2	1.2	1.6	2.2	3.9	<0.001
Education level (≥ high school), %	81.3	78.9	76.7	76.9	70.7	<0.001
LDL cholesterol, mg/dL	127	135	137	142	146	<0.001
HDL cholesterol, mg/dL	55.8	53.2	51.9	50.3	49.6	<0.001
Lipoprotein (a) (μg/mL)#	52	54	56	58	60	<0.001
Fibrinogen, mg/dL	295	296	302	304	314	<0.001
von Willebrand factor, %	117	116	118	118	118	0.15
White cell count (cells/mm^3)	5854	5908	6055	6176	6505	<0.001

*Adjusted for sex and race.

**Adjusted for age and race.

***Adjusted for age and sex.

#Geometric mean.

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Table 2

Rate ratios (RR) and 95% confidence intervals (CI) of hemorrhagic and ischemic strokes according to carotid intima-media thickness levels: ARIC 1987–2005

	Quintiles of carotid intima-media thickness (mm)					
	Q1 (Low)	**Q2**	**Q3**	**Q4**	**Q5 (High)**	**P for trend**
No. at risk	2,702	2,716	2,722	2,705	2,715	
Range, mm	<0.61	0.61–0.67	0.67–0.74	0.74–0.85	≥0.85	
Hemorrhagic stroke, no. of cases	8	16	15	20	23	
Person-years of follow-up	44,614	44,254	43,805	42,600	40,089	
Incidence rate/1000 person-years	0.2	0.4	0.3	0.5	0.6	
Age, sex, race-adjusted RR (95%CI)	Ref.	1.74 (0.74–4.09)	1.55 (0.65–3.69)	2.07 (0.89–4.81)	2.55 (1.09–5.94)	0.03
Multivariate-adjusted* RR (95%CI)	…	1.81 (0.77–4.25)	1.60 (0.67–3.81)	2.02 (0.86–4.71)	2.33 (0.99–5.49)	0.08
Multivariate-adjusted** RR (95%CI)	…	1.85 (0.79–4.36)	1.58 (0.66–3.79)	2.08 (0.89–4.88)	2.34 (0.99–5.58)	0.08
Ischemic stroke, no. of cases	46	79	100	157	239	
Person-years of follow-up	44,411	43,902	43,442	41,932	38,892	
Incidence rate/1000 person-years	1.0	1.8	2.3	3.7	6.1	
Age, sex, race-adjusted RR (95%CI)	Ref.	1.46 (1.02–2.10)	1.70 (1.20–2.42)	2.52 (1.80–3.52)	3.80 (2.73–5.28)	<0.001
Multivariate-adjusted* RR (95%CI)	…	1.31 (0.91–1.89)	1.39 (0.98–1.99)	1.92 (1.37–2.70)	2.42 (1.73–3.38)	<0.001
Multivariate-adjusted** RR (95%CI)	…	1.32 (0.92–1.90)	1.38 (0.97–1.97)	1.88 (1.34–2.65)	2.36 (1.69–3.31)	<0.001

*Adjusted for age, race-field center, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, smoking status, LDL cholesterol, HDL cholesterol, past history of coronary heart diseases, and education level.

**Further adjusted for heavy drinking, waist-hip ratio, left ventricular hypertrophy, white blood cell count, lipoprotein(a), fibrinogen, and von Willebrand factor.

Stroke. Author manuscript; available in PMC 2012 February 1.

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Table 3

Rate ratios (RR) and 95% confidence intervals (CI) of ischemic stroke subtypes according to carotid intima-media thickness levels: ARIC 1987–2005

	Quintiles of carotid intima-media thickness (mm)					
	Q1 (Low)	**Q2**	**Q3**	**Q4**	**Q5 (High)**	**P for trend**
Lacunar						
No. of cases	13	17	25	32	44	
Age, sex, race-adjusted RR (95%CI)	Ref.	1.11 (0.54–2.30)	1.55 (0.79–3.05)	1.97 (1.02–3.82)	2.89 (1.50–5.54)	<0.001
Multivariate-adjusted* RR (95%CI)	…	0.97 (0.47–2.00)	1.14 (0.58–2.26)	1.36 (0.69–2.65)	1.57 (0.81–3.06)	0.07
Nonlacunar						
No. of cases	26	51	50	87	144	
Age, sex, race-adjusted RR (95%CI)	Ref.	1.64 (1.02–2.63)	1.45 (0.90–2.34)	2.30 (1.47–3.60)	3.61 (2.33–5.59)	<0.001
Multivariate-adjusted* RR (95%CI)	…	1.46 (0.91–2.36)	1.19 (0.73–1.92)	1.72 (1.09–2.71)	2.25 (1.44–3.52)	<0.001
Cardioembolic						
No. of cases	7	11	25	38	51	
Age, sex, race-adjusted RR (95%CI)	Ref.	1.39 (0.54–3.58)	2.97 (1.28–6.90)	4.39 (1.93–9.98)	6.12 (2.70–13.9)	<0.001
Multivariate-adjusted* RR (95%CI)	…	1.32 (0.51–3.42)	2.50 (1.07–5.86)	3.49 (1.51–8.03)	4.24 (1.84–9.80)	<0.001

*Adjusted for age, race-field center, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, smoking status, heavy drinking, LDL cholesterol, HDL cholesterol, past history of coronary heart diseases, education level, waist-hip ratio, left ventricular hypertrophy, white blood cell count, lipoprotein(a), fibrinogen, and von Willebrand factor.

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Table 4

Rate ratios (RR) and 95% confidence intervals (CI) of ischemic stroke subtypes according to carotid intima-media thickness levels, stratified by race: ARIC 1987–2005

	Quintiles of carotid intima-media thickness (mm)					
	Q1 (Low)	**Q2**	**Q3**	**Q4**	**Q5 (High)**	**P for trend**
African Americans						
No. at risk	548	703	713	693	636	
Lacunar, no. of cases	4	7	18	20	28	
Age-, sex-adjusted RR	Ref.	1.32 (0.39–4.52)	3.24 (1.09–9.62)	3.66 (1.24–10.9)	5.81 (1.99–17.0)	<0.001
Non-lacunar, no. of cases	9	23	17	34	43	
Age-, sex-adjusted RR	Ref.	1.93 (0.89–4.17)	1.32 (0.59–2.98)	2.59 (1.23–5.48)	3.57 (1.70–7.51)	<0.001
Cardioembolic, no. of cases	4	5	9	16	16	
Age-, sex-adjusted RR	Ref.	0.94 (0.25–3.52)	1.66 (0.51–5.42)	3.02 (0.99–9.23)	3.54 (1.14–11.0)	0.002
Whites						
No. at risk	2,154	2,013	2,009	2,012	2,079	
Lacunar, no. of cases	9	10	7	12	16	
Age-, sex-adjusted RR	Ref.	1.06 (0.43–2.64)	0.68 (0.25–1.87)	1.10 (0.45–2.73)	1.43 (0.58–3.48)	0.29
Non-lacunar, no. of cases	17	28	33	53	101	
Age-, sex-adjusted RR	Ref.	1.44 (0.78–2.63)	1.50 (0.83–2.71)	2.14 (1.22–3.75)	3.56 (2.07–6.12)	<0.001
Cardioembolic, no. of cases	3	6	16	22	35	
Age-, sex-adjusted RR	Ref.	1.88 (0.47–7.54)	4.66 (1.34–16.1)	5.99 (1.76–20.4)	9.08 (2.69–30.6)	<0.001