Leukocyte Count Is Associated With Aortic Arch Plaque Thickness

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Background and Purpose—Leukocyte count has been associated with cardiovascular and cerebrovascular disease, including carotid plaque thickness, in several studies. We hypothesized that white blood cell count is associated with aortic arch plaque thickness (AAPT).

Methods—Leukocyte count was measured in randomly selected stroke-free community participants undergoing transesophageal echocardiography. AAPT was measured for each subject and dichotomized into <4 and ≥4 mm (thick plaque). Multivariate linear and logistic regression was used to calculate the effect of leukocyte count on AAPT after adjustment for potential confounding factors. Mean age of the 145 participants was 68.5±8.3 years; 43.5% were women; 15.9% were white; 31.7% were black; and 49.0% were Hispanic.

Results—Mean leukocyte count was $5.88\pm1.76\times10^9$/L. Each unit increase in leukocyte count was associated with a mean 0.28-mm increase in AAPT ($P=0.0036$). After adjustment for other atherosclerosis risk factors, including age, sex, hypertension, diabetes, hyperlipidemia, and smoking, the relationship persisted (mean increase in AAPT, 0.24 mm; $P=0.0064$). Thirty-five participants (24.1%) had AAPT ≥4 mm. Mean leukocyte count among those with thick plaque was significantly higher than among those with plaque <4 mm (6.54 ± 1.60 versus $5.65\pm1.76\times10^9$/L, respectively; $P=0.009$). Each unit increase in leukocyte count was associated with an increased risk of thick plaque (adjusted odds ratio, 1.38; 95% CI, 1.05 to 1.79). The relationships were similar for men and women and for those <70 or ≥70 years of age.

Conclusions—Leukocyte count is associated with AAPT and is specifically correlated with AAPT ≥4 mm, a degree of thickening associated with increased stroke risk. These findings are consistent with current hypotheses regarding the inflammatory or infectious etiology of risk of atherosclerosis and stroke. (***Stroke***. 2002;33:2587-2592.)

Key Words: aorta ■ atherosclerosis ■ echocardiography ■ epidemiology ■ risk factors

K nown risk factors fail to account for all cases of ischemic stroke and cardiovascular disease.[1] Recent evidence suggests that atherosclerosis is an inflammatory disease.[2] Leukocytes, including macrophages and lymphocytes, play an important role in the initiation and propagation of the atherosclerotic process. Chronic infection with *Chlamydia pneumoniae*, cytomegalovirus, and other organisms has also been postulated as a potential risk factor for atherosclerosis, heart disease, and stroke.[3–6] Consistent with these hypotheses, recent data from our laboratory provide evidence that subclinical carotid atherosclerosis, as assessed by duplex Doppler ultrasound, is associated with relatively elevated leukocyte counts in certain populations.[7] Other studies have found that leukocyte count is associated with incident heart disease[8] and stroke.[9]

Aortic arch atheroma is an increasingly recognized stroke risk factor, particularly among the elderly.[10–12] Aortic arch plaque thickness (AAPT) ≥4 mm has been found to increase the odds of stroke by as much as 9 times.[10] The underlying pathogenesis of aortic arch atheroma is thought to be similar to that of atherosclerosis affecting the rest of the arterial tree. There may be differences, however, because the aortic media is much thicker than that of other vessels. The carotid arteries, moreover, are more readily studied in large epidemiological studies of subclinical atherosclerosis, which typically rely on noninvasive measures of atherosclerosis such as high-resolution duplex Doppler ultrasound. Transesophageal echocardiography, the most reliable method to detect the presence and thickness of aortic arch plaque, is a semi-invasive test. The Aortic Plaque and Risk of Ischemic Stroke (APRIS) study, in which transesophageal echocardiography is performed in patients with acute ischemic stroke and in matching control subjects, affords a rare opportunity to examine risk factors associated with aortic arch atherosclerosis in a sample of stroke-free individuals ≥55 years of age. We hypothesized that white blood cell count (WBC) is associated with AAPT

in a cross-sectional analysis of a stroke-free, elderly, multi-ethnic urban population.

Subjects and Methods

The APRIS study was designed to test the hypothesis that aortic arch atheroma, as assessed by transesophageal echocardiography, is associated with ischemic stroke risk and to examine the effects on the stroke risk of associated hypercoagulability and lipid disorders. As part of the study, stroke-free participants ≥55 years of age are invited to undergo transesophageal echocardiography. All participants come from the northern Manhattan area, which is an area of New York City with a diverse ethnic background. Northern Manhattan consists of the area north of 145th Street and south of 218th Street that is bordered on the west by the Hudson River and on the east by the Harlem River. In 1990, ≈260 000 people lived in the community with 40% of them >39 years of age and a race-ethnic mixture consisting of 20% black, 63% Hispanic, and 15% white residents.[13]

Selection of APRIS Cohort

The participants in the APRIS study have been recruited from a larger population-based cohort study among residents of northern Manhattan (the Northern Manhattan Stroke Study [NOMASS]). The methods of subject recruitment and enrollment in NOMASS have been described in previous publications.[14] Briefly, random-digit dialing of ≈24 000 households was performed by Audits and Surveys, Inc. Community participants were enrolled in NOMASS if they (1) had never been diagnosed with stroke, (2) were >40 years of age, and (3) resided in Northern Manhattan for ≥3 months in a household with a telephone. Seventy percent of those invited to participate came to the medical center for an in-person evaluation. To enrich the sample for those likely to have aortic arch atheroma, participants in APRIS were limited to those ≥55 years of age. NOMASS participants ≥55 years of age were contacted by telephone and invited to come in for transesophageal echocardiogram. All participants who were unable to go to the medical center did not undergo transesophageal echocardiography and were not included in APRIS. The study was approved by the Institutional Review Board at Columbia-Presbyterian Medical Center. All participants gave consent directly or through a surrogate when appropriate.

Index Evaluation of Subjects

Information about risk factors was collected through interviews by trained research assistants, and physical and neurological examinations were performed by study physicians. Standardized questions were adapted from the Behavioral Risk Factor Surveillance System[15] of the Centers for Disease Control and Prevention regarding the following conditions: hypertension, diabetes, hypercholesterolemia, peripheral vascular disease, transient ischemic attack, cigarette smoking, and cardiac conditions such as myocardial infarction, coronary artery disease, angina, congestive heart failure, atrial fibrillation, other arrhythmias, and valvular heart disease. Assessments were conducted in English or Spanish, depending on the primary language of the participant. Race-ethnicity was based on self-identification through a series of interview questions modeled after the US census and conforming to the standard definitions outlined by Directive 15.[16] When possible, data were obtained directly from participants with the standardized data collection instruments. When the participant was unable to provide answers, a proxy knowledgeable about the participant's history was interviewed. Direct participant data were obtained from 99% of stroke-free participants in the cohort.

Standard techniques were used to measure blood pressure, height, weight, and fasting glucose as described in prior publications.[14,17] Fasting lipid panels (including total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglycerides) were measured with a Hitachi 705 automated spectrometer (Boehringer). Hypertension and diabetes mellitus were defined as in prior publications.[14,17] Hypercholesterolemia was defined as a history of elevated cholesterol, the taking of medications for elevated choles-terol, or a total cholesterol level >240 mg/dL. The definitions are noted in the table footnotes.

Assessment of Leukocyte Counts, C-Reactive Protein, and *C pneumoniae* Titers

Leukocyte counts were measured with automated cell counters via standard techniques (Coulter STK-R and Coulter STK-S, Coulter Electronics, and Sysmex SE-9500, TOA Medical Electronics). Whole blood was collected in 5-cm^3 EDTA-anticoagulated tubes by a trained phlebotomist. The automated cell counter aspirated a sample from the collection tube, and after lysis of red blood cells and platelets, white blood cells were counted with a standard direct-current detection method. Normal values for WBC in the hematology laboratory are 3.54 to 9.06×10^9/L. Quality control is maintained by the laboratory through standard procedures. The coefficient of variation for repeated measurements on samples from individual hospitalized patients is maintained at ≤2.5%.

High-sensitivity C-reactive protein (CRP) levels were measured in a subsample (n=71) of participants in batched samples with enzyme-linked immunosorbent assay using monoclonal antibodies to CRP (Biosource International). *C pneumoniae* titers (IgG and IgA) were also measured in a subsample (n=111) of participants with microimmunofluorescence performed at the Centers for Disease Control. Assays were performed blinded as to aortic plaque status of subjects.

Assessment of AAPT

The method for assessment of AAPT has been described fully in previous publications.[12,18] Briefly, transesophageal echocardiography was performed with an Agilent 2500, 4500, or 5500 system with a 5-MHz omniplane transducer. AAPT was assessed by a single experienced echocardiographer blinded to the participant's risk factors. AAPT was measured in the horizontal plane, perpendicular to the major axis of the aortic lumen. Measurements of plaque thickness were also made in the ascending aorta, aortic arch, and descending aorta. Echocardiographers were blinded to status of WBC and other risk factors.

Statistical Analysis

The distributions of the variable of interest, WBC, and other variables were examined. Means were calculated for continuous variables, and proportions were found for categorical variables. Simple and multiple linear regression was used to analyze the association between WBC and AAPT before and after adjustment for potential confounding demographic and medical variables; analyses were also performed stratified by sex and age. Similar analyses were performed for the association of WBC and plaque thickness at the ascending and descending aortic segments, as well as for the maximum value of all 3 segments. Participants were then dichotomized into those with aortic arch plaque <4 mm and those with plaque ≥4 mm (ie, thick plaque [TP]). This cutoff has been shown to correlate with risk of stroke in prior studies[10,19] and is generally accepted as the clinically relevant cutoff for increased stroke risk.[20] Participants with TP were further dichotomized according to the presence or absence of ulcerated or mobile plaque, which has also been shown to correlate with an increased risk of stroke.[10,11,18] A univariate comparison of WBC in these groups was performed with *t* tests. Univariate and multivariate logistic regression analyses were then performed with WBC as a continuous independent variable and TP as the dependent dichotomous variable. Results were also stratified by sex and age.

Statistical significance was determined at the α=0.05 level with 2-sided tests. Statistical analyses were conducted with SAS computer software (SAS Institute).

Results

The mean age of the 145 participants was 68.5±8.3 years. Eighty-two (56.6%) were men; 49.0% (n=71) of the participants were Hispanic; 15.9% (n=23) were white non-Hispanic; 31.7% (n=46) were black non-Hispanic; and 3.5%

TABLE 1.   Characteristics of Participants

	n	Prevalence, %, or Value, Mean±SD
Total	145	...
Age, y	145	68.5±8.3
Men	82	56.6
Race-ethnicity		
White, non-Hispanic	23	15.9
Black, non-Hispanic	46	31.7
Hispanic	71	49.0
Other	5	3.5
Completed high school	72	49.7
Hypertension	85	58.6
Diabetes mellitus	34	23.5
Cardiac Disease	44	30.3
Current smoking	26	17.9
Ever smoked	94	64.8
Total cholesterol, mg/dL	144	192.8±37.3
HDL, mg/dL	144	45.2±13.4
LDL, mg/dL	143	123.1±35.4
WBC, $\times 10^9$/L	145	5.87±1.76
AAPT, mm	145	2.16±2.02

Hypertension was defined as a systolic blood pressure recording of ≥160 mm Hg or a diastolic blood pressure recording of ≥95 mm Hg or the patient's self-report of a history of hypertension or antihypertensive use. Diabetes mellitus was defined by a fasting blood glucose level ≥126 mg/dL, the patient's self-report of such a history, or insulin or hypoglycemic use.

(n=5) were other race-ethnicities. The distribution of sociodemographic factors, comorbid vascular diseases, and conventional atherosclerotic risk factors is shown in Table 1. All WBC measurements were performed before transesophageal echocardiogram. The median time between measurements of WBC and aortic arch was 39 days.

The mean WBC for the entire cohort was 5.88±1.76×10^9/L (median, 5.60×10^9/L; interquartile range, 4.70 to 7.10×10^9/L; range, 2.60 to 10.80×10^9/L; Table 1). WBC was associated with current smoking but not with age, sex, hypertension, diabetes mellitus, or hypercholesterolemia. The mean WBC among current smokers was 6.65±1.89×10^9/L compared with a mean WBC of 5.70±1.69×10^9/L among current nonsmokers (P=0.02).

The mean AAPT for the entire cohort was 2.16±2.02 mm. AAPT was strongly associated in univariate analyses with age (P<0.0001), hypercholesterolemia (P=0.03), and current smoking (P=0.023). Cholesterol, HDL, LDL, and homocysteine levels did not correlate significantly with thickness as a continuous variable (AAPT) or with the dichotomous cutoff of ≥4 mm. There was no clear association of AAPT with diabetes mellitus (mean AAPT, 1.76±1.81 mm among diabetics versus 2.28±2.08 mm among nondiabetics; P=0.16). The presence of TP was associated with age (P=0.017) and hypercholesterolemia (P=0.025) in univariate analyses. There were trends toward an association with hypertension (P=0.081) and to a lesser extent with male sex (P=0.103) and current smoking (P=0.173).

In a univariate linear regression model, WBC was strongly associated with AAPT (0.28-mm increase in AAPT per unit increase in WBC, P=0.0036). After adjustment for age and sex, the association was essentially unchanged (0.29-mm increase in AAPT per unit increase in WBC, P=0.001). After further adjustment for the other conventional atherosclerotic risk factors of hypertension, diabetes mellitus, current cigarette smoking, and hypercholesterolemia, the association was only slightly attenuated (0.24-mm increase in AAPT per unit increase in WBC, P=0.0064). In this model, age, current smoking, and hypercholesterolemia were also independently associated with AAPT. There was an adjusted mean increase in AAPT of 1.06 mm (P=0.008) and 0.63 mm (P=0.037) for smokers and those with hypercholesterolemia, respectively. There were also trends toward associations of WBC with ascending and descending aortic plaque thickness, but these relationships were not statistically significant after adjustment for other risk factors (Table 2). There was a statistically significant association of the maximum plaque thickness at all 3 sites with WBC (mean change in plaque thickness per unit WBC, 0.28 mm; P=0.0029; Table 2).

In analyses stratified by sex, the association was similar for both men and women (an adjusted increase in AAPT of 0.22 mm in men and 0.26 mm in women; Table 3). The association between WBC and AAPT appeared to be stronger among younger participants than among older ones (an adjusted

TABLE 2.   Association of WBC With Plaque Thickness at Different Aortic Arch Sites

	Thickness (mean±SD), mm	Unadjusted		Adjusted for Demographic Factors†		Adjusted for Demographic and Conventional Risk Factors‡	
		Change per Unit WBC*	P	Change per Unit WBC*	P	Change per Unit WBC*	P
Ascending aorta	1.18±1.40	0.12	0.0768	0.12	0.0680	0.12	0.0700
Arch	2.16±2.02	0.28	0.0036	0.29	0.0010	0.24	0.0064
Descending aorta	2.17±2.33	0.25	0.0221	0.27	0.0114	0.14	0.1658
Maximum	3.03±2.21	0.36	0.0005	0.37	0.0001	0.28	0.0029

*Change in plaque thickness for each given segment in millimeters per unit increase in WBC.

†Demographic factors are age and sex.

‡Conventional risk factors are hypercholesterolemia, hypertension, diabetes mellitus, and current cigarette smoking. Hypertension was defined as a systolic blood pressure recording of ≥160 mm Hg or a diastolic blood pressure recording of ≥95 mm Hg or the patient's self-report of a history of hypertension or antihypertensive use. Diabetes mellitus was defined by a fasting blood glucose level ≥126 mg/dL, the patient's self-report of such a history, or insulin or hypoglycemic use. Hypercholesterolemia was defined as a history of elevated cholesterol, the taking of medications for elevated cholesterol, or a total cholesterol level >240 mg/dL.

TABLE 3.   Association of WBC With AAPT Overall and Stratified by Sex and Age

	Overall		Men		Women		Those <70 y		Those ≥70 y	
	Change in AAPT*	P	Change in AAPT*	P	Change in AAPT*	P	Change in AAPT*	P	Change in AAPT*	P
Unadjusted	0.28	0.0036	0.32	0.0014	0.24	0.0142	0.19	0.0521	0.34	0.0004
Adjusted for demographic factors†	0.29	0.0010	0.29	0.0100	0.29	0.0362	0.41	<0.0001	0.21	0.0220
Adjusted for demographic and conventional risk factors‡	0.24	0.0064	0.22	0.0422	0.26	0.0592	0.37	0.0002	0.16	0.0768

*Change in AAPT in millimeters per unit increase in WBC.

†Demographic factors are age and sex.

‡Conventional risk factors are hypercholesterolemia, hypertension, diabetes mellitus, and current cigarette smoking. Risk factors are as defined in Table 2.

increase in AAPT of 0.37 mm among those <70 years of age and 0.16 mm among those ≥70 years of age; Table 3).

TP was present in 35 participants (24.1%). Of these, 8 had ulcerated (n=7) or mobile (n=1) plaque. Mean WBC was significantly higher among those with than among those without TP (WBC, $6.54\pm1.60\times10^9$/L versus $5.65\pm1.76\times10^9$/L, respectively; P=0.009). There was also a higher mean WBC among those with ulcerated or mobile plaques (WBC, $6.56\pm1.37\times10^9$/L among those with ulcerated or mobile plaques versus $5.83\pm1.78\times10^9$/L among those without; P=0.18), although this result was not statistically significant because of the small number of subjects with ulcerated or mobile plaques. Among the 35 participants with TP, there was no difference in mean WBC between those with (n=8) and those without (n=27) ulcerated or mobile plaques (mean WBC, $6.56\pm1.37\times10^9$/L versus $6.53\pm1.68\times10^9$/L, respectively; P=0.96).

After adjustment for age, sex, hypertension, diabetes mellitus, hypercholesterolemia, and current smoking, WBC remained associated with TP (adjusted odds ratio [OR] per unit increase in WBC, 1.38; 95% CI, 1.05 to 1.79; Table 4). In analyses stratified by sex, WBC was associated with TP among both men and women, although the magnitude of the association was greater in women (men: adjusted OR per unit increase in WBC, 1.22; 95% CI, 0.89 to 1.65; women: adjusted OR, 1.84; 95% CI, 1.11 to 3.05; Table 4.) An independent statistically significant association could not be confirmed in men, who made up ≈57% of the participants. The association was similar and independently statistically significant among both those <70 and those ≥70 years of age (Table 4).

Among the subgroups in which CRP and *C pneumoniae* titers were measured, there were trends toward an association of AAPT with CRP and *C pneumoniae* titers but no statistically significant differences. The mean CRP was higher among those with TP (3.81±5.94 versus 1.87±3.53 mg/dL, P=0.11). Among those with *C pneumoniae* IgG titers ≥1:64 (n=50), 30.0% had TP compared

with 21.3% of those with IgG <1:64 (n=61; P=0.14). Among those with IgA titers ≥1:64 (n=24), 33.3% had TP compared with 23.0% of those with IgG<1:64 (n=87; P=0.3). Multivariable analyses were not performed.

Discussion

This cross-sectional study supports a previously described association between leukocyte count and subclinical atherosclerosis and extends that observation to aortic arch atheroma, for which data on risk factors are less readily available than for carotid and coronary atherosclerosis. We found an association for WBC and aortic arch atheroma in an elderly, urban, mostly Hispanic population, in whom the burden of stroke and other vascular diseases is high. There was both a continuous relationship of WBC with aortic arch plaque thickness and an association with plaque thickness of ≥4 mm, a degree of thickness which in clinical studies strongly correlated with risk of stroke.[10,19] The association was stronger for AAPT than it was for plaque at other segments of the aorta. The association of WBC and aortic arch thickness was similar in magnitude to that for the maximum measurement at the 3 sites. These associations were present independently of other traditionally defined risk factors, including age, sex, hypertension, hypercholesterolemia, smoking, and diabetes mellitus. The effect was present in subgroups defined by sex and age, although the associations may be more prominent among women and those <70 years of age.

Previous studies of atherosclerotic risk factors using another marker of subclinical atherosclerosis, high-resolution carotid duplex Doppler ultrasound, have examined WBC, among other hemostatic and infectious markers. Investigators found WBC to be independently predictive of atherosclerosis progression over 2 years in a small sample of Finnish men.[21]

TABLE 4.   ORs for AAPT ≥4 mm (TP) Per Unit Increase in WBC Overall and Stratified by Sex and Age

	Overall			Men		Women		Those <70 years		Those ≥70 years	
	n	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Unadjusted	145	1.33	1.07–1.66	1.40	1.11–1.77	1.26	1.00–1.60	1.23	0.97–1.56	1.39	1.10–1.75
Adjusted for demographic factors*	145	1.37	1.09–1.73	1.26	0.96–1.66	1.68	1.08–2.61	1.39	1.05–1.85	1.37	1.08–1.74
Adjusted for demographic and conventional risk factors†	145	1.38	1.05–1.79	1.22	0.89–1.65	1.84	1.11–3.05	1.44	1.05–1.97	1.35	1.03–1.78

*Demographic factors are age and sex in the overall analysis and age in the analysis stratified by sex.

†Conventional risk factors are hypercholesterolemia, hypertension, diabetes mellitus, and current cigarette smoking. Risk factors are as defined in Table 2.

In another study[22] investigators examined patients with established arterial diseases and did not find an association of carotid atheroma with any of several hematologic factors. An earlier study[7] from our laboratory of 1422 stroke-free participants provided evidence that among Hispanics there is an association between WBC and carotid atheroma. The numbers in each race-ethnic subgroup in the present study were too small to allow reliable estimates of the effect of WBC on aortic atheroma within those groups. Studies of clinical atherosclerotic outcome events, moreover, have found an association between leukocyte count and atherosclerotic heart disease[8,23] and stroke.[9,24] Our study provides additional evidence that in certain populations elevations in WBC may be independently associated with markers of subclinical atherosclerosis.

There are fewer data available on risk factors for aortic arch plaque than on atherosclerosis at other sites such as the coronary or carotid arteries. The available data are also limited by variability in techniques for identifying aortic atherosclerosis. Large-scale studies have used many different markers of atherosclerosis, including pathological assessment of lesion size in children at autopsy,[25,26] aortic calcification as seen on chest x-rays,[27] and atherosclerosis detected on transesophageal echocardiography.[28,29] These studies have generally found that age, systolic hypertension, smoking, and dyslipidemia are risk factors for arch atherosclerosis.[25–28,30,31] The relationship of sex and diabetes mellitus to aortic atheroma is less certain.[28,32] Several emerging risk factors such as plasma homocysteine,[29,33] maternal hypercholesterolemia during pregnancy,[26] and fibrinogen[34] have also been found to be associated with aortic atheroma. No previous large studies have reported a positive association between leukocyte count and aortic atheroma.

Smoking is probably at least a partial confounder in the relationship between WBC and aortic atherosclerosis. We and others have found that current cigarette smoking is associated with WBC.[7,35] Smoking is also associated with subclinical atherosclerosis.[21,36] Smoking itself could thus be the cause of the increased AAPT, with elevated WBC also resulting from smoking. We found, however, that there is an increase in AAPT even after adjustment for current smoking. Residual confounding or differential reporting of smoking history dependent on WBC status, which is unlikely, could mask the effect of smoking on AAPT. Other risk factors may also be associated with elevated WBC[36] and could confound the relationship between AAPT and WBC.

The magnitude of the effect of elevated WBC on thickened aortic plaque in our population may be clinically meaningful. Aortic arch atheroma ≥4 mm increases the odds of having a stroke by a factor of ≈9.[10] For every unit increase in WBC, the risk of having plaque ≥4 mm increased by ≈37% in our study. Thus far, no population-based estimates of the relative risk of developing stroke in association with aortic atheroma are available. There are also significant variations in the estimates of the prevalence of aortic arch atheroma. The prevalence of aortic arch atheroma ≥4 mm was 2% among those >60 years of age in a French population referred for transesophageal echocardiogram for purposes other than stroke.[10] In our population-based sample identified by random-digit dialing, among those >55 years of age, the prevalence is ≈26%. Differences in risk factors between these populations may explain the difference in prevalence of arch atheroma.

Elevated leukocytes may contribute to either initiation or progression of the atherosclerotic lesion. Monocyte-derived macrophages and T-lymphocytes have been found in human fatty streaks, even at the earliest stage of the disease process, suggesting that immune processes may play an initiating or early role in the development of the lesion.[2] Cytokines, including interleukins, interferons, tumor necrosis factor, and several growth factors and colony-stimulating factors, have also been found within atheromatous lesions at all stages through the use of various techniques.[2,37] As the atherogenic process continues, there is an increase in inflammatory cells in the atheroma, which are recruited from the blood and through multiplication within the lesion itself.[2,37] Recent evidence suggests that circulating levels of specific white cell types such as the $CD4^+CD28^{null}$ subset of T lymphocytes may be associated with unstable angina.[38] It remains unknown whether circulating levels of specific white blood cell types might be associated with subclinical atherosclerosis. We did not have data on individual leukocyte classes.

Our study has several limitations. Because of its cross-sectional design, we cannot claim that elevated WBC leads to an increase in plaque thickness. The converse could just as well be true, ie, that participants with greater AAPT develop elevated WBC. Our study also assesses a measure of subclinical atherosclerosis rather than clinical end points such as myocardial infarction or stroke. Therefore, the clinical significance of the association between WBC and atherosclerosis remains undetermined. Other markers of subclinical atherosclerosis, however, such as carotid intima-media thickness are predictive of clinical ischemic events.[39,40] We also did not have data on clinical infection and thus were unable to make statements about the underlying causes of the elevated WBC. There was a suggestion of an association of AAPT with both CRP levels and *C pneumoniae* titers, but the numbers of participants who had these markers measured were small, and the results are inconclusive. Future studies will need to incorporate more complete data on these and other inflammatory and infectious markers. However, no participants had signs of overt clinical infection at the time of the study, and WBC, although relatively higher in participants with TP, was still within the physiological range for the vast majority of subjects. We did not have measurements of changes in WBC over time.

In summary, our study supports an association between WBC and aortic arch atherosclerosis. Evidence from animal studies and pilot clinical trials in patients with coronary artery disease[41–43] suggests that the risk of atherosclerotic disease associated with certain infections may be modifiable. Corroboration from larger, prospective studies of the role of inflammatory and infectious markers in aortic arch atheroma and stroke might lead to clinical trials with novel anti-inflammatory or anti-infectious therapies to retard atherosclerosis or prevent incident and recurrent stroke.

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