Background and Purpose—Epidemiological studies in men suggest a relationship between endogenous testosterone and ischemic vascular events. We hypothesized that low testosterone is independently associated with ischemic stroke and ischemic brain changes.

Methods—In 1558 male participants (mean [SD] age, 63.1 [5.6] years; body mass index, 28.2 [4.3] kg/m²) from visit 4 (1996–1998) of the ARIC study (Atherosclerosis Risk in Communities) without cardiovascular disease, stroke, and previous testosterone therapy, we measured plasma total testosterone by liquid chromatography mass spectrometry using morning samples and divided levels into tertiles (median [25th–75th percentile], 377.6 [288.4–480.1] ng/dL). General linear models, for cross-sectional analyses, and proportional hazards regression, for time-to-event analysis, examined the association of testosterone with participant characteristics and incident stroke through 2011. Linear and logistic regression models examined the association of testosterone with percentage white matter hyperintensities and prevalent infarcts in participants (n=257) who underwent brain magnetic resonance imaging at visit 5 (2011–2013). Analyses were adjusted for age, race, and ARIC center, body mass index, waist circumference, smoking status, diabetes mellitus, hypertension, low-density lipoprotein, and high-density lipoprotein.

Results—Lower testosterone was significantly associated with higher body mass index, greater waist circumference, diabetes mellitus, hypertension, lower high-density lipoprotein, and never smoking. After adjustment, no association of testosterone with incident stroke was found (hazard ratios [95% confidence intervals] for tertile 1 or 3 versus 2, 1.47 [0.83–2.61], 1.15 [0.62–2.14]; median follow-up, 14.1 years), nor with percentage white matter hyperintensities, cortical infarcts, or subcortical infarcts.

Conclusions—After controlling for atherosclerotic risk factors, there was no association between endogenous testosterone and incident clinical stroke or ischemic brain changes in community-dwelling men. (Stroke. 2016;47:2682-2688. DOI: 10.1161/STROKEAHA.116.014088.)

Key Words: atherosclerosis ■ epidemiologic studies ■ risk factors ■ stroke ■ testosterone
In the current study, we analyzed data from the ARIC study (Atherosclerosis Risk in Communities) to assess the relationship between endogenous testosterone and cerebrovascular disease in men. Our study is one of the first to look at both clinical stroke events and subclinical ischemic disease as evident on brain imaging. We hypothesized that low testosterone independently predicts ischemic stroke events and the presence of ischemic changes on brain magnetic resonance imaging (MRI).

Methods

Study Population

The ARIC study is a prospective investigation of cardiovascular disease that included predominantly white and black men and women, age 45 to 64 years at visit 1, sampled from 4 communities within the United States: Forsyth County, NC; Minneapolis, MN; Washington County, MD; and Jackson, MI. The study was approved by the institutional review boards of all participating institutions. Informed consent was given by all participants enrolled in the study. Participants took part in visit 1 in 1987 and 1989 and were followed up by 3 triennial visits through 1996 to 1998, with a fifth visit completed in 2011 to 2013. We considered visit 4 (1996–1998) to be our baseline for the analysis. Men taking androgen therapy and those with prevalent coronary heart disease, stroke, myocardial infarction, or heart failure were excluded.

Sex Hormone Measurements

Blood samples obtained from male participants at our baseline visit (1996–1998) drawn in the AM with sufficient volume (>1 mL) were retrieved from freezers. Plasma total testosterone was performed by liquid chromatography mass spectrophotometry (Dr. Shalendar Bhasin’s Laboratory, Boston University) in 2012. All samples obtained after 10:30 AM were excluded to correct for diurnal variations in testosterone levels. One testosterone value >2000 mg/dL was excluded because this was felt to be nonphysiologically plausible and likely because of laboratory documentation error.

Ischemic Changes on Brain MRI

A subset of participants present at visit 5 (2011–2013) underwent brain MRI on 3 Tesla Siemens scanners at each field center, using a specific set of sequences.

Brain infarcts were identified and confirmed by a technician and radiologist trained in MRI. Cortical infarcts were identified using fluid attenuated inversion recovery sequences and characterized as large (>10 mm) or small (5–10 mm) lesions involving the cortical matter. Subcortical infarcts were identified using fluid attenuated inversion recovery sequences as hyperintense lesions below the cortex.

The amount of WMH was measured quantitatively using previously described algorithms (Mayo Clinic) in cubic centimeters. Percentage (%) WMH was calculated as the burden of WMH corrected for total brain volume. Total intracranial volume was measured on MP RAGE sequences using Freesurfer 5.1 software.

Incident Stroke

Clinical stroke events and deaths were thoroughly adjudicated and identified by continuous surveillance of participants’ hospitalizations, annual phone calls, and study examinations through 2011. Hospitalizations that included an International Classification of Disease-Ninth Revision code of 430 to 438 used stroke-related key words in the discharge summary or involved computed tomography or MRI with evidence of cerebrovascular disease were identified and abstracted for physician review. We included events defined as definite or probable stroke. Hemorrhagic stroke events were excluded. Minimum criteria for stroke included evidence of rapid or sudden neurological deficits lasting >24 hours or leading to death, in the absence of evidence for other nonstroke etiologies, as defined by the National Survey of Stroke. A computer algorithm further classified stroke events, and any disagreements between physician diagnosis and computer algorithm were adjudicated by a second physician reviewer.

Covariates

At our baseline visit, age, race/ethnicity, smoking status, medication use, and medical history were obtained. Because participants from 2 of the field centers were of a single race in our study sample, a composite variable of center and race was created. Sitting blood pressure was taken as the average of 2 measurements. Anthropometry measures included height, weight, and waist circumference, with calculation of body mass index. Venipuncture was performed in the fasting state. Serum lipids included total cholesterol, triglycerides, and high-density lipoprotein measured by enzymatic assay, with low-density lipoprotein calculated by the Friedewald equation. Hypertension was defined as receiving antihypertensive medications or as a blood pressure ≥140/90 mm Hg. Diabetes mellitus was defined as receiving diabetic medications, self-reported physician diagnosis, a fasting glucose of ≥126 mg/dL, or a nonfasting glucose of ≥200 mg/dL. Smoking status was defined as never, former, or current.

Statistical Analysis

Baseline characteristics were summarized using frequencies and percentages, means and SDs, or medians and interquartile ranges (expressed as 25th–75th percentile). Plasma testosterone values were divided into tertiles (tertile 1:317.7 ng/dL, tertile 2:317.8–441.2 ng/dL, and tertile 3:≥441.3 ng/dL) for analyses. Proportional hazards regression analysis was performed to assess the association of testosterone tertiles with incident ischemic stroke. Linear and logistic regression models were used to assess the association of testosterone tertiles with ischemic changes on brain MRI including % WMH and cortical and subcortical infarcts. % WMH, which are percent of brain volume, were log base 2 transformed before regression. The antilogs of the least squares means and confidence intervals are reported. Models were adjusted for age, race/center, BMI, waist circumference, smoking status, diabetes mellitus, hypertension, low-density lipoprotein, and high-density lipoprotein. All tests were 2 sided, and P<0.05 or a 95% confidence interval not overlapping 1.0 was considered significant. All statistical analysis was conducted using SAS version 9.3 (SAS Institute, Inc, Cary, NC).

Results

Baseline Characteristics

A total of 1943 samples were assayed at baseline. Six were duplicate samples, and we took the average of the 2 values. We excluded participants whose samples were drawn after 10:30 AM (n=9), those taking androgen therapy (n=4), and those with plasma testosterone >2000 ng/dL (n=1). Additionally excluded were those with prevalent coronary heart disease (n=270), prevalent stroke (n=39), prevalent myocardial infarction (n=35), and prevalent heart failure (n=21). The remaining 1558 men had mean (SD) age=63.1(5.6) years and BMI=28.2 (4.27) kg/m². The median (interquartile range) plasma testosterone was 377.6 (288.4–480.1) ng/dL.

Baseline demographic and clinical characteristics of all participants and stratified by testosterone tertile are presented in Table 1. Testosterone levels were not significantly associated with age, race, low-density lipoprotein, or use of lipid-lowering medications. Participants with lower testosterone had significantly higher BMI, greater waist circumference, higher

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prevalence of diabetes mellitus and hypertension, and lower high-density lipoprotein (all $P$ for trend<0.001). Participants with lower testosterone were less likely to be current smokers ($P$ for trend<0.001).

**Incident Stroke**

Median follow up was 14.1 years for incident ischemic stroke (79 events). To test our hypothesis that low or high testosterone might be associated with stroke, tertile 2 was used as the reference in our analysis. Unadjusted and adjusted hazard ratios for incident stroke are provided in Table 2. Lower tertile of testosterone was significantly associated with increased incidence of stroke ($P=0.03$) before adjustment for vascular risk factors as demonstrated in Figure 1. However, after multivariable adjustment, no association was seen between testosterone tertile and incident stroke.

**Brain MRI Changes**

Of the 257 participants who underwent brain MRI with quantitative evaluation of percentage WMH and infarcts, 83 had at least 1 ischemic infarct present on imaging. Of these, 19 participants had a large cortical infarct, 26 participants had

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**Table 1. Demographic and Clinical Characteristics of All Men and Stratified by Testosterone Tertile**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Participants (n=1558)</th>
<th>Tertile 1 (n=520)</th>
<th>Tertile 2 (n=519)</th>
<th>Tertile 3 (n=519)</th>
<th>$P$ for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone, ng/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>402.3 (165.1)</td>
<td>244.5 (60.5)</td>
<td>379.0 (35.7)</td>
<td>583.6 (136.2)</td>
<td>...</td>
</tr>
<tr>
<td>Median (IQR*)</td>
<td>377.6 (288.4–480.1)</td>
<td>260.0 (218.4–288.4)</td>
<td>377.7 (349.5–412.3)</td>
<td>547.1 (480.1–639.4)</td>
<td>...</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>63.1 (5.6)</td>
<td>63.1 (5.6)</td>
<td>62.8 (5.7)</td>
<td>63.4 (5.5)</td>
<td>0.46</td>
</tr>
<tr>
<td>Race/center, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forsyth County, NC: black</td>
<td>38 (2.4)</td>
<td>11 (29.0)</td>
<td>15 (39.5)</td>
<td>12 (31.6)</td>
<td></td>
</tr>
<tr>
<td>Forsyth County, NC: white</td>
<td>311 (20.0)</td>
<td>101 (32.5)</td>
<td>114 (36.7)</td>
<td>96 (30.9)</td>
<td></td>
</tr>
<tr>
<td>Jackson, MS: black</td>
<td>197 (12.6)</td>
<td>71 (36.0)</td>
<td>57 (28.9)</td>
<td>69 (35.0)</td>
<td></td>
</tr>
<tr>
<td>Minneapolis, MN: white</td>
<td>558 (35.8)</td>
<td>186 (33.3)</td>
<td>182 (32.6)</td>
<td>190 (34.1)</td>
<td></td>
</tr>
<tr>
<td>Washington County, MD: white</td>
<td>454 (29.1)</td>
<td>151 (33.3)</td>
<td>151 (33.3)</td>
<td>152 (33.5)</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>28.2 (4.3)</td>
<td>30.0 (4.5)</td>
<td>28.3 (3.9)</td>
<td>26.3 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>27.7 (25.4–30.7)</td>
<td>29.4 (27.0–32.3)</td>
<td>27.9 (25.6–30.9)</td>
<td>26.2 (24.1–28.3)</td>
<td></td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>102.4 (11.2)</td>
<td>106.9 (11.8)</td>
<td>102.6 (10.3)</td>
<td>97.5 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>102 (95–109)</td>
<td>106 (99–114)</td>
<td>101 (96–109)</td>
<td>97 (91–104)</td>
<td></td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01†</td>
</tr>
<tr>
<td>Current</td>
<td>240 (15.4)</td>
<td>61 (11.7)</td>
<td>80 (15.4)</td>
<td>99 (19.1)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>852 (54.7)</td>
<td>305 (58.6)</td>
<td>271 (52.3)</td>
<td>276 (53.2)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>465 (29.9)</td>
<td>154 (29.6)</td>
<td>167 (32.2)</td>
<td>144 (27.8)</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>121.9 (31.6)</td>
<td>118.9 (31.1)</td>
<td>124.3 (29.4)</td>
<td>122.4 (33.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>43.4 (12.9)</td>
<td>40.4 (11.6)</td>
<td>42.6 (12.4)</td>
<td>47.2 (13.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>139.1 (80.7)</td>
<td>158.4 (84.6)</td>
<td>144.0 (87.9)</td>
<td>115.0 (60.9)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>119 (85–171)</td>
<td>135 (100–198)</td>
<td>120 (87–175)</td>
<td>99 (72–140)</td>
<td></td>
</tr>
<tr>
<td>Lipid-lowering medications</td>
<td>183 (11.8)</td>
<td>71 (13.6)</td>
<td>64 (12.3)</td>
<td>48 (9.2)</td>
<td>0.04</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>109.7 (31.2)</td>
<td>117.6 (41.1)</td>
<td>108.2 (25.3)</td>
<td>103.4 (21.9)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>101 (95–111)</td>
<td>105 (98–118)</td>
<td>101 (96–111)</td>
<td>99 (93–107)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>220 (14.2)</td>
<td>113 (21.9)</td>
<td>63 (12.2)</td>
<td>44 (8.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>647 (41.6)</td>
<td>246 (47.5)</td>
<td>213 (41.1)</td>
<td>188 (36.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cut points for testosterone: tertile 1≤317.7 ng/dL, tertile 2=317.8–441.2 ng/dL, and tertile 3≥441.3 ng/dL. IQR indicates interquartile range; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

*IQR expressed as 25th–75th percentile.

†$P$ from $\chi^2$ test, not a test for trend.
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a small cortical infarct, and 60 participants had a subcortical infarct present. Odds ratios for the association of testosterone with the presence of cortical or subcortical infarcts are presented in Table 3. No association was seen with the presence of cortical infarcts or with subcortical infarcts on brain imaging (Table 3). The least squares means of percentage WMH by tertile of testosterone before and after multivariable adjustment are presented in Table 4. No association was seen by tertile of testosterone with % of WMH as demonstrated in Figure 2.

Discussion

In this study, we assessed the role of endogenous testosterone in ischemic stroke based on clinical events and brain imaging using men in the ARIC cohort. We did observe a significant association between lower testosterone and incident stroke events in our sample of men without androgen exposure and without previous cardiac disease or stroke. However, after multivariable adjustment, this association between endogenous testosterone and incident stroke or with the presence (cross-temporally) of cortical or subcortical infarcts and percentage WMH was no longer significant. To our knowledge, this is the first analysis looking at the association of endogenous testosterone with both clinical ischemic stroke events and subclinical ischemic disease evident on brain MRI.

Our analysis reflects comprehensive adjustment for demographic factors and metabolic parameters that are associated with incident cerebrovascular disease and testosterone status. In our sample, those men with lower testosterone had significantly higher BMI, greater waist circumference, higher prevalence of diabetes mellitus and hypertension, and lower high-density lipoprotein (all P for trend<0.001). The association between endogenous testosterone and markers of obesity and metabolic syndrome is well known. Of interest, despite the known decline in testosterone seen with aging, no association was seen between endogenous testosterone levels and age. One explanation for this discrepancy is that the age range of our participants was too narrow to observe a significant difference in testosterone status. In addition, no relationship was seen between endogenous testosterone and low-density lipoprotein or use of lipid medications. Previous studies confirm that the relationship between sex hormones and lipids may be complex and not fully understood.

There have been mixed results with regards to the role of endogenous testosterone in ischemic cerebrovascular disease. Studies have varied in their outcome measurement using single or composite outcomes including mortality, cardiovascular disease, heart failure, and ischemic stroke, and few solely focused on ischemic stroke events and subclinical ischemic disease. In addition, the assay used for measuring sex hormones in previous studies has varied with use of both immunoassay and mass spectrophotometry. In earlier studies of older men using immunoassays, no relationship was seen between endogenous testosterone and stroke or with a composite outcome including heart disease, stroke, and peripheral vascular disease. In contrast, in a prospective sample of community-dwelling men aged 70 to 89 years from Australia followed up for approximately 6.6 years, higher testosterone was associated with a reduced incidence of ischemic stroke after correction for other risk factors, and no relationship was seen with circulating estrogen levels. In another prospective case–cohort study of endogenous testosterone and ischemic arterial events in men over the age of 65 years from France (French 3 C cohort), a J-shaped relationship was seen between total and bioavailable testosterone and incident ischemic arterial event. However, this analysis was limited in that there were fewer stroke events compared with cardiovascular events (32 versus 112), and follow-up was limited to 4 years. In a Danish-based cohort of adult men and women followed up for a mean of 20 years with 524 clinical stroke events in men, very low testosterone concentrations <10th percentile were associated with highest incidence of stroke before and after adjustment, with part of this risk

---

Table 2. Association of Testosterone Tertile With Incident Ischemic Stroke

<table>
<thead>
<tr>
<th>Testosterone Level</th>
<th>Unadjusted Model</th>
<th>Adjusted Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Events/n</td>
<td>79/1558</td>
<td>0.03</td>
</tr>
<tr>
<td>Tertile 1</td>
<td>1.81 (1.04–3.13)</td>
<td>0.03</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>1 (reference)</td>
<td>…</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>1.22 (0.67–2.21)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Multivariable model adjusted for age, race/center, body mass index, waist circumference, cigarette smoking, diabetes mellitus, hypertension, and low-density lipoprotein and high-density lipoprotein cholesterol. CI indicates confidence interval.

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Figure 1. Cumulative incidence of ischemic stroke by tertile of testosterone.
mediated by overweight status and hypertension. This study also relied on a single plasma testosterone value for analysis, but used an immunoassay rather than mass spectrophotometry. In contrast to these studies, the Cardiovascular Health Study found no significant association between total testosterone and ischemic clinical stroke (n=114 events) in US men over the age of 65 years during 10 years of follow-up. In comparison with these studies, our analysis relied on testosterone by liquid chromatography mass spectrometry, which is felt to be highly accurate and reliable when compared with immunoassays.

There is growing literature on the importance of silent or subclinical brain infarcts as a marker for future risk of clinical stroke, comorbidity, and mortality, with little known about the role of endogenous testosterone. The prevalence of subclinical brain infarcts increases with age, just as testosterone level changes with age although there is no known direct association. Windham et al observed in a similarly aged sample to our current study from ARIC that even small silent infarcts were associated with increased incidence of stroke and mortality, suggesting the importance of their role in ischemic cerebrovascular disease. Other prospective analyses have suggested that subclinical ischemic infarcts are associated with decline in cognition and dementia. Cardiometabolic risk factors including hypertension and diabetes mellitus seem to play a role in the incidence of subclinical infarcts. Therefore, the lack of direct association between testosterone status and prevalent brain infarcts in our analysis is reassuring and should direct further investigation into risk factors associated with subclinical brain infarcts.

WMH is another marker for preclinical and subclinical ischemic cerebrovascular disease of growing significance. These lesions are more prevalent with age and are seen commonly in patients with cardiovascular and cerebrovascular disease. They seem to reflect small-vessel disease where chronic hypoperfusion leads to disruption and leakage into the white matter. Their role as a biomarker for clinical ischemic cerebrovascular disease has been evidenced by associations with future clinical strokes, cognitive decline, and mortality. Given the high prevalence of white matter disease in older patients, we chose to use percentage WMH as our outcome. Both cross-sectional and longitudinal analyses have shown that the prevalence and progression of white matter disease are associated with cardiovascular risk factors particularly age, hypertension, and diabetes mellitus. Another longitudinal imaging study using the ARIC cohort found that central obesity and markers of insulin resistance predicted small-vessel disease seen on brain MRI. So although endogenous testosterone may not be associated with these ischemic changes on brain MRI, more investigation is necessary to examine the impact of treating modifiable cardiometabolic risk factors on ischemic brain changes.

Strengths of our analysis include the use of a large sample of community-dwelling men, comprehensive stroke surveillance, and longitudinal follow-up ≥13 years. The adjudication of all clinical stroke events also strengthens the validity of our results. Standardized methods used for MRI allows for the reliable classification of infarcts and assessment of ischemic white matter disease. All testosterone assays were performed using liquid chromatography mass spectrometry, which has advantages over previous assays. Given the diurnal variation

<table>
<thead>
<tr>
<th>Testosterone Level</th>
<th>Cortical Infarct OR (95% CI)</th>
<th>P Value</th>
<th>Subcortical Infarct OR (95% CI)</th>
<th>P Value</th>
<th>Any Infarct OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/n</td>
<td>42/257</td>
<td></td>
<td>59/257</td>
<td></td>
<td>83/257</td>
<td></td>
</tr>
<tr>
<td>Tertile 1</td>
<td>0.95 (0.41–2.22)</td>
<td>0.91</td>
<td>0.87 (0.38–1.95)</td>
<td>0.73</td>
<td>1.14 (0.57–2.29)</td>
<td>0.71</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>1 (reference)</td>
<td></td>
<td>1 (reference)</td>
<td></td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>Tertile 3</td>
<td>0.73 (0.30–1.74)</td>
<td>0.47</td>
<td>1.66 (0.79–3.46)</td>
<td>0.18</td>
<td>1.61 (0.83–3.15)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Adjusted for age, race/center, body mass index, waist circumference, cigarette smoking, diabetes mellitus, hypertension, and low-density lipoprotein and high-density lipoprotein cholesterol. CI indicates confidence interval; and OR, odds ratio.
of testosterone in men with peak levels in the morning, we limited our samples to those drawn before 10:30 AM. Although some were excluded from our analysis because of prevalent coronary heart disease and heart failure, few were excluded because of androgen therapy, suggesting that our sample was generally healthy and testosterone naive.

One limitation in our study was the use of plasma samples, which did not allow us to capture sex hormone binding globulins or free testosterone. However, general consensus suggests that plasma and serum testosterone are generally equivalent in men. Although our study relied on testosterone measured at a single time point, this is felt to be adequate in large population studies. Another limitation was the relatively small number of clinical stroke events (n=79), which may limit power to detect a true association; however, this may reflect the general good health of our participants. We also recognize that the long time lag between testosterone measurement and brain imaging for evaluation of subclinical ischemic changes could limit interpretation of our results. Therefore, it is possible that changes in testosterone level could have occurred between the time of measurement (visit 4) and the MRI (visit 5), which could have influenced brain ischemic changes. Our data are strengthened by using both clinical stroke events and the presence of infarcts and % WMH on imaging so as to capture those with both clinical and subclinical disease.

Conclusions

Our study is one of the first to look at the role of endogenous testosterone in both clinical ischemic stroke events and ischemic changes on brain imaging in men. Lower endogenous plasma testosterone was associated with incident clinical stroke events; however, this association was no longer present after adjustment for other cardiovascular risk factors. Endogenous testosterone did not predict ischemic infarcts or white matter disease on MRI. This analysis contributes to previous studies looking at the role of endogenous testosterone in atherosclerosis and ischemic cerebrovascular disease in men by providing reassurance that both low and high testosterone levels are not associated with incident ischemic stroke. Our findings also confirm that low testosterone is associated with metabolic risk factors. Therefore, the focus of intervention should be treatment of other comorbidities and cardiovascular risk factors, rather than treating testosterone to a specific level. Further prospective, randomized studies are needed to look at the risks and benefits of exogenous hormone therapy in this population specific to ischemic cerebrovascular disease.

Acknowledgments

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Disclosures

None.

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Association Between Endogenous Testosterone and Cerebrovascular Disease in the ARIC Study (Atherosclerosis Risk in Communities)
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