Blood Pressure and White-Matter Disease Progression in a Biethnic Cohort
Atherosclerosis Risk in Communities (ARIC) Study

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Background and Purpose—Blood pressure (BP) is a predictor of concurrent and subsequently measured white-matter hyperintensity (WMH), but longitudinal studies of WMH changes and data in black participants are lacking. We hypothesized that WMH progression would be (1) strongly related to BP in blacks and whites and (2) predicted more strongly by earlier (midlife) or cumulative BP measurements than by measures at older ages.

Methods—Participants were 983 individuals (49% black) from the Atherosclerosis Risk in Communities (ARIC) Study who underwent cerebral magnetic resonance imaging in 1993–1995 and 2004–2006. Associations between BP (measured at each of 5 visits, in addition to a time-averaged cumulative BP) and progression of WMHs were analyzed and compared.

Results—Cumulative systolic BP (SBP) was the strongest BP predictor of WMH progression in adjusted models. Higher cumulative SBP (by 20 mm Hg) was associated with greater progression of WMHs and was similar in blacks (2.5 cm³, \( P < 0.0001 \)) and whites (2.6 cm³, \( P < 0.0001 \)). Higher cumulative SBP (per 20 mm Hg) was also associated with being in the top quintile of WMH progression (adjusted odds ratio = 2.0; 95% CI, 1.6 to 2.6). Earlier SBP measurements were stronger predictors of WMH progression than were later SBP measurements, but in blacks only.

Conclusions—In this population-based cohort, cumulative SBP was a stronger predictor of WMH progression than SBP from individual visits, in both blacks and whites. Earlier BPs were stronger predictors than BPs measured at later time points in blacks only. (Stroke. 2010;41:3-8.)

Key Words: leukoaraiosis ■ hypertension ■ epidemiology ■ MRI

Cerebrovascular injury from systemic disease takes the form not only of discrete strokes but also of white-matter injury. In past epidemiologic studies, associations between vascular risk factors and resultant white-matter disease1,2 or cognitive impairment3–5 have been strongest when the risk factor was measured in midlife.

In general, blacks have more hypertension and more white-matter disease than do whites.6 Whether the excess of white-matter disease in blacks is entirely due to differences in hypertension prevalence, severity, or control or whether hypertension differentially affects blacks compared with whites is not fully explored. In addition, whether measurement of risk in midlife is as important in blacks compared with whites has not been evaluated. Finally, few prior studies have explored associations between vascular risk factors, such as blood pressure (BP), and the progression of white-matter disease. Progression of white-matter disease has been identified as a more important predictor of cognitive decline than is baseline white-matter disease volume,7 and it therefore warrants further study.

In the Atherosclerosis Risk in Communities (ARIC) cohort, we investigated associations between BP measurements at different time points for nearly 20 years and the progression of white-matter hyperintensity (WMH) volume. We hypothesized that BP would be strongly associated with WMH progression and that this relation would be (1) at least as strong in black as in white participants and (2) stronger when BP was measured earlier in life or summarized by a cumulative average compared with BP measured at later time points.

Subjects and Methods
Study Population
ARIC is a prospective study of middle-aged black and white men and women designed to investigate the natural history of atherosclerosis...
and its sequelae. At baseline (1987–89), 15 792 participants were sampled from 4 US communities: Forsyth County, NC; Jackson, Miss; the suburbs of Minneapolis, Minn; and Washington County, Md. Blacks were sampled exclusively in Jackson and oversampled in Forsyth County to facilitate race-specific analyses. The other 2 sites were predominantly white. Race and ethnicity were self-identified.

Study design and procedures have been published. After the baseline visit (visit 1), participants returned in 1990 to 1993 (visit 2), 1993 to 1995 (visit 3), 1996 to 1999 (visit 4), and for a subset, 2004 to 2006 (brain magnetic resonance imaging [MRI] visit, visit 5). At all visits, concurrent medical, social, and medication history was collected and BPs were measured.

Participants age 55 and older at the Jackson, Miss, and Forsyth County sites were invited for a brain MRI at visit 3 (1949 individuals completed an MRI). All subjects without MRI contraindications who completed the visit 3 MRI were invited for a second MRI scan between 2004 and 2006. These participants were more likely to be black than the remainder of the living ARIC sample, with comparable numbers of females.

**Brain MRI**

**Visit 3**

Visit 3 brain MRIs were performed with 1.5-T scanners, and 5-mm-thick contiguous axial images were obtained and interpreted at the ARIC MRI Reading Center. Proton density–weighted images were viewed to grade the relative severity of WMHs on a 0 to 9 scale developed for the Cardiovascular Health Study (CHS) (referred to in this article as “white-matter grade”). Subcortical and periventricular WMHs were visually evaluated together. The reproducibility of visual scoring of WMHs in CHS was good, with inter- and intra-reader agreement within 1 grade of 92% and 94.5% and relaxed kappas of 0.81 and 0.93, respectively. White-matter grade was evaluated on all visit 3 brain MRIs.

**Visit 5**

In 2004 to 2006, as part of the ARIC Brain MRI ancillary study (visit 5), 1134 participants underwent a second 1.5-T brain MRI. These scans were rated according to both the qualitative white-matter grade and a semiautomated volumetric analysis. Brain and leukoaraiosis volumes were determined from axial fluid–attenuated inversion recovery images. An automated algorithm was used to segment each of the axial fluid–attenuated inversion recovery images into voxels assigned to 1 of 3 categories based on signal intensity: normal brain, cerebrospinal fluid, or leukoaraiosis. The leukoaraiosis maps were manually edited to exclude infarcts and other lesions. The mean absolute error and test-retest coefficient of variation for this method were 6.6% and 1.4%, respectively, for leukoaraiosis volume. Total intracranial volume was manually measured from T1-weighted sagittal images. Volumetric measurements of WMH were standardized to an intracranial volume of 1500 cm³.

Two individuals with severe WMHs at visit 3 were excluded (white-matter grade 7), because they would have been unlikely to show progression. Nine subjects were excluded because of prevalent stroke at visit 3. The final sample included 983 individuals with interpretable MRI scans from both visits.

**Calculation of WMH Change**

Fully quantitative WMH volumes were not possible from all visit 3 scans. Therefore, WMH volume at visit 3 was estimated from a prediction equation ($R^2=0.80$) that related volume from visual grades (Figure 1). The prediction equation was created from actual data from visit 5 (visual grades and quantitative volumes). Visit 3 visual grades were then entered into the equation to calculate estimated visit 3 volumes. Change in WMH volume was calculated by subtracting the estimated WMH volume at visit 3 from the WMH volume at visit 5. One value with an apparent decrease of $>20$ cm³ was excluded, as this was likely due to measurement error.

**Blood Pressures**

Sitting brachial BP was measured according to standardized protocols by trained technicians using a random-zero sphygmomanometer, with 5 minutes’ rest between measurements. At all visits, BP was measured 3 times, and our analyses used the average of the last 2 values for that visit.

Antihypertensive medications were recorded at each visit. A cumulative, time-averaged value was calculated, yielding a value between 0 and 1 for each individual’s proportion of time they had spent over the duration of the study on the medication.

**Statistical Analysis**

Stata version 8.2 for Macintosh was used. White-matter disease progression was analyzed continuously and as quintiles of WMH volume change. Cross-sectional measures of systolic BP (SBP) at each of the ARIC visits were considered, as well as cumulative SBP measurements. The cumulative values, determined as the area under the curve of examination-specific values divided by the time between the first and last examinations, can be interpreted as the estimated mean daily SBP for the entire period. Other covariates included age, sex, race, body mass index from visit 3, visit 3 smoking status, diabetes (fasting glucose $\geq 126$ mg/dL at visit 3), education (categorized as $<8$, 9 to 11, 12 to 13, 14 to 16, 17 to 20, or $>21$ years), and prevalent coronary heart disease (visit 3). Linear regression was used to determine the association between SBP and WMH volume change (with larger values indicating a larger increase in WMH volume from visit 3 to 5), and logistic regression was used to estimate its effect on the risk of being in the highest quintile (vs the lower 4 quintiles) of WMH volume change. Models were analyzed for the entire sample and separately by race.

A separate analysis was performed to compare the effect of “early” (visits 1 and 2) versus “late” (visits 4 and 5) SBP on WMH volume change by using averages of visits 1 and 2 SBP (“early”) and of visits 4 and 5 SBP (“late”). Both of these averaged SBPs were entered into the same race-, sex-, and age-adjusted model to determine the association of early versus late SBP with WMH volume change independent of SBP at the other time point.

We also analyzed the role of antihypertensive medications in the association between SBP and white-matter disease. Based on methods reported previously, a constant of 10 mm Hg was added to the SBP value from a given visit for any individual on antihypertensive medication at the time of that visit. For cumulative SBP modeling, when the individual had been on an antihypertensive medication at least 50% of the time, the same constant was added to the cumulative SBP value. Additional analyses were conducted after adjusting for cumulative antihypertensive use (between 0 and 1) as a covariate. Secondary analyses were also performed after adjusting for baseline...
Finally, we performed a secondary analysis by using change in WMH visual grade from visit 3 to visit 5 as the dependent variable. These models were estimated by ordinal logistic regression. Change in WMH visual grade was calculated by subtracting the grade at visit 3 from that at visit 5.

Table 1. Characteristics of ARIC Participants Who Completed 2 Interpretable Brain MRI Scans (N=983)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Black, n (%)</th>
<th>Female, n (%)</th>
<th>Age at visit 5, y, mean (SD)</th>
<th>Visit 1 SBP, mm Hg, mean (SD)</th>
<th>Visit 2 SBP, mm Hg, mean (SD)</th>
<th>Visit 3 SBP, mm Hg, mean (SD)</th>
<th>Visit 4 SBP, mm Hg, mean (SD)</th>
<th>Visit 5 SBP, mm Hg, mean (SD)</th>
<th>Cumulative mean SBP, mm Hg (SD)</th>
<th>Hypertension† (visit 1), n (%)</th>
<th>History of myocardial infarction (visit 1), n (%)</th>
<th>Diabetes mellitus‡ (visit 1), n (%)</th>
<th>Current smoking (visit 1), n (%)</th>
<th>Prevalent coronary heart disease (visit 1), n (%)</th>
<th>Body mass index (visit 1), kg/m², mean (SD)</th>
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<tr>
<td>Black, n (%)</td>
<td>485 (49.3%)</td>
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<td>72 (4)</td>
<td>121 (17)</td>
<td>120 (18)</td>
<td>126 (19)</td>
<td>129 (19)</td>
<td>133 (19)</td>
<td>127 (14)</td>
<td>358 (37%)</td>
<td>10 (1%)</td>
<td>78 (8%)</td>
<td>189 (19%)</td>
<td>13 (1%)</td>
<td>27 (4)</td>
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<td>Female, n (%)</td>
<td>605 (61.6%)</td>
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<td>Hypertension† (visit 1), n (%)</td>
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*Brain MRI was also done at these visits.
†Defined as BP ≥140/90 mm Hg or hypertension medication use in the preceding 2 weeks.
‡Defined as fasting glucose ≥126 mg/dL.

Table 1. Characteristics of ARIC Participants Who Completed 2 Interpretable Brain MRI Scans (N=983)

Results

Patient Characteristics

As shown in Table 1, approximately half of the participants were black, and SBP was generally higher at later than at earlier visits. Distribution of white-matter grade among individuals who underwent MRI at both visits (3 and 5) is displayed in Figure 2. Fewer than 4% of whites, compared with 10% of blacks, progressed by >2 grades (P<0.001). WMH volume (standardized to 1500 cm³ total intracranial volume) at visit 5 averaged 13 cm³; the median was 9.1 cm³; SD was 11 cm³; and maximum value was 90 cm³. The average WMH change (from visit 3 to 5) was 5.2 cm³ (median, 2.7 cm³; SD, 8.6 cm³).

Analysis of WMH Volume Change as a Continuous Variable

Analyzed as a continuous variable, SBP was strongly associated with WMH volume change (Table 2). Cumulative mean SBP was a stronger predictor than SBP measured at the different examinations. Earlier SBP values had stronger associations with the change in WMH than did SBP values measured later, but in stratified analysis, this was seen only in blacks. In adjusted models, each 20 mm Hg higher cumulative mean SBP was associated with a 2.4-cm³ greater increase in WMH volume between visits 3 and 5, with a similar association in blacks and whites (2.5 and 2.6 cm³, respectively, Table 2).

A race×SBP interaction term was significant for visits 1 and 2, indicating that the association between WMH volume and SBP measured at these early visits was stronger in blacks. The race×SBP interaction was not significant in the models for visits 3, 4, or 5 or for cumulative SBP.

Analysis of ‘Significant Progression’

Figure 3 shows the adjusted odds ratio (per 20 mm Hg; an ∼1-SD increase in SBP) of being in the highest quintile of change in WMH volume in the range of 1.3 to 2.3 for SBP measured at the different visits (or for a cumulative value).

Analysis of Effect of Timing of SBP Measurement in Prediction of WMH Volume Change

Inclusion of both early SBP (an average of SBP from the first 2 visits) and late SBP (average of values from visits 4 and 5) in the same age- and sex-adjusted model permitted assessment of the importance of the timing of BP in predicting WMH progression. In a model including all participants, coefficients were similar (0.91 and 1.51 cm³ of progression per 20 mm Hg for early vs late SBP values, respectively). Findings were similar in white participants. However, in black participants, the coefficient associated with an equivalent difference (20 mm Hg) in SBP from early visits was 2.17 cm³ (95% CI, 0.96 to 3.38), after adjustment for later SBP, compared with only 0.68 cm³ additional WMH progression associated with a difference of 20 mm Hg in later visits (after adjustment for earlier SBP).

Secondary Analyses

When use of antihypertensive medications was accounted for by adding a 10-mm Hg constant, as described in the Methods section, the association with SBP was partially attenuated but remained significant. Complete results when cumulative use of antihypertensive medication was included as a covariate, in the prediction of worst amount of WMH change (top quintile), are included in the supplemental Table, available online at http://stroke.ahajournals.org. Cumulative SBP remained the most important predictor.
When the continuous analyses were repeated including adjustment for WMH grade at visit 3, results remained statistically significant, but point estimates were moderately decreased. When the primary analyses were repeated but using change in WMH grade (without using the estimated volumes), similar results were found, with the strongest effect from the cumulative SBP value. The adjusted odds ratio for advancing 1 category in WMH visual grade, per 20 mm Hg of SBP, was 1.27 when SBP was measured from visit 1 (95% CI, 1.10 to 1.48), 1.24 (95% CI, 1.07 to 1.44) from visit 2, 1.14 (95% CI, 1.00 to 1.30) from visit 3, 1.30 (95% CI, 1.13 to 1.48) from visit 4, 1.18 (95% CI, 1.04 to 1.35) from visit 5, and 1.46 for cumulative SBP (95% CI, 1.22 to 1.75).

Discussion

In this large cohort with serial BP measurements and 2 MRI studies per subject, cumulative mean SBP was a much stronger predictor of white-matter disease progression than were SBPs from individual time points. In blacks, earlier (midlife) measurements of SBP had slightly stronger associations with WMH change than did later measurements. More blacks than whites had substantial progression of WMH, although an equivalent increase in cumulative mean SBP was associated with a similar increases in WMH volume change in blacks and whites. Substantially more blacks had a known diagnosis of hypertension (41.6%) at the start of the ARIC study than did whites (16.6%). Perhaps the ethnic differences in progression may reflect a longer duration of hypertension in blacks, even earlier than measured in this study.

Although others have hypothesized that WMH may result from degenerative or demyelinating injury, our results support a significant vascular component to the progression of WMH. Our findings are also consistent with previous studies suggesting the importance of measurement of vascular risk factors in midlife in predicting subsequent cognitive impairment and white-matter disease. Other studies have supported a relatively weak cross-sectional association between measurement of BP and WMH. In the CHS, in participants >65 years, higher SBP was associated with higher white-matter grade (graded categorically). Our focus was on the progression of WMH; we did find evidence for an association between SBP measured at the time of the first MRI and WMH progression but found that in blacks (who have not been as well represented in other epidemiologic studies), it was not as strong as associations with SBP measured before the first MRI. We cannot explain the relative lack of influence of earlier SBP values in whites in this study.

Whites had less-severe baseline WMHs and so had lower

### Table 2. Adjusted β Coefficients for Effect of SBP (per 20 mm Hg) on WMH Volume Change (in cm³) Between Cerebral MRI Visits (From Visit 3 to Visit 5) in the ARIC Study

<table>
<thead>
<tr>
<th>SBP Measurement</th>
<th>Median Years From Baseline MRI</th>
<th>β Coefficient* (95% CI) for All Participants</th>
<th>β Coefficient† (95% CI) for Whites Only</th>
<th>β Coefficient† (95% CI) for Blacks Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>-5.8</td>
<td>1.44 (0.80–2.09)</td>
<td>1.07 (0.19–1.97)</td>
<td>1.98 (1.04–2.92)</td>
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<tr>
<td>Visit 2</td>
<td>-3.0</td>
<td>1.47 (0.85–2.10)</td>
<td>1.26 (0.38–2.13)</td>
<td>1.89 (0.99–2.79)</td>
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<tr>
<td>Visit 3: baseline MRI</td>
<td>0</td>
<td>1.10 (0.54–1.67)</td>
<td>1.18 (0.39–1.96)</td>
<td>1.14 (0.32–1.96)</td>
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<tr>
<td>Visit 4</td>
<td>+3.0</td>
<td>1.31 (0.73–1.88)</td>
<td>1.93 (1.18–2.68)</td>
<td>0.78 (–0.09–1.66)</td>
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<tr>
<td>Visit 5: follow-up MRI</td>
<td>+10.6</td>
<td>1.28 (0.70–1.85)</td>
<td>1.39 (0.61–2.16)</td>
<td>1.36 (0.51–2.22)</td>
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<tr>
<td>Cumulative mean SBP</td>
<td>2.35 (1.58–3.12)</td>
<td>2.56 (1.56–3.56)</td>
<td>2.48 (1.30–3.67)</td>
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</table>

*Adjusted for age, sex, education, prevalent coronary heart disease at visit 3, diabetes at visit 3, body mass index at visit 3, race, and smoking status at visit 3.
†Same as above but without adjustment for race.

Figure 3. Adjusted odds ratios for the top quintile of change in WMH volume, per 20-mm Hg-higher SBP at varying time points and shown by race. Cumulative time-averaged SBP and SBP measurements from each visit are displayed.
volumes of WMH in general. The effect of SBP on WMH progression in whites was quite variable from visit to visit. This variability remained, even after adjustment for antihypertensive medication use. BP variability in general warrants further study, as wide fluctuations in BP may be problematic for the integrity of the white matter.

To our knowledge, a cumulative variable, taking into account SBP levels for ≈15 years, has not been explored previously to describe relations with white-matter disease. Its effect size portends the potential utility of this measure in future studies on the long-term effects of hypertension. The association between WMH progression and a 20 mm Hg-higher cumulative SBP was equivalent to the increase in progression associated with a 7- to 8-year difference in baseline age.

In the Rotterdam Study, higher SBP and diastolic BP both predicted the progression of periventricular white-matter disease, but this was on a categorical scale, their effect sizes tended to be smaller for comparable differences in WMH progression, and their results were not significant consistently. This may be because the Rotterdam Study recruited primarily white participants with access to excellent health care, who, as our results suggest, may have weaker associations between early BP measurements and white-matter disease. We also believe that the additional information provided by volumetric measurement of white-matter disease helps to better define the extent of disease progression.

Mechanisms underlying WMHs are important to explore, given the known relations between WMHs and subsequent dementia or cognitive impairment. Progression may be particularly important; in 1 recent study, individuals who became cognitively impaired had an average increase in WMH of 2.4 cm^3/y, compared with those who were cognitively intact (mean WMH increase of 0.8 cm^3/y).

A limitation of this study is the lack of direct volumetric imaging at the third visit. However, the validity of our approach for estimating visit 3 WMH volumes, based on the relation between categorical and volumetric ratings at visit 5, is supported by the excellent fit of the equation that we used for making those estimates. Another limitation is the lack of information about ambulatory BP. Given that cumulative SBP was a strong predictor of white-matter disease, detailed ambulatory BP measurements might provide even stronger prediction but are cost-prohibitive and impractical for any lengthy time frame. Associations were still present, though attenuated, when antihypertensive use was included in the models, suggesting that some injury from hypertension might be eliminated by the use of antihypertensives. However, the degree to which an individual’s SBP was lowered by medications could not be well examined in this study, with our methods, because some individuals might have better BP control on antihypertensive medications, others might require 3 or 4 medications, and still others might be on antihypertensive medications but for reasons other than BP control (eg, β-blockers for rate control in atrial fibrillation).

Persons who completed both cerebral MRIs may represent a biased sample of the population. Individuals with more advanced leukoaraiosis or with dementia might be underrepresented. This potential bias might be conservative, leading us to underestimate the strength of the associations between BP and white-matter disease progression.

The strengths of this study include the large sample size with excellent follow-up, standardized measurement of BP and other vascular risk factors, and the availability of serial MRI scans in a largely asymptomatic population. We believe that our use of volumetrics provides an advantage over the use of categorical ratings, as has been typically used in other studies. We have shown the importance of BP in subclinical vascular disease. Further studies may focus on clinical sequelae. Because white-matter disease has been associated with cognitive dysfunction, a reduction in white-matter disease progression may be a means by which long-term antihypertensive treatment might prevent cognitive impairment and dementia. In our study, the relation between SBP and white-matter disease was linear, suggesting that changes in SBP are critical across a wide range of values. The relative health of the sample, however, limited our ability to make conclusions about individuals with very high or very low BP values, as there were very few individuals at those extremes.

Summary
Cumulative SBP provides valuable information in estimating the risk of progression of white-matter disease, beyond that of BP measurements taken at individual time points. In blacks, earlier BPs may be more important than later life BPs in predicting white-matter disease progression. These findings further emphasize the importance of persistently elevated BP in the development of subclinical cerebral vascular disease.

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

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Disclosures
Dr Knopman has served on a data safety monitoring board for Sanofi-Aventis Pharmaceuticals, will serve on a data safety monitoring board for Lilly, and is an investigator for clinical trials sponsored by Baxter Pharmaceuticals, Elan Pharmaceuticals, and Forest Pharmaceuticals. He has served as a 1-time consultant to GlaxoSmithKline regarding an anti-Alzheimer drug. He is an associate editor of Neurology, for which he receives compensation from the American Academy of Neurology. Dr Jack has received research support from and has been a consultant for Pfizer. The other authors have neither conflicts of interest nor other financial disclosures.

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