Brain arterial aging and its relationship to Alzheimer dementia

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ABSTRACT

Objective: To test the hypothesis that brain arterial aging is associated with the pathologic diagnosis of Alzheimer disease (AD).

Methods: Brain large arteries were assessed for diameter, gaps in the internal elastic lamina (IEL), luminal stenosis, atherosclerosis, and lumen-to-wall ratio. Elastin, collagen, and amyloid were assessed with Van Gieson, trichrome, and Congo red staining intensities, and quantified automatically. Brain infarcts and AD (defined pathologically) were assessed at autopsy. We created a brain arterial aging (BAA) score with arterial characteristics associated with aging after adjusting for demographic and clinical variables using cross-sectional generalized linear models.

Results: We studied 194 autopsied brains, 25 (13%) of which had autopsy evidence of AD. Brain arterial aging consisted of higher interadventitial and lumen diameters, thickening of the wall, increased prevalence of IEL gaps, concentric intima thickening, elastin loss, increased amyloid deposition, and a higher IEL proportion without changes in lumen-to-wall ratio. In multivariable analysis, a high IEL proportion ($B = 1.96$, $p = 0.030$), thick media ($B = 3.50$, $p = 0.001$), elastin loss ($B = 6.16$, $p < 0.001$), IEL gaps ($B = 3.14$, $p = 0.023$), and concentric intima thickening ($B = 7.19$, $p < 0.001$) were used to create the BAA score. Adjusting for demographics, vascular risk factors, atherosclerosis, and brain infarcts, the BAA score was associated with AD ($B = 0.022$, $p = 0.002$).

Conclusions: Aging of brain large arteries is characterized by arterial dilation with a commensurate wall thickening, elastin loss, and IEL gaps. Greater intensity of arterial aging was associated with AD independently of atherosclerosis and brain infarcts. Understanding the drivers of arterial aging may advance the knowledge of the pathophysiology of AD. *Neurology*® 2016;86:1507–1515

GLOSSARY

AD = Alzheimer disease; **BAA** = brain arterial aging; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **EVG** = elastic Van Gieson; **IEL** = internal elastic lamina; **IQR** = interquartile range.

Dementia and stroke are the most frequent neurologic syndromes in the aging population, with stroke the leading cause of disability in the United States and dementia projected to affect 14 million Americans by 2050 at a great financial cost.^{1,2} Vascular disease influences the risk of dementia. For example, dementia, mostly Alzheimer disease (AD), increases with age, and arterial disease and vascular risk factors are considered risk factors for AD and vascular dementias.³ The risk between stroke and dementia is reciprocal: there is a higher risk of stroke (ischemic or hemorrhagic) among those with dementia, and there is an increased risk of dementia among those with strokes.^{4–7}

Intracranial atherosclerosis is among the most important causes of stroke,^{8,9} and it has also been associated with a greater risk of AD.^{10,11} Although atherosclerosis increases with age, atherosclerosis is not the only arterial phenotype described in aging brain arteries.¹² Nonatherosclerotic aging phenotypes are usually described as degenerative changes in the arterial wall consisting of elastin loss and fragmentation of the internal elastic lamina (IEL), some of which

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may also overlap with atherosclerosis.^{13,14} Determining whether arterial aging is associated with dementia may expand the perspective on the role that arterial disease plays in this condition.

In this analysis, we tested the hypothesis that brain arterial aging is associated with AD independent of intracranial large artery atherosclerosis and brain infarcts.

METHODS Brain large arteries were selected from the Brain Arterial Remodeling Study, a large collection of brain arteries from 336 patients with and without HIV obtained at 4 different brain collections. For this analysis, 194 participants without HIV were analyzed. The sources of these brains were the Macedonian/New York State Psychiatric Institute Brain Collection (n = 104), the Manhattan HIV Brain Bank (n = 52, none with HIV), the New York Brain Bank/Alzheimer's Disease Research Center at Columbia University (n = 25), and the Brain Endowment Bank at University of Miami (n = 13). Demographics and clinical variables including vascular risk factors were obtained from the medical chart or from structured interviews with the patient's proxies. The methods and sampled populations in each brain collections have been described previously.¹⁵

Brain infarcts were defined at autopsy as a focal cavity within an expected arterial territory. The infarct etiology was inferred by reviewing the medical records and autopsy materials. Twenty-five participants had neuropathologically proven AD and cognitive symptoms suggestive of dementia.¹⁶ Of these, 19 of 25 were Consortium to Establish a Registry for Alzheimer's Disease (CERAD) definite AD while 6 were CERAD probable.¹⁷ Braak stages were all stage IV (n = 1), V (n = 9), or VI (n = 15).¹⁸ The cases without pathologically proven AD did not have exhaustive or systematic staining for ruling it out, as these cases lacked a history of dementia, cognitive problems, or memory loss (either reported by proxies or self-reported), and they lacked evidence of neurofibrillary tangles or amyloid deposition in routine neuropathologic examination.

From each case, the arteries from the circle of Willis and posterior circulation were removed from formalin-fixed brains. The methods used to characterize each brain artery have been described previously.¹⁵ Briefly, 5-mm cross-sectional segments were obtained from each large artery and stained with hematoxylin & eosin, elastic Van Gieson (EVG), Masson trichrome (for collagen), and Congo red (the Bannhold method for amyloid). Each stained slide was digitized with 10× magnification and scale = 0.643 μm/pixel. Using color-based segmentation with ImageJ software (WS Rasband, ImageJ, US NIH, Bethesda, MD, 1997–2011; imagej.nih.gov/ij/), we quantified the total arterial area, the lumen area, as well as the area of each arterial layer. Using standard geometrical formulas, we derived the interadventitial and luminal diameters, the thickness of each arterial layer, the degree of stenosis (the Glagov method), and the proportion of the arterial area encircled by the IEL (i.e., IEL proportion), with a higher IEL proportion suggestive of outward remodeling.¹⁹ By visual assessment, we ascertained IEL gaps, IEL duplication, concentric intima thickening, and the revised American Heart Association classification for atherosclerosis (figure e-1 on the *Neurology*® Web site at Neurology.org).²⁰

To quantify automatically the intensity of staining in EVG, trichrome, and Congo red slides, we used Visiopharm Integrator System version 4.6.3.857 (Hoersholm, Denmark) by color

thresholding. By applying a prespecified mask (for red or blue), we enhanced the differentiation of the target colors to calculate the mean pixel intensity (figure e-2). Because the overall intensity varied slightly by batches of staining, we controlled for the overall background intensity. We considered arteries to have a high intensity staining for elastin (using EVG), collagen (using trichrome), and amyloidosis (using Congo red) if the background-adjusted mean average intensity were in the upper quartile of the respective distribution.

Standard protocol approvals, registrations, and patient consents. Each brain collection was approved by the respective institutional review board and consents were obtained accordingly.

Statistical analysis. The analysis was carried out in 2 stages. In the first stage, each individual artery was analyzed independently. For the first stage of the analysis, we excluded any artery with evidence of atherosclerosis to be able to contrast aging changes not directly related with atherosclerosis. Each arterial characteristic described above was considered the dependent variable and age the independent variable to assess for an association with aging. We used multivariable linear or logistic regressions (as indicated) to obtain the beta estimates for associations and their 95% confidence intervals after adjusting for demographic and clinical variables listed in table e-1. We then ran regression models and cross-tabulations of all the significant variables to assess for collinearity, which we defined arbitrarily as an $R^2 > 0.50$ (for continuous variables) or more than 50% overlap between categorical variables (appendix e-1, tables e-2 and e-3). We chose to keep in the model the variables with a significant association. The arterial characteristics that remained independently associated with aging were used to create the brain arterial aging (BAA) score. If a selected variable was continuous, we categorized it to its upper quartile to harmonize its weight in the final score compared with categorical variables. Consequently, each of the scored arterial characteristics had a value of 1 or 0.

The second analysis stage consisted of assessing the independent association of the BAA score with the presence of AD. For this stage, we used a multilevel generalized linear model to adjust for the codependence among arteries obtained from the same individual. A sensitivity analysis was carried out to evaluate subgroups in which the BAA score may have differentially associated with AD. A *p* value <0.05 was considered statistically significant. The figures were produced with IBM SPSS Statistics 21 (release 21.0.0, IBM 2012) and the statistical analysis was carried out with SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS Sample studied. We studied 194 patients with a mean age of 55 ± 17 years (median 53, interquartile range [IQR] 44–63). Patients with AD had a mean age of 82 ± 10 years compared to 52 ± 14 years in cases without AD. Demographic and clinical characteristics are described in table 1.

Arterial-level results. There were a total of 1,362 large brain arteries for analysis (median 7, IQR 5–10 per case) but we excluded for this stage arteries with evidence of atherosclerosis, defined categorically as pathologic intimal thickening (n = 160), atheroma (n = 149), or fibrocalcific plaques (n = 5), leaving a total of 1,048 arteries for the computation of the BAA

Table 1 Demographic and clinical characteristics of the sample studied

	Total (n = 194)	Alzheimer disease + (n = 25)	Alzheimer disease – (n = 169)	p Value ^a
Age, y, mean ± SD	55 ± 17	82 ± 10	52 ± 14	<0.001
Male sex, %	63	66	44	0.028
Ethnicity, %				0.037
Non-Hispanic white	76	96	73	
Non-Hispanic black	12	0	14	
Hispanic	12	4	14	
Hypertension, %	40	56	36	0.047
Diabetes, %	17	20	16	0.396
Dyslipidemia, %	21	16	52	<0.001
Smoking, %	52	32	55	0.026
History of vascular disease, %	39	33	84	<0.001
Prevalence of brain infarcts, %	17	52	11	<0.001

^a Student test or χ^2 test in univariate analysis.

score (252 with normal intima, 155 with intima xanthoma, and 641 with intima thickening but no evidence of lipid depositions). Arteries with atherosclerosis were assigned a BAA score of zero. Subsequently, we used atherosclerosis as covariate for all subsequent models to be able to assess the independence of nonatherosclerotic arterial aging from the better established atherosclerotic changes noted with age.

As shown in table e-1 and figure 1, aging was associated with progressive luminal dilation, thickening of the wall including the media and intima, but with no changes in lumen-to-wall ratios, suggesting a commensurate increase in the wall thickness to the lumen dilation. Aging was also associated with a higher prevalence of IEL gaps, concentric intima thickening, and more frequent large artery amyloidosis and elastin loss. Five arterial characteristics were independent markers of brain arterial aging: outward remodeling (i.e., upper quartile of IEL proportion, $B = 1.96$, $p = 0.030$), thick media (upper quartile of media thickness, $B = 3.50$, $p = 0.001$), elastin loss (i.e., lower quartile of elastin staining, $B = 6.16$, $p < 0.001$), IEL gaps ($B = 3.14$, $p = 0.023$), and concentric intima thickening ($B = 7.19$, $p < 0.001$). With these 5 binary variables, we computed the BAA score (possible range 0–5), which we used subsequently to define arterial aging (figure e-1).

Patient-level results. In the 194 patients presented here, 46 (24%) had a normal circle of Willis, 37 (19%) had predominantly atherosclerosis (i.e., >50% of their brain arteries had atherosclerosis), 78 (40%) had predominantly aging (i.e., >50% of their brain arteries had a BAA score >0, 42/78 cases

had only of aging without atherosclerosis), and 33 (17%) had an equal number of arteries with atherosclerosis and aging (figures 2 and 3). We did not find evidence that the percentage of arteries with aging varied by the numbers of arteries studied in each case ($p = 0.08$).

The distribution of atherosclerosis and arterial aging in each circle of Willis varied with age. Some of the components of the BAA score started rising in the third decade of life, but the prevalence and the aggregate of the components as reflected in the BAA score rose steadily with age (figure 1).

Brain arterial aging and pathologic outcomes. Using a multilevel model, age remained associated with the BAA score ($B = 0.017$, $p < 0.001$) after adjusting for covariates including atherosclerosis, brain bank source, country of origin, and vascular risk factors. In this same adjusted model, the BAA score was higher in arteries from the posterior circulation (0.52 , $p < 0.001$) but we could not find an association with hypertension, diabetes, or dyslipidemia, after adjusting for age. Among those with hypertension and evidence of elastin loss, however, the BAA score was higher ($p < 0.001$ for the interaction).

The BAA score was associated with AD, independent of age ($B = 0.018 \pm 0.007$, $p = 0.002$, table 2). Adjustment for potential confounders such as demographics, vascular risk factors, brain infarct, atherosclerosis, and large artery amyloidosis did not modify the association between BAA score and AD ($B = 0.022 \pm 0.008$, $p = 0.007$). Atherosclerosis ($B = 0.063 \pm 0.025$, $p = 0.013$), brain infarcts ($B = 2.93 \pm 1.47$, $p = 0.047$), age ($B = 0.138 \pm 0.044$, $p = 0.002$), and large artery

Figure 1 Prevalence of arterial phenotypes by age

(A) Internal elastic lamina (IEL) gaps, (B) outward remodeling, (C) elastin loss, (D) concentric intima thickening, (E) thick media. With aging, brain large arteries undergo disruption of the IEL, increased deposition of amyloid, elastin loss, and outward remodeling with relative preservation of the lumen-to-wall ratio due to a commensurate concentric intima and media thickening. Within the same individuals, the average brain arterial aging score of the circle of Willis also increased with aging (F). CI = confidence interval.

amyloidosis ($B = 0.053 \pm 0.025$, $p = 0.036$) were also independent predictors of AD in this sample. Among the 25 cases with AD, the mean BAA score

in Braak stage V was 1.3 and in Braak stage VI was 1.7, and between moderate vs frequent presence of neuritic plaques was 1.8 vs 2.0.

Figure 2 Relationship between atherosclerosis and aging within each individual

Although arterial characteristics of aging were noted in individuals <40 years, the overall intensity of aging raises with mean age. In the oldest group (i.e., >80 years), there was heterogeneity of arterial characteristics within the same individuals, ranging from exclusively or predominantly atherosclerotic phenotypes to exclusively or predominantly aging phenotypes.

Sensitivity analysis. To evaluate whether the association between BAA score and AD varied by age, sex, or the presence of atherosclerosis or brain infarcts, we carried out subgroup analyses. We found a statistical interaction between the BAA score with age ($p < 0.001$). We then ran model 3 only in those 60 years of age or older (24 AD and 36 non-AD) and found that BAA score remained associated with AD ($B = 0.015 \pm 0.006$, $p = 0.019$) but chronological age was not ($B = 0.021$, $p = 0.08$). We did not find an interaction between the BAA score by sex ($p = 0.16$). Finally, the association between the BAA score and AD persisted even after excluding patients with evidence of brain infarcts ($B = 0.009 \pm 0.004$, $p = 0.04$) or after excluding from the analysis the arteries with atherosclerosis (0.154 ± 0.038 , $p < 0.001$).

DISCUSSION Aging is among the most important nonmodifiable risk factors for stroke and dementia, 2 of the most prevalent and disabling neurologic diseases in the United States and in the world. We present here evidence that with age and even in the absence of atherosclerosis, the brain large arteries undergo degenerative changes characterized by elastin loss and IEL gaps, concentric thickening of the wall, and increasing IEL proportion with a relative preservation of the lumen-to-wall ratio. These changes suggest outward remodeling matched by a

concomitant thickening of the wall and validate the prediction that the larger the vessel radius, the larger the wall tension required to withstand a given internal fluid pressure (LaPlace Law).²¹ Furthermore, patients with AD in our cohort had evidence of greater brain arterial aging independent of their chronological age, brain infarction, and large artery atherosclerosis compared with non-AD cases. We interpret this cross-sectional association as evidence that brain arterial aging may play a role in the pathophysiology of dementia, which will require further attention and study.

The main physiologic stimulus for brain arterial aging is chronic and perhaps physiologic wall shear stress due to the wear and tear of blood flow over the years. This is based on the data presented here as well as evidence from other laboratories. For example, in animal models of surgical fistulas, increasing blood flow is accompanied by IEL gaps, endothelial thickening, and enlargement of the vessel, presumably to re-establish a predetermined level of tolerated wall shear stress.^{22–24} Although elastin fibers increase upon exposure to high shear stress, outward remodeling is mostly mediated in vitro by metalloproteinase cleavage of elastin, thus rendering the wall more susceptible to dilation and hypertension.^{25,26} In humans, the presence of IEL disruption has been considered evidence of too much wear.²⁷ Furthermore, because of a linear relationship between arterial diameter and flow, evidence of aging is noted earlier in more proximal (and larger) arteries in the circle of Willis.¹⁴ These reports collectively support the hypothesis that the mechanical forces of blood flow are the most likely driver of arterial aging.

Assuming blood flow is the most likely explanation for the observed arterial changes, it is worth contextualizing this hypothesis with the noted association with AD. It is unlikely that AD causes arterial aging given that a degenerating brain parenchyma would need less and not more blood supply. The 2 most likely hypotheses for the association are first, that aging occurs simultaneously in the brain arteries and parenchyma, for example due to a shared susceptibility for aging or shared exposure to environmental triggers; or second, that arterial aging contributes in some way to AD pathology.

The concurrent aging hypothesis is supported by evidence that polymorphisms in the *APOE4*, *CRI*, *BINI*, and *PICALM* genes contribute both to an earlier time of onset of AD and to the development of coronary artery disease.^{28–30} Evidence supporting accelerated arterial aging associated with these genes or their respective proteins, however, is not yet available. *APOE* and *CR1* polymorphisms are noted to affect the rate of amyloid deposition in the brain and in the capillaries, and given that we noted an

Figure 3 Examples of phenotypic expression of aging and atherosclerosis

With aging, the brain large arteries show heterogeneous pathologic changes that vary from normal or near normal (case 1), predominantly atherosclerotic aging (case 2), predominantly nonatherosclerotic aging (case 3), or mixed aging (case 4). Among 57 patients >60 years old, 12 had evidence of brain arterial aging alone in their circle of Willis, 3 had evidence of atherosclerosis only, 38 had mixed aging and atherosclerotic phenotype (21 had predominantly atherosclerosis and 17 had predominantly aging), and 4 had normal or near-normal arteries in the circle of Willis. ACAD = anterior cerebral artery distal A1 segment; ACAP = anterior cerebral artery proximal A1 segment; BAD = distal basilar artery; BAP = proximal basilar artery; ICAD = distal internal carotid artery; ICAP = proximal internal carotid artery (supraclinoid); MCA2 = middle cerebral artery proximal M2 segment; MCAD = middle cerebral artery distal M1 segment; MCAP = middle cerebral artery proximal M1 segment; PCAD = posterior cerebral artery distal P1 segment; PCAP = posterior cerebral artery proximal P1 segment; VAD = vertebral artery distal V4 segment; VAP = vertebral artery proximal V4 segment.

Table 2 Relationship between the brain arterial aging (BAA) score and Alzheimer disease

	Model 1 (B ± SE); p Value	Model 2 (B ± SE); p Value	Model 3 (B ± SE); p Value
BAA score (per point)	0.025 ± 0.008; 0.002	0.082 ± 0.031; 0.008	0.024 ± 0.008; 0.002
Age (per year)	0.128 ± 0.040; 0.002	0.155 ± 0.056; 0.006	0.138 ± 0.044; 0.001
Atherosclerosis (yes/no)	—	—	0.047 ± 0.018; 0.009
Brain infarcts (yes/no)	—	—	2.93 ± 1.47; 0.047
Large artery amyloidosis (yes/no)	—	—	0.059 ± 0.025; 0.021

Model 1: Adjusted for number of arteries per case, artery type (anterior cerebral artery, internal carotid artery, middle cerebral artery), location of the arterial cut (proximal vs distal), anterior vs posterior circulation, and country of origin for each specimen. Model 2: Model 1 plus sex, ethnicity, and vascular risk factors (hypertension, diabetes, dyslipidemia, and smoking). Model 3: Model 2 plus atherosclerosis, brain infarcts, and large artery amyloidosis.

association between large artery amyloidosis with age and with AD, it is possible that older individuals with a high BAA score may have some of these genetic variants.^{31,32} Among younger individuals with AD, their lifetime risk of intracranial hemorrhage is increased, suggesting perhaps underlying amyloidosis linking both processes.⁷

An alternative hypothesis is that brain arterial aging increases the susceptibility of the brain parenchyma to aging and AD pathology. For example, dilated brain arteries may represent low impedance to flow. In this context, dilated arteries may render the brain more susceptible to pulse-wave velocities and pulse pressure, both representing increased stiffness.³³ Indirect and direct measures of aortic stiffness have been associated with poorer cognitive performance, with parenchymal biomarkers of vascular disease, and with increased rate of amyloid deposition in the brain.^{21,34,35} These hypotheses are not necessarily mutually exclusive. Further understanding of the interplay among systemic hemodynamics, arterial biology (systemic and cerebral), and brain health may lead to new approaches to modify cerebral outcomes.

The interplay between atherosclerosis and aging needs to be highlighted. As evidenced in the Results, the majority of aged individuals have mixed phenotypic expression of aging and atherosclerosis. At first, it may appear counterintuitive that atherosclerosis, a pathology characterized by inward remodeling and luminal narrowing, may coexist in the same circle of Willis with brain arterial aging, reported as dilative changes with no changes in lumen-to-wall ratios. Reports on a dilatory phenomenon in studies using brain magnetic resonance angiography have noted compensatory dilation in the setting of small arterial diameters in the circle of Willis. For example, there is compensatory dilation in the anterior cerebral arteries when the contralateral anterior cerebral artery is small or absent, in the basilar artery when there is poor anteroposterior collaterals through the posterior communicating arteries, or in the intracranial arteries in the setting of extracranial carotid

atherosclerosis.^{36,37} Based on this, in the setting of intracranial atherosclerosis, compensatory blood flow increments may cause accelerated aging in these collaterals. We did not record collateral status in any of these cases, thus precluding the formal testing of this hypothesis. The radiographic evidence cited before, however, supports this hypothesis. An alternative hypothesis would be that vascular risk factors are differentially associated with atherosclerosis or with certain vascular beds or with certain individuals.

The strengths of this study include the careful histopathologic description of brain large arteries and the availability of a large sample with well-characterized neuropathologic outcomes. The associations between the proposed BAA score as a measure of arterial aging with AD are novel. Because of the relatively high prevalence of vascular risk factors, the lack of data on the intensity of these vascular risks, and the young age of the AD-negative cases, the association between the BAA score and AD needs to be replicated in other cohorts. There are also limitations of our study. For example, each brain collection may have a differential emphasis in the diagnosis of brain infarcts or AD in autopsy and lead to underdiagnosis. If present, it would bias the result towards the null rather than towards the alternative hypothesis. The methods used to determine elastin, collagen, and amyloid contents are rudimentary compared with novel quantitative approaches. By automating the quantification of pixel intensity, we can at least assure reproducibility. Finally, these cases are not necessarily representative of the population and we do not imply generalizability. But given the inability to measure brain arterial aging in living individuals, we consider this to be an important step in the search for serologic, genetic, or radiographic biomarkers of brain arterial aging that can be used to identify individuals at a higher risk of stroke and dementia.

AUTHOR CONTRIBUTIONS

Jose Gutierrez: design and conception of the work, acquisition, analysis, and interpretation of the data, drafting the manuscript, final approval of the manuscript. Lawrence Honig: acquisition and interpretation of the

data, revising the manuscript for intellectual content. Mitchell S.V. Elkind: interpretation of the data, revising the manuscript for intellectual content. Jay P. Mohr: interpretation of the data, revising the manuscript for intellectual content. James Goldman: interpretation of the data, revising the manuscript for intellectual content. Andrew J. Dwork: acquisition and interpretation of the data, revising the manuscript for intellectual content. Susan Morgello: conception of the work, acquisition and interpretation of the data, revising the manuscript for intellectual content. Randolph S. Marshall: conception of the work, interpretation of the data, revising the manuscript for intellectual content.

ACKNOWLEDGMENT

The authors thank the staff at the Herbert Irving Cancer Center Molecular Pathology Laboratory at Columbia University and the Histology Shared Resource Facility of the Icahn School of Medicine at Mount Sinai for facilitating this work.

STUDY FUNDING

AHA 13CRP14800040 (PI Jose Gutierrez), NIH R01MH64168 (PI Andrew Dwork), NIH R25MH080663 and U24MH100931 (PI Susan Morgello), NIH P50AG08702 (PI Scott Small), NIH N271201300028C (Deborah Mash).

DISCLOSURE

J. Gutierrez and L. Honig report no disclosures relevant to the manuscript. M. Elkind receives compensation for providing consultative services for Biogen IDEC, Biotelemetry/Cardionet, BMS-Pfizer Partnership, Boehringer-Ingelheim, Daiichi-Sankyo, and Janssen Pharmaceuticals; receives research support from diaDexus, Inc., and NIH/NINDS; has given expert legal opinions on behalf of Merck/Organon (NuvaRing and stroke litigation); and serves on the National, Founders Affiliate, and New York City chapter boards of the American Heart Association/American Stroke Association. He receives royalties from UpToDate for chapters related to stroke. J. Mohr, J. Goldman, A. Dwork, S. Morgello, and R. Marshall report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received July 31, 2015. Accepted in final form January 8, 2016.

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