Association of Chronic Kidney Disease With Cerebral Microbleeds in Patients With Primary Intracerebral Hemorrhage

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Background and Purpose—To investigate the relationship between chronic kidney disease (CKD) and MRI-defined cerebral microbleeds (CMB), a harbinger of future intracerebral hemorrhage (ICH), among patients with a recent history of primary ICH.

Methods—Using data from a predominantly black cohort of patients with a recent ICH-enrolled in an observational study between September 2007 and June 2011, we evaluated the association between CKD (defined as estimated low glomerular filtration rate<60 mL/min per 1.73 m²) and CMB on gradient-echo MRI. Multivariable models were generated to determine the contribution of CKD to the presence, number, and location of CMB.

Results—Of 197 subjects with imaging data, mean age was 59 years, 48% were women, 73% were black, 114 (58%) had ≥1 CMBs, and 52 (26%) had CKD. Overall, CKD was associated with presence of CMB (adjusted odds ratio, 2.70; 95% confidence interval [CI], 1.10–6.59) and number of CMB (adjusted relative risk, 2.04; 95% CI, 1.27–3.27). CKD was associated with CMB presence (adjusted odds ratio, 3.44; 95% CI, 1.64–7.24) and number (adjusted relative risk, 2.46; 95% CI, 1.11–5.42) in black patients, but not CMB presence (adjusted odds ratio, 3.00; 95% CI, 0.61–14.86) or number (adjusted relative risk, 1.03; 95% CI: 0.22–4.89) in non-Hispanic white patients (interactions by race were statistically not significant).

Conclusions—CKD is associated with a greater presence and number of CMB in ICH patients, particularly in patients of black race. Future studies should assess whether low estimated glomerular filtration rate may be a CMB risk marker or potential therapeutic target for mitigating the development of CMB. (Stroke. 2013;44:2409-2413.)

Key Words: antihypertensive therapy ■ black ■ cerebral hemorrhage ■ cerebral microbleeds ■ hemorrhagic stroke ■ MRI ■ prevalence ■ renal ■ renal insufficiency, chronic ■ renin-angiotensin ■ stroke

Several lines of evidence link chronic kidney disease (CKD) to higher risk of primary stroke. The overwhelming majority of these studies focus on the relationship of CKD with ischemic stroke risk.1,2 However, the few studies that have specifically examined the association of baseline CKD with incident stroke by type suggest that the relationship of CKD with stroke is stronger with primary intracerebral hemorrhage (ICH) than ischemic stroke.3,4 Of the many mechanisms underlying cerebrovascular disease, small vessel microangiopathy would presumably be the type with the strongest association with CKD, because the primary underlying pathology for both disease entities is thought to be the induction of endothelial permeability because of high volume blood flow to these low-resistance-end arterial organs (brain and kidney).5 Indeed, among patients without symptomatic cerebrovascular disease and those with ischemic stroke, CKD has been linked to a higher prevalence of microangiopathy on MRI, including white matter hypertensities, white matter volume, lacunar infarcts, and cerebral microbleeds.5–9

Cerebral microbleeds (CMB) are discrete or isolated punctate hypointense lesions, typically <5 to 10 mm in size, evident on gradient-recalled echo (GRE) T2*-weighted MRI.10 Pathological studies of CMB have shown focal deposition of hemosiderin in the perivascular space associated with abnormal small blood vessels affected by lipofibrohyalinosis (most commonly involving deep structures and associated...
with hypertension) or amyloid angiopathy (typically lobar locations). \textsuperscript{11,12} CMB are generally considered to be clinically silent, but are a harbinger for future ICH, \textsuperscript{13,14} and may develop quite rapidly after an index cerebrovascular event. \textsuperscript{15} Similar to primary ICH, \textsuperscript{16} there seems to be a greater frequency of CMB in blacks compared with whites, \textsuperscript{17} underscoring the potential role that CMB could play in providing insights into ICH pathophysiology, prognosis, disease progression, and therapeutic strategies. \textsuperscript{12}

As far as we are aware, no study has examined the link between CKD and CMB among patients with ICH, nor looked at the potential influence of race on this relationship. The objective of this study was to investigate the association of CKD with CMB among ICH patients, and how race may influence this link.

**Methods**

**Cohort**

We retrospectively reviewed data collected in an ongoing, prospective, longitudinal MRI study of racial differences in primary ICH (DiffErenCes in the Imaging of Primary Hemorrhage based on Ethnicity or Race [DECIPHER]). Since 2007, successive patients have been recruited from the inpatient services of 5 hospitals in the Washington, DC, metropolitan area. DECIPHER inclusion criteria are: age ≥18 years, diagnosis of primary ICH (not limited to first ICH), and brain MRI within 1 month of symptom onset. Exclusion criteria are: contraindication to MRI, pregnancy, central nervous system tumor/active inflammatory process, central nervous system arteriovenous malformation/aneurysm, central nervous system trauma within prior 2 weeks, cranietomy, or international normalized ratio >3. Baseline demographic information, medical history, medications, neurological assessments, and laboratory data are collected on all patients. As part of the DECIPHER protocol, MRIs and outcome assessments are performed at admission (baseline), 1 month, 1 year, and 3 years. Baseline MRIs are acquired on either 1.5T or 3.0T magnetic resonance (MR) scanners. All follow-up MR scans are preferentially acquired on a 3.0T scanner.

A standardized protocol is used for all the follow-up time points that include diffusion-weighted imaging with apparent diffusion coefficient maps, fluid attenuated inversion recovery, and GRE sequences. For the baseline time point, we used a conventional GRE sequence if available. If no conventional GRE was available, we used a susceptibility-weighted sequence. T2*-weighted sequence parameters were: repetition time, 46 to 825 ms; echo time, 12 to 30.5 ms; flip angle, 20 to 40 degrees; and slice thickness, 3.5 to 7 mm. Susceptibility-weighted imaging parameters were: repetition time, 28 to 50 ms; echo time, 20 to 40 ms; flip angle, 15 degrees; and slice thickness, 1.5 to 2 mm.

**Imaging Analyses**

The current analysis is limited to baseline MRI assessments for which 3 investigators (R.E.B., R.S.M., C.S.K.) performed the imaging evaluations. An initial series of 15 cases were analyzed as consensus reads to establish inter-rater reliability. All imaging analyses were performed using Mango (Multi-Image Analysis GUI, http://tic.uthscsa.edu/mango/). GRE sequences were evaluated for the following: hematoma volume (using a semiautomated segmentation tool) and location; number and location of microbleeds and chronic hematomas; and presence of intraventricular hemorrhage. CMB were defined as punctate, homogeneous, rounded, hypointense lesions <5 to 10 mm on GRE sequences within the brain parenchyma. \textsuperscript{12} Hypointense lesions in the subarachnoid space were considered likely to represents adjacent pial blood vessels, and therefore, were not included. Hypointensities within close proximity to the primary hemorrhage were conservatively not counted as microbleeds because of concern that these may represent acute satellite foci of blood related to the index event. Symmetrical hypointensities in the globi pallidi (likely to represent calcification or iron deposition) and flow voids from cortical vessels were disregarded. \textsuperscript{15} White matter disease was rated using the Fazekas scale and creating a summary score per patient (ranging from 0–12) including right and left deep white matter and periventricular white matter disease.

**Variables**

Baseline demographic and clinical covariates to be examined were preselected on the basis of prior studies of factors that influence the occurrence of CMB, recurrent stroke, and CKD. \textsuperscript{16–27} Estimated glomerular filtration rate (eGFR) per the Modification of Diet in Renal Disease Study Group equation was calculated for each eligible patient. \textsuperscript{23} CKD was defined as eGFR<60 mL/min per 1.73 m². eGFR was measured using the first available laboratory tests drawn after admission for the index ICH. DECIPHER subjects without CKD (controls) were the referent group for purposes of comparison. Renin–angiotensin system (RAS) modulator treatment was defined as anyone on angiotensin-converting enzyme inhibitor or angiotensin receptor blocker–based therapy before admission for their index ICH. Patients with ≥1 deep microbleeds were counted as having deep microbleeds regardless of whether they had lobar microbleeds. Adjustments for baseline characteristics were made by forcing the following prespecified covariates into the stepwise model: age, sex, average seated blood pressure (BP), history of hypertension, white matter disease, and selecting other covariates with a P value ≤0.10.

**Standard Protocol Approvals, Registrations, and Patient Consents**

The DECIPHER study is being performed with approval of the institutional review boards of the admitting hospitals and Georgetown University, which serves as the institutional review board of record.

**Statistical Analyses**

Differences in dichotomous variables were analyzed using χ² analysis or the Fisher exact test. Student t test or the Wilcoxon rank-sum test was used to analyze differences in the mean or median of continuous variables between groups. Multivariable models were generated to determine the contribution of CKD to the presence, number, and location of CMB after adjusting for confounders (age, sex, systolic BP, antihypertensive drug use, non-RAS drug use, and diabetes mellitus). Variables that indicated a univariate relationship with CKD (P<0.1) and were not strongly correlated with each other were considered for multivariate logistic or Poisson modeling. Tests for 2-way interactions involving presence of CKD were performed for prespecified baseline features including age, race, and RAS modulator treatment. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

**Results**

During the study period, 197 patients were enrolled. None were excluded. Among those with complete data, mean age was 59 years, 48% were women, 73% were black, 114 (58%) had ≥1 CMBS, and 52 (26%) had CKD. On imaging, mean hematoma volume on baseline MRI was 22.6 mL (median, 13.8 mL; range, 0.4–147.1 mL), and 47% of hematomas originated in deep structures. The underlying mechanism of the hemorrhage was determined to be hypertension in 62% of patients, cerebral amyloid angiopathy in 3%, >1 contributing cause in 31%, and unknown (no risk factors) in 4%. The Figure provides an example of a patient with multiple baseline CMB lesions.

Baseline demographic and clinical characteristics between those with CKD versus those without are shown in Table 1. Several of these characteristics were comparable, but patients with CKD were significantly more likely to have a baseline
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The results of this study are in accordance with studies associating proteinuria with CMB among patients with ischemic stroke,\(^7\) and low eGFR with CMB among predialysis patients with no known stroke,\(^7\) thereby reinforcing the notion of a link between renal dysfunction and this promising imaging biomarker of ICH.\(^29\) However, because CMB is present in up to 80% of primary ICH patients,\(^13\) and can be especially predictive of future ICH risk, observing a relationship between CKD and CMB among primary ICH patients who carry a risk of recurrent ICH as high as 3% per year,\(^30\) could be a key affirmation of CKD as a prognosticator or potential therapeutic target in patients at risk for developing CMB/ICH.

It is important to note that CKD was not just associated with presence of CMB, but also number of CMB, suggesting a dose-dependent relationship between these entities, of which a potential causal association could be inferred, but certainly not established given the cross-sectional nature of this study. Furthermore, we observed that primary ICH patients with CKD were more likely to have a baseline history of hypertension, higher systolic BP levels, CMB in deep locations, and a more frequent pattern of deep location of the index ICH, possibly pointing to a contribution by CKD to, or shared pathophysiology with hypertensive ICH rather than ICH attributable to cerebral amyloid angiopathy.

Explanations that have been proposed for the link between CKD and vascular disease include the observation that a decline in kidney function often happens in tandem with prevalence of nontraditional vascular risk factors, such as anemia, oxidative stress, and chronic inflammation, and therefore, may enhance the adverse effects of these risk factors,\(^31\) as well as a theory that an initial insult to the renal endothelium may activate the RAS (ie, angiotensin II acting on the angiotensin II type 1 receptor) leading to stimulation of nicotinamide adenine dinucleotide phosphate oxidase, up-regulation of inflammatory mediators (cytokines, chemokines, adhesion molecules, etc) and superoxide scavenging of nitric oxide,\(^32–34\) resulting in generalized endothelial dysfunction and systemic vascular remodeling.\(^35\) Interestingly, drugs like RAS modulators that limit CKD progression\(^4\) have also been related to greater vascular risk reduction benefit among cardiac disease patients with CKD, independent of their BP reducing effects,\(^3–11\) and in a systematic review comprising mostly ischemic stroke patients were associated with very modest overall vascular risk protection.\(^36\)

This study has several limitations. First, the DECIPHER cohort is likely composed of patients with milder/smaller hemorrhages because patients with more severe hemorrhages may have been too unstable for MRI. Second, despite conducting a multivariable analysis, we cannot exclude the possibility that unmeasured confounding variables may explain some of our findings. Third, there was some slight variability in baseline imaging parameters to the extent that although the overwhelming majority was conventional GRE images, a few were susceptibility weighted images. Finally, given the cross-sectional design of the study, we were unable to distinguish whether CMBs simultaneously occurred with ICH (and thus, were part of that index event) or whether they occurred earlier because of the underlying ongoing pathology. Future prospectively collected data will be needed to make this distinction.

Discussion

This analysis of prospectively collected data on consecutive recent ICH patients in a cohort study showed that baseline CKD was significantly associated with presence and number of overall CMB, as well as presence of CMB in deep locations (Table 2). After adjusting for additional confounders, presence of CKD was still associated with presence and number of overall CMB, whereas the relation of CKD to presence of deep CMB became no longer significant (Table 2). CKD was associated with CMB presence (adjusted odds ratio 3.44; 95% confidence interval, 1.64–7.24) and number (adjusted relative risk, 2.46; 95% confidence interval, 1.11–5.42) in black patients, but not CMB presence (adjusted odds ratio, 3.00; 95% confidence interval, 0.61–14.86) or number (adjusted relative risk, 1.03; 95% confidence interval, 0.22–4.89) in non-Hispanic whites (interactions by race: \(P=0.97\) for presence of CMB and 0.35 for number of CMB).

Figure. Representative axial slice from gradient-recalled echo/T2* MRI sequence from a 65-year-old black patient with a recent presumed hypertensive thalamic hemorrhage and low estimated glomerular filtration rate, with several microbleeds.

history of hypertension, history of diabetes mellitus, to be on antihypertensive drugs, or to be on RAS modulators. Patients with CKD were also more likely to have higher serum creatinine, systolic BP, CMB, and number of CMB, as well as a deep location of CMB. Patients with CKD versus no CKD showed a lower statistical trend in median size of the index ICH.

In multivariable analyses adjusting for only age and sex, the presence of CKD was significantly associated with presence and number of overall CMB, as well as presence of CMB in deep locations (Table 2). After adjusting for additional confounders, presence of CKD was still associated with presence and number of overall CMB, whereas the relation of CKD to presence of deep CMB became no longer significant (Table 2). CKD was associated with CMB presence (adjusted odds ratio 3.44; 95% confidence interval, 1.64–7.24) and number (adjusted relative risk, 2.46; 95% confidence interval, 1.11–5.42) in black patients, but not CMB presence (adjusted odds ratio, 3.00; 95% confidence interval, 0.61–14.86) or number (adjusted relative risk, 1.03; 95% confidence interval, 0.22–4.89) in non-Hispanic whites (interactions by race: \(P=0.97\) for presence of CMB and 0.35 for number of CMB).
ICH is associated with substantial morbidity and mortality, necessitating a better understanding of its underlying complex pathophysiology, as well as its black race predilection. We found that baseline CKD on the basis of easily obtainable serum creatinine–based eGFR formula is significantly related to higher presence and number of CMB, especially among black primary ICH patients. As such, low eGFR may be a CMB risk marker or potential therapeutic target for mitigating the development of CMB and therefore ICH. Further investigation is warranted.

**Table 1. Baseline Characteristics of DECIPHER Study Participants by Presence of CKD (n=197)**

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Description</th>
<th>Chronic Kidney Disease* (n=52)</th>
<th>No Chronic Kidney Disease (n=145)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Mean (SD)</td>
<td>59.2 (13.8)</td>
<td>58.9 (12.5)</td>
<td>0.905</td>
</tr>
<tr>
<td>Sex</td>
<td>Women</td>
<td>24 (46.1%)</td>
<td>70 (48.3%)</td>
<td>0.793</td>
</tr>
<tr>
<td>Race</td>
<td>Black</td>
<td>40 (76.9%)</td>
<td>103 (71.0%)</td>
<td>0.414</td>
</tr>
<tr>
<td>Current smoker</td>
<td>Yes</td>
<td>13 (25.0%)</td>
<td>34 (23.5%)</td>
<td>0.822</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>Yes</td>
<td>14 (28.0%)</td>
<td>34 (24.3%)</td>
<td>0.604</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>Yes</td>
<td>52 (100%)</td>
<td>114 (78.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>Yes</td>
<td>19 (36.5%)</td>
<td>30 (20.8%)</td>
<td>0.025</td>
</tr>
<tr>
<td>Any antplatelet use</td>
<td>Yes</td>
<td>12 (23.5%)</td>
<td>33 (23.2%)</td>
<td>0.967</td>
</tr>
<tr>
<td>Any anticoagulant use</td>
<td>Yes</td>
<td>3 (5.9%)</td>
<td>10 (7.0%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Any statin use</td>
<td>Yes</td>
<td>14 (27.5%)</td>
<td>30 (21.1%)</td>
<td>0.356</td>
</tr>
<tr>
<td>Any antihypertensive use</td>
<td>Yes</td>
<td>39 (76.5%)</td>
<td>74 (52.1%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Any RAS modulator use</td>
<td>Yes</td>
<td>23 (45.1%)</td>
<td>39 (27.5%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Any antithrombotic use</td>
<td>Yes</td>
<td>14 (27.5%)</td>
<td>39 (27.5%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Admission systolic BP (mm Hg)</td>
<td>Median (IQR)</td>
<td>187.8 (39.1)</td>
<td>175.4 (31.8)</td>
<td>0.024</td>
</tr>
<tr>
<td>Admission serum creatinine (mg/dL)</td>
<td>Median (IQR)</td>
<td>2.0 (1.5, 3.0)</td>
<td>0.9 (0.8, 1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission white matter grade</td>
<td>Median (IQR)</td>
<td>6.0 (6.0, 10.0)</td>
<td>6.0 (4.0, 8.0)</td>
<td>0.012</td>
</tr>
<tr>
<td>MRI microbleeds</td>
<td>Yes</td>
<td>40 (76.9%)</td>
<td>74 (51.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of MRI microbleeds</td>
<td>Median (IQR)</td>
<td>3.5 (1.0, 14.5)</td>
<td>1.0 (0, 6.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Deep location of index ICH</td>
<td>Yes</td>
<td>41 (78.9%)</td>
<td>101 (69.7%)</td>
<td>0.205</td>
</tr>
<tr>
<td>Size of index ICH</td>
<td>Median (IQR)</td>
<td>7.7 (3.0, 33.0)</td>
<td>14.5 (5.9, 31.0)</td>
<td>0.084</td>
</tr>
<tr>
<td>Deep microbleeds</td>
<td>Yes</td>
<td>33 (63.5%)</td>
<td>59 (40.7%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Number of MRI deep microbleeds</td>
<td>Median (IQR)</td>
<td>2 (0, 3.5)</td>
<td>0 (0, 2)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; CKD, chronic kidney disease; DECIPHER, DifferEnCes in the Imaging of Primary Hemorrhage Based on Ethnicity or Race study; eGFR, estimated glomerular filtration rate; ICH, intracerebral hemorrhage; IQR, interquartile range; and RAS, renin–angiotensin system.

*CKD defined as eGFR<60 mL/min per 1.73 m².

**Table 2. Association of CKD With Outcomes in DECIPHER Subjects**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Disease Category</th>
<th>Adjusted OR (1) or RR</th>
<th>Adjusted 95% CI (1)</th>
<th>P Value</th>
<th>Adjusted OR (2)</th>
<th>Adjusted 95% CI (2)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of CMB</td>
<td>No CKD*</td>
<td>Reference</td>
<td>—</td>
<td>0.001</td>
<td>—</td>
<td>—</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td>CKD</td>
<td>3.30</td>
<td>1.59–6.86</td>
<td>2.70</td>
<td>1.0–6.59</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Number of CMB</td>
<td>No CKD</td>
<td>Reference</td>
<td>Reference</td>
<td>0.06</td>
<td>—</td>
<td>—</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>CKD</td>
<td>2.00</td>
<td>1.23–3.28</td>
<td>2.04</td>
<td>1.2–3.27</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Deep location of CMB</td>
<td>No CKD</td>
<td>Reference</td>
<td>—</td>
<td>0.005</td>
<td>—</td>
<td>—</td>
<td>0.188</td>
</tr>
<tr>
<td></td>
<td>CKD</td>
<td>2.57</td>
<td>1.34–4.97</td>
<td>1.72</td>
<td>0.77–3.86</td>
<td>0.057</td>
<td></td>
</tr>
<tr>
<td>Number of Deep CMB</td>
<td>No CKD</td>
<td>Reference</td>
<td>—</td>
<td>0.480</td>
<td>—</td>
<td>—</td>
<td>0.578</td>
</tr>
<tr>
<td></td>
<td>CKD</td>
<td>1.21</td>
<td>0.72–2.04</td>
<td>0.87</td>
<td>0.54–1.41</td>
<td>0.353</td>
<td></td>
</tr>
<tr>
<td>Deep location of ICH</td>
<td>No CKD</td>
<td>Reference</td>
<td>—</td>
<td>0.130</td>
<td>—</td>
<td>—</td>
<td>0.62–3.83</td>
</tr>
<tr>
<td></td>
<td>CKD</td>
<td>1.90</td>
<td>0.83–4.36</td>
<td>1.54</td>
<td>0.62–3.83</td>
<td>0.003</td>
<td></td>
</tr>
</tbody>
</table>

*CKD defined as eGFR<60 mL/min per 1.73 m².

Adjusted (1): adjusted for age and sex. Adjusted (2): adjusted for age, sex, systolic BP, white matter disease, antihypertensive drug use, and diabetes mellitus. P<0.05. BP indicates blood pressure; CI, confidence interval; CKD, chronic kidney disease; CMB, cerebral microbleeds; DECIPHER, DifferEnCes in the Imaging of Primary Hemorrhage Based on Ethnicity or Race study; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ICH, intracerebral hemorrhage; OR, odds ratio; and RR, relative risk.
Acknowledgments
All authors were involved in the final decision to submit the article. Study concept and design: B. Ovbiagele and C.S. Kidwell; acquisition of data: Dr Edwards, R.S. Menon, Dr Burgess, A. Jayam-Trouth, L. German, I. Sobotka, and C.S. Kidwell; analysis and interpretation of data: B. Ovbiagele, J.J. Wing, R.S. Menon, Dr Burgess, M.C. Gibbons, A. Jayam-Trouth, S. Fernandez, Dr Shara, and C.S. Kidwell; drafting of the article: B. Ovbiagele; critical revision of the article for important intellectual content: B. Ovbiagele, J.J. Wing, R.S. Menon, Dr Burgess, M.C. Gibbons, A. Jayam-Trouth, Dr Edwards, and C.S. Kidwell; and statistical analysis: J.J. Wing.

Sources of Funding
This work was supported by award number, U54NS057405, from the National Institute of Neurological Disorders and Stroke and National Institute on Minority Health and Health Disparities; and U01 NS079179 from the National Institute of Neurological Disorders and Stroke.

Disclosures
None.

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Stroke. 2013;44:2409-2413; originally published online July 11, 2013; doi: 10.1161/STROKEAHA.113.001958

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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