Ischemic Thresholds for Gray and White Matter
A Diffusion and Perfusion Magnetic Resonance Study

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Background and Purpose—Although gray matter (GM) and white matter (WM) have differing neurochemical responses to ischemia in animal models, it is unclear whether this translates into differing thresholds for infarction. We studied this issue in ischemic stroke patients using magnetic resonance (MR) techniques.

Methods—MR studies were performed in patients with acute hemispheric ischemic stroke occurring within 24 hours and at 3 months. Cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and apparent diffusion coefficient (ADC) were calculated. After segmentation based on a probabilistic map of GM and WM, tissue-specific diffusion and perfusion thresholds for infarction were established.

Results—Twenty-one patients were studied. Infarction thresholds for CBF were significantly higher in GM (median 34.6 mL/100 g per minute; interquartile range 26.0 to 38.8) than in WM (20.8 mL/100 g per minute; interquartile range 18.0 to 25.9; P<0.0001). Thresholds were also significantly higher in GM than WM for CBV (GM: 1.67 mL/100 g; interquartile range 1.39 to 2.17; WM: 1.19 mL/100 g; interquartile range 0.94 to 1.53; P<0.0001), ADC (GM: 918×10⁻⁶ mm²/s; 686 to 975×10⁻⁶; WM: 805×10⁻⁶; 747 to 870×10⁻⁶; P<0.001), and there was a trend toward a shorter MTT in GM (GM 4.94 s, 4.44 to 5.38; WM 5.15, 4.11 to 5.68; P=0.11).

Conclusions—GM has a higher infarction threshold for CBF, CBV, and ADC than WM in patients within 24 hours of ischemic stroke onset. Hence, when assessing patients for potential therapies, tissue-specific rather than whole-brain thresholds may be a more precise measure of predicting the likelihood of infarction. (Stroke. 2006;37:1211-1216.)

Key Words: magnetic resonance imaging, diffusion-weighted ■ magnetic resonance imaging, perfusion-weighted ■ stroke, acute ■ penumbra ■ white matter
Improvement within 24 hours of stroke onset to establish a model in which it was more likely that a significant proportion of the tissue at risk would infarct.

Methods

Subjects
The study subjects were recruited from the patients admitted to our stroke unit. Inclusion criteria were: (1) first-ever acute hemispheric ischemic stroke; (2) >18 years of age; (3) ability to have DWI/PWI within 24 hours of symptom onset; and (3) all imaging of good quality with minimal motion artifact. Exclusion criteria were: (1) early clinical improvement diagnosed by a >4-point decrease on the National Institutes of Health Stroke Scale (NIHSS) score within 24 hours of onset; (2) thrombolytic therapy; (3) enrollment in neuroprotective trials; (4) follow-up magnetic resonance (MR) or computed tomography (CT) imaging unable to be acquired; (5) no diffusion–perfusion mismatch region visible on acute MRI; (6) lack of >1 mL of diffusion–perfusion mismatch region progressing to infarction in both GM and WM; (7) pregnancy; (8) a medically unstable condition; and (9) patients with a contraindication to MRI scanning. Cranial CT was performed in all patients to exclude cerebral hemorrhage before MRI study. The local ethics committee approved the study, and informed consent was obtained from all patients or their next of kin.

Imaging Protocol
Initial MRI was acquired within 24 hours of stroke onset followed by T2-weighted imaging at 3 months. MRI studies were performed on a 1.5-T whole body scanner (Signa Horizon Echospeed; General Electric). Acute imaging included T1-weighted sagittal localization, T2-weighted fast spin-echo sequence (slice thickness 5 mm, interslice gap 1.7 mm, repetition time [TR]/echo time [TE] 3500/100 ms, field of view 24×24 cm, matrix 256×256), diffusion-weighted single-shot echo planar sequence (slice thickness 5 mm, interslice gap 1.7 mm, TR/TE 10 000/100 ms, field of view 40×20 cm, matrix 256×128, b value 0 and 1000 s/mm²), and perfusion-weighted echo planar sequence (gradient echo, slice thickness 6 mm, interslice gap 1.0 mm, TE 60 ms, field of view 40×20 cm, matrix 256×128). For the perfusion study, the contrast agent (Gd-DTPA; 0.2 mmol/kg) was injected with a power injector followed by 15 mL saline. The total imaging time was ~25 minutes. For the patients who could not undergo follow-up MRI 3 months after stroke onset, a CT scan was performed 7 to 10 days after onset and used in the analysis.

Image Processing
Apparent diffusion coefficient (ADC) values were calculated from b0 and b1000 images using the following formula: ADC = −ln(Sb1000/Sb0)/(b1000−b0), where S denotes DWI signal intensities. To avoid cerebrospinal fluid (CSF) contamination, voxels with ADC values >1500×10⁻⁶ mm²/s were removed from the ADC map. Postprocessing of perfusion raw images was performed using a commercially available software of Stroketool (DIS). Semiquantitative perfusion indices including CBF, CBV, and MTT were calculated with deconvolution using a single-value decomposition method and an automated arterial input function unless artifact precluded its use. For automated arterial input function, pixels with an early and steep decrease of signal intensity on PWI were detected regardless of the side of hemisphere, and their values were averaged. We found no difference between this automated method and manual selection of the contralateral middle cerebral artery in a subset of patients. Whenever artifact was a problem, the manual technique was used. To obtain estimates of actual CBF, CBF values were normalized to a value of 22 mL/100 g per minute in the centrum semiovale contralateral to the DWI lesion.

Normalization and Definition of Regions of Interest
First, 3 lesions were identified in each patient’s space. Abnormal DWI lesion included voxels that were hyperintense on DWI and their ADC values <8000×10⁻⁶ mm²/s. Hyperperfused regions were defined as tissue with MTT delay of >2 seconds beyond the average MTT value of the unaffected hemisphere. The final infarct was manually segmented on the follow-up T2 or CT image. Then these regions and all MR images were transformed into standard coordinate space (Figure 1A) using the Automated Image Registration software (AIR 3.0). The accuracy of registration was assessed by visual inspection by an experienced observer for all steps. In standard space, 4 regions of interest (ROIs) were defined: (1) ischemic core, which included voxels inside the abnormal DWI lesion; (2) infarcted mismatch region, which included voxels inside the hyperperfused region but outside the ischemic core (mismatch region) and inside the final infarct; (3) salvaged mismatch region, which included voxels inside the mismatch region but outside the final infarct; and (4) normal brain tissue, which included voxels outside the ischemic core, hyperperfused region, and the final infarct. Figure 1 illustrates these definitions.

Statistical Analysis
Nonparametric tests were used for statistics because the data were not normally distributed. First, the mean values of CBF, CBV, MTT, and WM probabilistic maps.

Figure 1. Images of standard coordinate space (A) and distribution probabilistic maps of gray and WM (B and C). All MR images were transformed into standard space (D through F, original images of a representative case; G and H, transformed images). The abnormal lesion on acute DWI represents the ischemic core (G, orange), and the mismatch region was identified by the MTT map (delay of >2 seconds beyond mean of unaffected hemisphere) outside the ischemic core (G, blue). When coregistered with the final infarct region (H), the mismatch ROI was divided into infarcted (I, red) and salvaged mismatch regions (l, green). These ROIs were then segmented by the gray and WM probabilistic maps.
and ADC were calculated for each ROI of each patient. The values were compared among 8 ROIs by Friedman's test. When this test showed significant difference, we performed post hoc analysis using Nemenyi’s test. Second, to determine the threshold for infarction, a voxel-based analysis was performed in GM and WM separately using voxels from the infarcted and salvaged mismatch ROIs. Voxels with values below the threshold for CBF, CBV, and ADC and above for MTT were termed “infarcting voxels,” whereas those with values on the other side of the threshold were termed “salvaging voxels.” Thus, the sensitivity and specificity of each threshold value for each MR parameter were calculated. An optimal threshold for predicting tissue fate of the voxels in mismatch region with these threshold values between GM and WM were compared among 8 ROIs by Friedman’s test. When this test showed significant difference, we performed post hoc analysis using Wilcoxon signed-rank test. The accuracies for predicting tissue fate of the voxels in mismatch region with these threshold values were also calculated. Statistical significance was set at $P<0.05$.

**Results**

**Baseline Clinical Data**
The patient sample included in the analysis consisted of 21 patients (8 males and 13 females; mean±SD age 72.2±13.8 years). The median MRI scan time was 3.7 hours after symptom onset (range 1.6 to 20.8 hours). Associated risk factors were hypertension in 44%, diabetes mellitus in 22%, hyperlipidemia in 17%, smoking in 17%, and atrial fibrillation in 44%. The median NIHSS score on admission was 12 (range 2 to 27) and 15 (range 1 to 28) at 24 hours after stroke onset. For the identification of the final infarct lesion, follow-up T2-weighted and CT images were used in 16 and 5 patients, respectively.

**Mean Values for Each ROI**
Mean CBF, CBV, MTT, and ADC values were significantly different among the ROIs ($P<0.0001$). CBF values increased gradually from ischemic core through infarcted and salvaged mismatch regions to normal tissue in both GM and WM. Infarcted and salvaged mismatch regions showed higher values in GM than in WM (Table 1; Figure 2A). Concerning CBV, in both GM and WM, the ischemic core showed the lowest values, and the other 3 ROIs showed similar values. Corresponding ROI values were higher in GM than in WM except in the ischemic core (Table 1; Figure 2B). Regarding MTT, infarcted and salvaged mismatch regions showed significantly higher values than normal tissue. Corresponding ROI values were not different between GM and WM (Table 1; Figure 2C). Concerning ADC, in both GM and WM, the ischemic core showed the lowest values and other 3 ROIs showed similar values. Infarcted and salvaged mismatch regions showed higher values in GM than in WM (Table 1; Figure 2D).

**Threshold Values for Infarction**
Infarction thresholds for CBF were significantly higher in GM (median 34.6 mL/100 g per minute; interquartile range 26.0 to 38.8) than in WM (20.8 mL/100 g per minute; interquartile range 18.0 to 25.9; $P<0.0001$). Thresholds were also significantly higher in GM than WM for CBV (GM: 1.67 mL/100 g; interquartile range 1.39 to 2.17; WM: 1.19 mL/100 g; interquartile range 0.94 to 1.53; $P<0.0001$) and ADC (GM: 918×10⁻⁶ mm²/s, 868 to 975×10⁻⁶; WM: 805×10⁻⁶, 747 to 870×10⁻⁶; $P<0.001$). There was a trend toward a shorter MTT threshold in GM than in WM (GM: 4.94 s, 4.44 to 5.38; WM: 5.15, 4.11 to 5.68; $P=0.11$). The accuracies for predicting the fate of mismatch region with each threshold are shown in Table 2 and were highest for CBF thresholds in both GM and WM (GM 63.7%; WM 64.7%).

**Discussion**
Our results showed that GM and WM have different diffusion and perfusion thresholds for infarction in patients with acute ischemic stroke without early clinical improvement. Compared with WM, GM had higher infarction thresholds for CBF, CBV, and ADC. This implies that tissue-specific thresholds might be a more precise measure of predicting the likelihood of infarction rather than the whole-brain threshold, which is usually used. Because the whole-brain threshold lies between GM and WM thresholds, the likelihood of infarction would be underestimated in GM and overestimated in WM.

### TABLE 1. Mean Values of MRI Parameters for Each ROI

<table>
<thead>
<tr>
<th></th>
<th>Ischemic Core</th>
<th>Infarcted Mismatch</th>
<th>Salvaged Mismatch</th>
<th>Normal Tissue</th>
<th>$P$ (difference among 8 ROIs)</th>
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<tbody>
<tr>
<td><strong>CBF (mL/100 g per minute)</strong></td>
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<tr>
<td>GM</td>
<td>24.4 (18.3–29.7)††‡</td>
<td>30.3 (24.7–37.6)‡§</td>
<td>42.9 (34.1–46.1)§</td>
<td>45.1 (42.4–49.6)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>WM</td>
<td>18.1 (15.0–21.8)††‡</td>
<td>22.6 (17.0–25.7)‡</td>
<td>27.8 (23.4–33.5)</td>
<td>35.4 (33.1–39.9)</td>
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<tr>
<td><strong>CBV (mL/100 g)</strong></td>
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<tr>
<td>GM</td>
<td>1.15 (0.77–1.36)††‡</td>
<td>1.72 (1.23–2.25)§</td>
<td>2.12 (1.91–2.52)§</td>
<td>1.86 (1.71–2.20)§</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>WM</td>
<td>0.98 (0.53–1.10)††‡</td>
<td>1.19 (0.96–1.66)</td>
<td>1.40 (1.28–1.71)</td>
<td>1.44 (1.16–1.67)</td>
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<td><strong>MTT (s)</strong></td>
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<tr>
<td>GM</td>
<td>3.54 (2.93–4.03)††‡</td>
<td>5.04 (4.21–5.49)‡</td>
<td>4.87 (4.18–5.55)‡</td>
<td>2.92 (2.76–3.17)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>WM</td>
<td>3.82 (3.05–4.42)††‡</td>
<td>5.22 (4.35–5.79)‡</td>
<td>5.07 (4.17–5.57)‡</td>
<td>3.23 (2.97–3.42)</td>
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<tr>
<td><strong>ADC (×10⁻⁶ mm²/s)</strong></td>
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<tr>
<td>GM</td>
<td>602 (562–626)††‡</td>
<td>907 (875–956)§</td>
<td>971 (919–1007)§</td>
<td>947 (907–1001)§</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>WM</td>
<td>543 (508–618)††‡</td>
<td>768 (688–861)</td>
<td>848 (826–909)</td>
<td>875 (837–916)</td>
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</table>

*Post hoc Nemenyi’s test to establish abnormal ROIs within groups: †$P<0.05$ vs infarcted mismatch region; ‡$P<0.05$ vs salvaged mismatch region; §$P<0.05$ vs normal tissue; ††$P<0.05$ vs WM value.

Data are shown in median value (interquartile range).
when whole-brain thresholds rather than a tissue-specific approach was adopted.

The difference of infarction thresholds between GM and WM is probably attributable to differences in the susceptibility of the constituent cells between both compartments (neurons > oligodendrocytes > astrocytes > microglia). Further, the neurochemical cascade of events does seem to be quite different in the 2 compartments. In GM, as mentioned earlier, the classical cascade commences with energy failure and glutamate release and is followed by voltage-gated calcium channel impairment, potassium and calcium influx, and cell death. Other processes such as free radical generation, lipase activation, and membrane destruction also occur. Conversely, the response of WM to ischemia has been less extensively studied, but it is known that glutamate plays a lesser role because WM has virtually no NMDA (N-methyl-D-aspartate) receptors and only a sparse population of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors. More important, there appears to be an autoproductive feedback loop mediated by adenosine, which is activated by the ischemic process and may provide an additional explanation for the differing vulnerabilities to ischemia.

Based on information from studies in animal models, there has been conflicting evidence for the vulnerability of GM versus WM. Marcoux et al reported that GM infarcts both earlier and at higher levels of CBF than WM using a monkey model of focal ischemia. The infarction thresholds were 10 to 12 mL/100 g per minute in GM and 5 mL/100 g per minute in WM within the time window of 1 to 3 hours of middle cerebral artery occlusion. Conversely, Pantoni et al used a rat model to show that GM was somewhat more resistant to ischemia. In humans, the first evidence for a differential vulnerability between gray and WM compartments was provided by Falcao et al, who showed that the ischemic penumbra evolved more slowly in WM than GM using 18F-Fluoromisonidazole (18F-FMISO) PET as a penumbra marker. This has been confirmed more recently using MR techniques. In another recent study, Bristow et al reported that compared with WM, GM has higher infarction thresholds for CBF, CBV, and ADC and a shorter infarction threshold.

Figure 2. MR parameters for each of CBF, CBV, MTT, and ADC in 21 patients imaged within 24 hours of ischemic stroke. Values are medians with interquartile ranges. CBF increased gradually from the ischemic core through infarcted and salvaged mismatch regions to normal tissue in both GM and WM. Infarcted and salvaged mismatch regions showed higher values in GM than in WM (A). CBV was lowest in the ischemic core. Corresponding ROI values were higher in GM than in WM except in the ischemic core (B). MTT was longer in infarcted and salvaged mismatch regions than normal tissue. The ischemic core included voxels of 0 intensity because of the severity of ischemia, and these voxels erroneously generated the MTT values in the normal range. Corresponding ROI values were not different between GM and WM (C). ADC was lowest in the ischemic core. Infarcted and salvaged mismatch regions showed higher values in GM than in WM (D). Core indicates ischemic core; InfM, infarcted mismatch region; SalM, salvaged mismatch region; Nor, normal brain tissue.
TABLE 2. Threshold Values for Infarction

<table>
<thead>
<tr>
<th></th>
<th>Threshold</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>P (difference in thresholds)</th>
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<tbody>
<tr>
<td>CBF (mL/100 g per minute)</td>
<td></td>
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<tr>
<td>GM</td>
<td>34.6 (26.0–38.8)</td>
<td>64.6±8.5</td>
<td>65.4±8.3</td>
<td>63.7±8.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>WM</td>
<td>20.8 (18.0–25.9)</td>
<td>65.9±7.7</td>
<td>67.2±7.8</td>
<td>64.7±7.7</td>
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<tr>
<td>CBV (mL/100 g)</td>
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<tr>
<td>GM</td>
<td>1.67 (1.39–2.17)</td>
<td>63.7±9.7</td>
<td>64.4±9.3</td>
<td>61.3±9.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>WM</td>
<td>1.19 (0.94–1.53)</td>
<td>61.9±9.8</td>
<td>62.8±9.9</td>
<td>59.7±9.6</td>
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<tr>
<td>MTT (s)</td>
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<tr>
<td>GM</td>
<td>4.94 (4.44–5.38)</td>
<td>61.8±10.7</td>
<td>62.3±11.2</td>
<td>58.2±12.7</td>
<td>0.11</td>
</tr>
<tr>
<td>WM</td>
<td>5.15 (4.11–5.68)</td>
<td>64.1±12.0</td>
<td>65.0±11.4</td>
<td>63.2±12.0</td>
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<tr>
<td>ADC (×10⁻⁶ mm²/s)</td>
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<tr>
<td>GM</td>
<td>918 (868–975)</td>
<td>57.5±8.9</td>
<td>57.9±8.7</td>
<td>55.7±8.3</td>
<td>&lt;0.001</td>
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<tr>
<td>WM</td>
<td>805 (747–870)</td>
<td>62.2±10.0</td>
<td>62.7±9.6</td>
<td>59.5±9.6</td>
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</table>

Threshold values are shown in median values (interquartile range). Other data are shown in mean±SD values.

for MTT.14 Hence, taking all these studies together, there now seems to be adequate evidence that GM is more vulnerable to ischemia than WM in both humans and primates.

The robustness of the finding in both the study by Bristow et al and ours deserves comment. The smaller sample size and inclusion of patients with or without reperfusion, some of whom had received thrombolytic therapy, had the potential to confound their study, but the results were compatible with ours and a similar differential in vulnerability of tissue compartments demonstrated (eg, infarct threshold for CBF 20.0±10.2 mL/min per 100 g in GM; 12.3±4.9 in WM). Another point of difference between the 2 studies was the ROI setting. To determine each compartmental threshold, Bristow et al compared the salvaged mismatch region with the final infarct area (infarction core+infarcted mismatch region), whereas we compared the salvaged mismatch region with the infarcted mismatch region. Because the infarct core is likely to contain the most severe levels of ischemia, the threshold values determined by Bristow et al for CBF, CBV, and ADC might be lower and those for MTT longer than ours. Hence, it is reassuring that despite some differences in methodology, the results from both studies were concordant.

However, there are a number of limitations to our study. First, as in previous studies, we used a probabilistic map of GM and WM for segmentation rather than individual high-resolution T1 images. Because of variance of GM and WM distribution among patients, individual high-resolution T1 images are superior for segmentation; however, they are time consuming and difficult to perform in the acute stroke clinical setting. Hence, the probabilistic map approach is a reasonable alternative because it allows the inclusion of a larger number of patients. Second, we used day-7 CT to define final infarct volume in 5 cases because MRI was not able to be performed 3 months after the onset. This probably gave an overestimate of final infarct volume in these cases because of the likely greater presence of edema earlier and the likelihood of shrinkage on later scans. To be assured that this would not influence our results, we performed the analysis with and without these cases included, and no significant difference occurred (data not shown). However, because of this and the use of the probabilistic map, the observed moderate accuracy for predicting tissue fate with the infarction thresholds is explicable. Third, MTT maps sometimes demonstrated voxels of 0 intensity, where transit time could not be calculated because of the severity of ischemia.9 These voxels usually exist in the ischemic core and erroneously generate mean MTT values in the normal range (Figure 2). However, because we did not include ischemic core voxels in the threshold analysis, this problem was minimized. Fourth, the perfusion values in this study are semiquantitative and are, therefore, not always easy to compare with other studies. For example, Bristow et al presented similar CBF values in normal GM (39.7±15.9 mL/100 g per minute) but lower values in normal WM (19.4±7.7 mL/100 g per minute) than ours. However, given that the hypothesis to be tested was to determine the relationship between white and GM compartments, this issue assumes a lesser importance. Finally, as has been recognized previously, ADC values in GM might be influenced by CSF contamination, although the voxels with ADC values >1500×10⁻⁶ mm²/s were removed from this study. In other words, it is possible that our observed higher ADC thresholds in GM might be partially attributable to CSF contamination in the cortex in addition to structural and functional differences between GM and WM.

In conclusion, our results show that diffusion and perfusion thresholds for infarction differ between GM and WM in acute ischemic stroke. This provides additional evidence for a differential vulnerability to cerebral ischemia between the 2 compartments. Further, when predicting the likelihood of infarction with DWI and PWI, tissue-specific thresholds might be a more precise measure than whole-brain thresholds. For this to be performed in an acute stroke setting, more sophisticated and user-friendly software will need to be developed.

Acknowledgments

This work was supported in part by a National Health and Medical Research Council (NHMRC, Australia) program grant. H.M. is supported...
by the NHMRC postgraduate medical research scholarship (336106) and received a cardiovascular lipid research grant (Pfizer, Australia).

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Stroke. 2006;37:1211-1216; originally published online March 30, 2006;
doi: 10.1161/01.STR.0000217258.63925.6b
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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