Low Incidence of Stroke in Southern Italy
A Population-Based Study

Giovanni Manobianca, MD; Stefano Zoccolella, MD; Antonella Petruzzellis, MD; Annamaria Miccoli, MD; Giancarlo Logroscino, MD, PhD

Background and Purpose—Although a lower incidence of stroke has been observed in the Mediterranean area compared to other European countries, this is based on only a few studies. We sought to determine the incidence and 28-day case-fatality of stroke through a population-based stroke register in a rural area in Southern Italy, characterized by a stroke unit in the referral hospital.

Methods—We established a multisource prospective population-based register in a well defined geographic area of 38 735 inhabitants in Puglia, Southern Italy. We identified all subjects in the study area with a first-ever stroke between January 1, 2001 and December 31, 2002.

Results—We identified 127 first-ever strokes (77 males, 50 females) during the two-year study period. Hospitalization was 95%: 92 cases (72.4%) were cerebral infarction, 24 (18.9%) intracerebral hemorrhage, 3 (2.4%) subarachnoid hemorrhage, and 8 (6.3%) were unclassifiable strokes. The overall crude annual incidence was 1.6 per 1000 (95%CI: 1.4 to 1.9), 2.0 for males (95% CI:1.6 to 2.5), and 1.3 for females (95% CI:0.9 to 1.6). The incidence rates standardized to the 2001 European and world populations were respectively 1.5 (2.0 for males and 1.3 for females) and 0.8 (0.9 for males and 0.6 for females). Incidence rates progressively increased with age in both sexes, reaching their peak at 85 years or more (21.4/1000 overall, 35.0 for men and 13.4 for women). The 28-day case-fatality was 18.1%.

Conclusions—Our study supports previous findings of lower incidence of stroke in the Mediterranean area, whereas the case-fatality in our study was lower than in previous studies from Italy. Further studies are needed to determine the role of prompt referral and stroke units on prognosis in population-based setting. (Stroke. 2008;39:2923-2928.)

Key Words: stroke ■ incidence ■ registry ■ stroke unit ■ population-based ■ Italy ■ Mediterranean area

Geographical variations in the incidence of stroke may be related to differences in the prevalence of genetic and environmental risk factors in populations.1,2 The Mediterranean populations are characterized by a specific diet, lifestyle, and other cultural factors that may contribute to differences in the incidence, pathology, and sex distribution of stroke.2 Compared with Northern European populations, a trend toward lower incidence for stroke has been observed in the Mediterranean area by five population-based studies.3–7 However, these lower estimates could be attributable to limitations in some of these studies, including retrospective collection of data8 and absence of specialized care in the study area.3,7

We established a prospective population-based stroke register to determine the incidence and 28-day case-fatality of stroke in a well-defined area in Puglia, Southern Italy, with a high level of a specialized care, including a stroke unit in the referral hospital.

Materials and Methods
In 2000, we established a registry based on the prospective, community-based collection of data on stroke incidence and outcome. Surveillance began on January 1, 2001 and was continued until December 31, 2002. The study was based on the “standard ideal criteria” for population-based stroke studies as proposed by Malmgren et al in 1987,8 Bonita et al in 1995,9 and updated by Sudlow and Warlow in 1996 and 1997.10,11

Study Area and Population
The study was conducted in a well-defined geographic district in Puglia, a region located in south-east Italy (4 086 613 residents according to the 2001 census, 19 357 km2).12 The district is 208.46 km2 in area and includes two towns, Acquaviva delle Fonti and Casamassima.

The study population on January 1, 2001 comprised 38 735 inhabitants (19 068 males, 19 667 females). The proportion of individuals aged 65 years or more was 15.7% (14.2% of men, 17.1% of women), which is comparable to that in the entire Italian population (18.6% overall, men 15.8%, and women 21.2%).12 To be counted as a resident, each stroke case should have been resident in the study area for at least one year.

Received March 14, 2008; accepted April 11, 2008.
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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.108.519421
The study area is served by only one regional general hospital (Ospedale F. Miulli), which has a department of neurology and a semi-intensive stroke unit of 6 beds. Almost all patients with acute neurological diseases are referred to the department of neurology, and stroke patients admitted to the internal medicine or cardiology departments are routinely assigned to a neurologist.

The population is also served by 32 general practitioners (GPs) and 2 first aid stations that were periodically contacted by the study staff. This study has been approved by the Ethical and Scientific Committee of Ospedale F. Miulli.

**Stroke Definition and Classification**

Stroke was defined according to the WHO criteria as “rapidly developing clinical symptoms or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.”13 14 This definition excludes on clinical grounds cases of primary cerebral tumors, cerebral metastasis, subdural hematoma, postseizure palsy, and brain trauma.

Stroke was classified as either first-ever (occurring for the first time in a patient’s lifetime) or recurrent (defined though anamnestic recall, general physician interview, or hospital records). Only cases of first-ever stroke were included in the study; patients with transient ischemic attacks (TIA) or recurrent stroke were excluded. Strokes subtypes were identified on the basis of either computed tomography (CT) or magnetic resonance (MR) performed within 28 days of symptom onset. Patients with first-ever strokes were categorized based on neuroimaging as cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage, or as undetermined, when no neuroimaging tests were performed.

**Case Ascertainment**

Complete case ascertainment was ensured through multiple sources of information in the study area. Hospitalized patients included those admitted directly to the department of neurology, those admitted to the departments of medicine or cardiology, and patients who, for any reason, were identified by either the referring physician or the neurologist acting as consulting physician. Emergency room records were periodically searched for cases who were not admitted to Ospedale F. Miulli but were referred to other hospitals because of a lack of beds in the appropriate departments or because of death before admission. We also regularly examined the Hospital Discharge Diagnosis Data Bank, a regional computerized system that includes the diagnosis of each hospitalized patient in the study area in both public and private clinics. We looked for any patient with a discharge diagnosis including codes 430 to 438, according to the International Classification of Disease, 9th revision.

The search for nonhospitalized stroke cases was performed in collaboration with the GPs in the study area. Each GP was informed of the aims and methods of the study and was provided with the study protocol and the research team’s telephone numbers and addresses. The GPs were invited to promptly report any suspected case of nonhospitalized stroke to the research team. GPs were contacted on average every 3 months. Nursing and residential homes were contacted every month. To identify possible cases not caught by other sources of information, the death certificates of all area residents were contacted every month. To identify possible cases not caught by the other sources of information, the death certificates of all area residents were reviewed with the referring physician, using the GP’s medical records, and interviews with relatives.

**Statistical Methods**

Data were stored in a computerized database, in separate, anonymous files. Age- and sex-specific incidence rates of first-ever stroke were estimated per 1000 inhabitants. Rates were calculated as the number of cases divided by the person-year. Age- and sex-specific incidence rates were also adjusted by the direct method15 to the 2001 Italian,12 European,16 and world16 populations. To make results comparable with other population-based studies, data were presented in 10-year age bands.

The 95% confidence intervals (CI) were estimated according to Poisson distribution. Univariate analyses employed either t test (for continuous variables) or x² (for categorical variables). Significance was tested at the 5% level.

**Results**

During the 2-year surveillance period, 127 first-ever strokes were identified. Seventy-seven (60.6%) were males with a mean age of 72.5 years (range 13 to 93), and 50 (39.4%) were females with a mean age of 77.5 years (range 47 to 96). Of these 127 cases, 121 (95.2%) were hospitalized (2 of whom died in the emergency room), and 6 were treated at home and died without a neuroimaging test. One hundred twenty-five cases were prospectively included in the study, mostly within 24 hours of their event. Two cases hospitalized outside the study area were identified through examination of the Hospital Discharge Diagnosis data bank, and no patients were identified only by death certificates examination. Of these 127 strokes, 92 were classified as cerebral infarction (72.4%), 24 intracerebral hemorrhage (18.9%), 3 subarachnoid hemorrhages (2.4%), and 8 (6.3%) undetermined strokes. The 8 cases of undetermined stroke did not undergo a neuroimaging test, because they were already deceased (6 at home and 2 in the emergency room). At least one CT or MR was performed on the other 119 patients (93.7%).

The overall crude incidence rate was 1.6 (95% CI: 1.3 to 1.9) per 1000, 2.0 (95% CI: 1.6 to 2.6) for males and 1.3 (95% CI: 0.9 to 1.6) for females. The stroke incidence rate adjusted to the 2001 Italian population was 1.8 overall (95% CI: 1.5 to 2.1), 2.0 (95% CI: 1.6 to 2.5) for males and 1.4 (95% CI: 1.1 to 1.9) for females. The incidence rate adjusted to the 2001 European population was 1.5 overall (95% CI: 1.3 to 1.9), 1.7 (95% CI: 1.3 to 2.0) for males and 1.3 (95% CI: 0.9 to 1.7) for females. Finally, the incidence rate adjusted to the 2001 world population was 0.8 overall (95% CI: 0.6 to 0.9), 0.9 (95% CI: 0.7 to 1.1) for males and 0.6 (95% CI: 0.4 to 0.7) for females. Stroke incidence progressively increased with age in both sexes, reaching a peak at 85 years or more (21.4/1000 overall, 35.0 for men and 13.4 for women; Table 1).

The overall crude incidence rates per 1000 population for the different pathological subtypes of first-ever stroke were: cerebral infarction 1.2 (1.5 for men, 0.9 for women); intracerebral hemorrhage 0.3 (0.4 for men, 0.3 for women); subarachnoid hemorrhage 0.04 (0.05 for men, 0.02 for women); and undetermined stroke 0.1 (0.1 for both men and women). The incidence rates for cerebral infarction and intracerebral hemorrhage increased significantly with age; the highest incidence for both these pathological subtypes was among men aged 85 years or more (26/1000 for CI and 5.3/1000 for IH).

The overall 28-day case-fatality rate was 18.1% (23/127 patients), 15.5% for males and 22% for females. The overall mean age at death was 83 years (81.5 for males, 84.8 for females). The highest case-fatality rate was among undetermined strokes (100%), compared to intracerebral hemorrhage (20.8%), cerebral infarction (10.8%), and subarachnoid hemorrhage (0%).

**Discussion**

In this population-based study, the incidence rates of first-ever stroke were similar to those in other population-based
Table 1. Age- and Sex-Specific Incidence Rates of First-Ever Stroke per 1000 in Acquaviva and Casamassima Southern Italy

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Population at Risk</th>
<th>Cases</th>
<th>Rate</th>
<th>95% CI</th>
<th>Population at Risk</th>
<th>Cases</th>
<th>Rate</th>
<th>95% CI</th>
<th>Population at Risk</th>
<th>Cases</th>
<th>Rate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–14</td>
<td>12,651</td>
<td>1</td>
<td>0.07</td>
<td>nc</td>
<td>6486</td>
<td>1</td>
<td>0.15</td>
<td>nc</td>
<td>6165</td>
<td>0</td>
<td>0</td>
<td>nc</td>
</tr>
<tr>
<td>15–24</td>
<td>10,261</td>
<td>0</td>
<td>0</td>
<td>nc</td>
<td>5248</td>
<td>0</td>
<td>0</td>
<td>nc</td>
<td>5013</td>
<td>0</td>
<td>0</td>
<td>nc</td>
</tr>
<tr>
<td>25–34</td>
<td>11,815</td>
<td>0</td>
<td>0</td>
<td>nc</td>
<td>5770</td>
<td>0</td>
<td>0</td>
<td>nc</td>
<td>6045</td>
<td>0</td>
<td>0</td>
<td>nc</td>
</tr>
<tr>
<td>35–44</td>
<td>12,474</td>
<td>1</td>
<td>0.08</td>
<td>nc</td>
<td>6191</td>
<td>1</td>
<td>0.16</td>
<td>nc</td>
<td>6283</td>
<td>0</td>
<td>0</td>
<td>nc</td>
</tr>
<tr>
<td>45–54</td>
<td>10,156</td>
<td>6</td>
<td>0.6</td>
<td>0.2–1.3</td>
<td>5038</td>
<td>5</td>
<td>1.0</td>
<td>0.3–2.2</td>
<td>5118</td>
<td>1</td>
<td>0.2</td>
<td>nc</td>
</tr>
<tr>
<td>55–64</td>
<td>7,817</td>
<td>17</td>
<td>2.2</td>
<td>1.2–3.5</td>
<td>3838</td>
<td>12</td>
<td>3.1</td>
<td>1.7–5.4</td>
<td>3979</td>
<td>5</td>
<td>1.2</td>
<td>0.4–2.9</td>
</tr>
<tr>
<td>65–74</td>
<td>6,685</td>
<td>23</td>
<td>3.5</td>
<td>2.2–5.2</td>
<td>3148</td>
<td>16</td>
<td>5.1</td>
<td>2.9–8.2</td>
<td>3437</td>
<td>7</td>
<td>2</td>
<td>0.8–4.2</td>
</tr>
<tr>
<td>75–84</td>
<td>4,174</td>
<td>46</td>
<td>11</td>
<td>8–14.7</td>
<td>1775</td>
<td>22</td>
<td>12.4</td>
<td>7.7–18.7</td>
<td>2399</td>
<td>24</td>
<td>10</td>
<td>6.4–14.9</td>
</tr>
<tr>
<td>&gt;85</td>
<td>1,537</td>
<td>33</td>
<td>21.4</td>
<td>14.8–30.1</td>
<td>570</td>
<td>20</td>
<td>35</td>
<td>21.4–54.2</td>
<td>967</td>
<td>13</td>
<td>13.4</td>
<td>7.1–23</td>
</tr>
<tr>
<td>TOTAL</td>
<td>77,470</td>
<td>127</td>
<td>1.6</td>
<td>1.4–1.9</td>
<td>38,064</td>
<td>77</td>
<td>2.0</td>
<td>1.6–2.5</td>
<td>39,406</td>
<td>50</td>
<td>1.3</td>
<td>0.9–1.6</td>
</tr>
</tbody>
</table>

* Adjusted to the Italian population; † Adjusted to the European population; ‡ Adjusted to the world population.
nc indicates not calculated.

studies from Southern Italy3–7 but lower than those from Central and Northern Italy17–20 and other European populations21–37 (Table 2). In this study the 28-day case-fatality was lower than in previous studies conducted in Italy (3 to 17 to 20).

Only 5 population-based studies on stroke incidence and pathology in the Mediterranean area have been published as full papers3–7; 4 were prospective3,5–7 and 1 was retrospective.4 Three of these studies have certain limitations: the incidence of subarachnoid hemorrhage and undermined stroke were not evaluated in the study from Foggia province4; adjusted data on stroke incidence were available only for patients aged between 45 and 85 years in the study from Southern Italy.3–7 but lower than those from Greece6; and although the small sample size and isolation of patients aged between 45 and 85 years in the study from Puglia could be related to the age structure of the study population,1 the proportion of subjects in the age groups at high risk of stroke is very similar to both the overall Italian and European populations, as the comparison of crude and adjusted estimates of incidence rates clearly shows.12–16

Although the lower stroke incidence in Puglia could be related to the age structure of the study population,1 the proportion of subjects in the age groups at high risk of stroke is very similar to both the overall Italian and European populations, as the comparison of crude and adjusted estimates of incidence rates clearly shows.12–16

We found a strong relationship between stroke incidence and advancing age. This is consistent with the vast majority of epidemiological studies on stroke,1–3,5,6,11,17 in which incidence progressivelly increases with age, particularly after 65 years, reaching a peak in individuals aged 85 years or more. This finding may have important implications for the burden of stroke in future years, because this is the fastest growing age group in industrialized countries.38,39 Age is one of the most important predictors of unfavorable stroke outcomes, and the oldest average age of incident stroke will affect the statistics for stroke prognosis.39,41

As observed in most of population-based studies including the Mediterranean area,1,5,6 we found that incidence rates were higher for men than women. This difference was observed in all age groups and across the different pathological subtypes. Although this could be explained by underascertainment of stroke among women, this seems unlikely, as the difference in age-incidence rates between the two sexes was consistent across age groups, which would be unlikely if the referral process were different for men and women. A more likely explanation is that the difference in incidence between genders is real. Differences in certain lifestyle factors, such as smoking, could at least partially determine these results, and a lower frequency of smoking in women of the birth cohorts that are now at risk for stroke is usually observed in Southern Italy. The distribution and incidence of stroke subtypes observed in this study were similar to those observed by other studies,1,5,6,11 with the exception of the higher incidence of intracerebral hemorrhage, which is similar to the results in the Greek study.6 In our study, only 5% of stroke patients were not hospitalized, which is lower than reported in other studies from industrialized countries conducted in recent years.5,17,19,30 Because of the widespread use of neuroimaging, a subtype diagnosis of stroke was reached in 94% of our cases.

In this study the 28-day overall case-fatality of 18.1% was the lowest reported in Italy compared to 24% in Vibo Valentia, 25% in L’Aquila, and 31% in Valle d’Aosta,5,17,20 and this good prognosis was consistently present both for cerebral infarction and hemorrhage. As recently demonstrated in the Dijon Stroke Registry,32,42 the differences between current and previous stroke fatality rates found in studies conducted in the same geographical area could be related to better overall health in the population at large42 as well as to improvements in the standard of care provided by stroke units.43,44

Our epidemiological study presents several strengths. A stroke event was defined according to the established WHO criteria,13,14 and only first-ever strokes were included in the
analyses. The study was conducted in a well-defined geographic district in the Mediterranean area, using a prospective cohort design with a multisource population-based registry as the primary source of case ascertainment. Complete case ascertainment in our study is highly likely. First, the national health system in Italy is the only medical provider of stroke services, free of charge to all residents, regardless of age or socioeconomic status. Second, the study area contains only one hospital with a stroke unit, which is well known to the community. This prompts immediate and accurate detection with neuroimaging for almost all stroke cases that came to medical attention in the area. Compared to studies conducted in population-settings in several other European countries, the rate of hospitalization and use of neuroimaging for stroke in our study area is one of the highest reported.1

Our study has limitations that are common to population-based studies compared to clinical-based studies: the small sample size of the reference population, and the short period of observation (2 years).

The low incidence found in our study may be attributable to protective factors related to lifestyle, such as diet.2,10 The diet in the study area, especially in the age groups at high risk for stroke, includes olive oil, fruits, vegetables, and other fiber-containing foods that may be protective against stroke, particularly of the ischemic subtype.45–50 It is possible that the Mediterranean diet, characterized by a high intake of antioxidants such as omega-3 fatty acids, oleic acid, polyunsaturated fatty acids, and vitamins,45,47–50 at least partially explains the low incidence of stroke in this population, particularly of cerebral infarction, which is more closely associated with atherosclerosis.

The presence of a permanent stroke surveillance system in the study area may help us better understand the temporal trends for stroke incidence and survivorship. If the best prognosis will be confirmed, the increased number of stroke survivors will be important for health care planning and for resource allocation to stroke services and long-term care in the region.

Further studies are needed to determine the positive role of prompt referral and stroke units on the short-term prognosis.

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Study Period</th>
<th>Crude Incidence for Strokes per 1000 Person-Years (95%CI)</th>
<th>Incidence for Strokes per 1000 Person-Years Adjusted to the European Population (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Northern Europe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malmoe, Sweden (21)</td>
<td>1989</td>
<td>2.3 (na)</td>
<td>na</td>
</tr>
<tr>
<td>Oxfordshire, UK (31)</td>
<td>1981–2004</td>
<td>1.9 (1.7–2.1)</td>
<td>na</td>
</tr>
<tr>
<td>Innherred, Norway (24)</td>
<td>1994–1996</td>
<td>3.1 (2.8–3.4)</td>
<td>2.2 (na)</td>
</tr>
<tr>
<td>Novosibirsk, Russia (27)</td>
<td>1982–1992</td>
<td>2 (na)</td>
<td>2.2 (na)</td>
</tr>
<tr>
<td>Uzhgorod, west Ukraine (26)</td>
<td>1999–2000</td>
<td>2.8 (2.5–3.1)</td>
<td>na</td>
</tr>
<tr>
<td>Soderhamn, Sweden (25)</td>
<td>1987–1990</td>
<td>3.6 (3.3–4)</td>
<td>2.6 (2.4–2.9)</td>
</tr>
<tr>
<td>Frederiksberg, Denmark (29)</td>
<td>1989–1990</td>
<td>3.1 (2.7–3.4)</td>
<td>na</td>
</tr>
<tr>
<td>South London, UK (36)</td>
<td>1995–1998</td>
<td>1.3 (1.2–1.5)</td>
<td>1.28 (1.2–1.35)</td>
</tr>
<tr>
<td>Warzaw, Poland (37)</td>
<td>1991–1992</td>
<td>1.27 (1.1–1.5)</td>
<td>1.1 (1–1.3)</td>
</tr>
<tr>
<td>Espo-Kauniainen, Finland (28)</td>
<td>1989–1991</td>
<td>2.2 (2.0–2.4)</td>
<td>na</td>
</tr>
<tr>
<td>Erlangen, Germany (30)</td>
<td>1994–1998</td>
<td>1.7 (1.6–1.9)</td>
<td>1.3 (1.2–1.4)</td>
</tr>
<tr>
<td>Scottish Borders, UK (33)</td>
<td>1998–2000</td>
<td>2.8 (2.6–3.0)</td>
<td>na</td>
</tr>
<tr>
<td>Tbilisi, Georgia (34)</td>
<td>2000–2003</td>
<td>1.7 (1.4–1.9)</td>
<td>1.5 (1.3–1.7)</td>
</tr>
<tr>
<td>Orebro, Sweden (35)</td>
<td>1999–2000</td>
<td>3.1 (2.8–3.5)</td>
<td>2.5 (2.3–2.8)</td>
</tr>
<tr>
<td>Tartu, Estonia (22)</td>
<td>2001–2003</td>
<td>2.2 (2–2.4)</td>
<td>1.9 (1.7–2.1)</td>
</tr>
<tr>
<td><strong>Southern Europe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dijon, France (32)</td>
<td>1985–2004</td>
<td>na</td>
<td>1 (0.9–1.1)</td>
</tr>
<tr>
<td>Porto, Portugal (23)</td>
<td>1999–2000</td>
<td>2.8 (2.6–3)</td>
<td>1.8 (1.6–2)</td>
</tr>
<tr>
<td>Umbria, Central Italy (18)</td>
<td>1986–1989</td>
<td>2.5 (2.3–2.8)</td>
<td>1.5 (1.4–1.8)</td>
</tr>
<tr>
<td>Belluno, Northern Italy (19)</td>
<td>1992–1993</td>
<td>2.2 (1.7–2.3)</td>
<td>1.7 (na)</td>
</tr>
<tr>
<td>Valle d’Aosta, Northern Italy (20)</td>
<td>1989</td>
<td>2.2 (2–2.5)</td>
<td>2.1 (na)</td>
</tr>
<tr>
<td>L’Aquila, Central Italy (17)</td>
<td>1994</td>
<td>2.8 (2.6–2.9)</td>
<td>2.3 (na)</td>
</tr>
<tr>
<td><strong>Mediterranean area</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aeolian Archipelago, Southern Italy (3)</td>
<td>1999–2002</td>
<td>1.5 (1.2–1.9)</td>
<td>1.5 (1.3–1.8)</td>
</tr>
<tr>
<td>Vibo Valentia, Southern Italy (5)</td>
<td>1996</td>
<td>1.8 (1.6–2.0)</td>
<td>1.4 (1.2–1.5)</td>
</tr>
<tr>
<td>Benghazi, Libya (7)</td>
<td>1984</td>
<td>0.6 (na)</td>
<td>na</td>
</tr>
<tr>
<td>Acquaviva-Casamassima, Southern Italy</td>
<td>2001–2002</td>
<td>1.6 (1.4–1.9)</td>
<td>1.5 (1.3–1.8)</td>
</tr>
</tbody>
</table>

na indicates not available.
of incident strokes also in population-based setting similarly to what has been already well established in clinical setting.43,44

Acknowledgments

The authors thank Donald Halstead of Harvard School of Public Health for his critical comments on the manuscript.

Disclosures

None.

References


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Stroke. 2008;39:2923-2928; originally published online August 14, 2008;
doi: 10.1161/STROKEAHA.108.519421

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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