Incidence, Types, Risk Factors, and Outcome of Stroke in a Developing Country
The Trivandrum Stroke Registry

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Background and Purpose—Despite increasing burden of stroke in developing countries, population-based data are rare. Through the Trivandrum Stroke Registry, we intend to assess incidence, types, risk factors, and outcome of stroke among urban and rural dwellers of a South Indian community.

Methods—We ascertained all first-ever strokes occurring among 741,000 urban and 185,000 rural inhabitants of Trivandrum, Kerala. In addition to Steps 1 and 2 of World Health Organization STEPS Stroke Manual, we used multiple supplementary methods to maximize ascertainment of nonfatal and nonhospitalized fatal stroke events in the community.

Results—During a 6-month period, 541 strokes were registered, 431 in the urban and 110 in the rural communities. Stroke occurred at a median age of 67 years; only 3.8% of patients were aged ≤40 years. Adjusted annual incidence rates per 100,000 were 135 (95% confidence interval 123 to 146) for total, 135 (122–148) for urban, and 138 (112–164) for rural populations, and 74.8 (66.3 to 83.2), 10.1 (7.0 to 13.2), and 4.2 (2.2 to 6.1) for ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage, respectively. There was more stroke of undetermined type in the rural community. One or more modifiable risk factors were identified in 90% patients. More rural male patients smoked tobacco. The 28th day case fatality rate was 24.5% for urban and 37.1% for rural populations (P = 0.011).

Conclusions—There are more similarities than differences between developing and developed countries in the epidemiology of stroke. Compared to urban stroke patients, rural ones are less likely to be optimally investigated and treated. (Stroke. 2009;40:1212-1218.)

Key Words: epidemiology ■ incidence ■ outcome ■ risk factors ■ stroke

Stroke is a global health problem and is a leading cause of adult disability.1 Of 35 million deaths attributable to chronic noncommunicable diseases that occurred worldwide in 2005, stroke was responsible for 5.7 million (16.6%) deaths, and 87% of these deaths occurred in low-income and middle-income countries.2 Driven by increasing size and aging of populations, and escalating prevalence of risk factors such as hypertension, tobacco use, unhealthy diet, physical inactivity, and obesity, stroke is becoming a major cause of premature death and disability in developing countries.3 This prompted the World Health Organization (WHO) to launch the Global Stroke Initiative aimed to generate population-based data on burden of stroke and to use such data to evolve strategies for prevention and management.4 The feasibility of WHO STEPS Stroke Surveillance System (STEPS Stroke),5 which provides a standardized approach to stroke data collection, analysis, interpretation, and dissemination, has been successfully tested in several developing countries.6 India, with more than 1 billion inhabitants, is undergoing remarkable economic and demographic changes in recent years resulting in a transition from poverty-related infectious and nutritional deficiency diseases toward lifestyle-related cardiovascular and cerebrovascular diseases.7,8 Despite rapid economic boom, a large segment of the Indian population still lives in poverty. Given the anticipated increase in burden of stroke in coming years and limited availability of organized stroke care services to the majority of people in India, it would be logical to place greater emphasis on population-based stroke prevention strategies. However, very little reliable information is currently available regarding epidemiology of stroke in India. The reported frequency, pattern, risk factors, and outcome of stroke from India are largely derived from hospital-based observations.8,9 Very few epidemiological studies on stroke that are available from India10–12 do not fulfill the criteria for an ideal study of stroke incidence.13 The Trivandrum Stroke Registry intends to overcome this deficiency. Using WHO STEPS Stroke protocol, we intensively monitored first-ever-in-a-lifetime (first-ever) stroke occurrences among urban and rural dwellers of a...
South Indian community to ascertain information on incidence, types, risk factors, morbidity, and mortality of stroke.

Subjects and Methods

Study Area

The southern state of Kerala covers an area of 39,000 km² spread over 14 districts along the western coast of Indian peninsula (Figure) and is inhabited by more than 32 million people, who are distinguished from the rest of India by the high level of literacy (91%) and health awareness. The life expectancy of Kerala population is 71 years for males and 76 years for females. The per capita domestic product of Kerala state at current prices is Indian Rupees 39,315 (U.S. dollar 983). This study was conducted in Trivandrum (Thiruvananthapuram in the regional language Malayalam), the southernmost district of Kerala (Figure), under the supervision of Sree Chitra Tirunal Institute for Medical Sciences and Technology, a medical institution of national importance for cardiovascular and neurological disorders situated in Trivandrum city.
The Trivandrum Stroke Registry
The Trivandrum Stroke Registry is based on the WHO STEPS Stroke Manual. STEPS Stroke consists of gathering information using standardized questionnaire about hospitalized stroke events (Step 1), fatal stroke events in the community (Step 2), and nonfatal stroke events in the community (Step 3). In addition to Steps 1 and 2, we used multiple overlapping supplementary methods as described below to maximize ascertainment nonfatal and nonhospitalized fatal stroke events in the community.

Preparatory Phase
During January and February 2005, we defined the geographical area of the study and its population, and all medical care facilities existing in the study area. We choose an urban area of Trivandrum Corporation covering 140 km² with a population of 741,307 (363,704 males and 377,603 females) and a rural area covering 60 km² situated 20 km away from the Trivandrum City comprising a population of 184,560 (92,067 males and 92,493 females; Figure). The medical care facilities were personally visited by the principal investigator (K.R.) along with the other 2 neurologists involved with the study (P.N.S., S.D.N.) and a medical social worker (J.P.U.) to ensure cooperation of local physicians and to decide on the frequency of hospital visits to be undertaken for case ascertainment. We then classified the medical facilities in the study area according to the number of stroke cases encountered by them into those which needed to be visited daily (=6 stroke admissions per week); those which needed to be visited twice a week (3 to 5 stroke admissions per week), and those which could be visited once a week or on call (=2 stroke admissions per week). Two research assistants and a medical social worker once a week contacted each general practitioner in the urban and rural study areas and the hospitals bordering them to gather information about possible cases of stroke. Three brain imaging centers in the urban study area were accessed weekly as a supplementary search strategy. In addition, patients attending the physiotherapy and rehabilitation facilities at the Trivandrum Medical and Ayurveda Colleges were also monitored to ascertain incident stroke cases. One of the neurologists (K.R., P.N.S., or S.D.N.) accompanied the research assistants during their visits periodically to supervise data collection and to verify accuracy of the data collected. The study had the approval of the institutional review boards of all participating hospitals.

To ascertain fatal stroke events, we scrutinized the death registry maintained by the Trivandrum Corporation Office to which more than 95% of all deaths occurring in the community are registered. On scanning through the death registrations, we noticed that nearly 90% of the deaths reported were from the hospitals and 10% were domiciliary deaths. Whereas for deaths reported from the hospital, the cause of death was evident, for deaths occurring at homes, the cause was often obscure. We authorized the medical social worker (J.P.U.) to visit the houses of all unattended domiciliary deaths during the study period (excluding those attributable to accidents and suicides) to conduct verbal autopsies. The verification process continued until August 2006, when the data were considered suitable for analyses.

Verification Phase
We verified the residential status of each case, and ≥1 year residency in the study area was considered as eligibility for inclusion. At least 2 of the 3 study neurologists (K.R., P.N.S., S.D.N.) reviewed each case data to verify the diagnosis of stroke, and completeness and accuracy of the information collected, and to avoid duplication of cases collected through multiple sources. Problem CT scans were discussed with neuroradiologists. The death certificates were carefully scrutinized, and supporting evidence for a stroke death was obtained from hospital records. The medical social worker (J.P.U.) visited the houses of all unattended domiciliary deaths during the study period (excluding those attributable to accidents and suicides) to conduct verbal autopsies. The verification process continued until August 2006, when the data were considered suitable for analyses.

Statistical Methods
The 2001 Indian official census provided the population data. The incidence rates were adjusted by direct method using WHO World Standard Population, which has been constructed based on the projected average world population age-structure for the period 2000 to 2025. We calculated 95% confidence intervals (CI) of crude and adjusted incidence rates assuming a Poisson distribution for observed rates. To compare data from urban and rural populations, we used Student t test, Fisher exact test, and Pearson χ² test, as appropriate. A probability value of ≤0.05 was considered significant.

Results
Incidence Data
Of the 541 validated first-ever stroke events ascertained during the study period, 431 occurred in the urban community and 110 occurred in the rural community. Of them, 36 (8.4%) urban patients and 24 (21.8%) rural patients were ascertained by verbal autopsy. From the rural community, whereas 52 (47.3%) patients were ascertained from hospitals outside the survey area, 21 (19.1%) patients had seen only the general practitioner and were not hospitalized. Table 1 shows crude and age- and sex-specific and adjusted stroke incidence rates. The crude annual incidence per 100,000 for all strokes was 117 for the total population (115 for males and 119 for females), 116 for the urban population, and 119 for the rural population. The age-adjusted incidence rates per 100,000 per year were 135 (95% CI 123 to 146) for total, 143 (125–160) for male and 128 (113–143) for female, and 135 (122–148) for urban and 138 (112–164) for rural populations.

Age Distribution
The median age of stroke patients was 67 years, which did not differ between urban and rural populations. Seventy-seven percent of patients were aged ≥60 years. Stroke in the young, defined as first stroke occurring at ≤40 years, comprised only 18 (3.8%) patients in this population-based study. The incidence rates increased steadily with age for both genders in urban and rural communities (Table 1).

mellitus, fasting plasma glucose ≥126 mg/dL or single value ≥200 mg/dL, previous diagnosis and treatment; smoking, current use of inhaled tobacco; and hypercholesterolemia, previous diagnosis, receiving lipid lowering drugs, or total cholesterol ≥240 mg/dL or low density lipoprotein ≥160 mg/dL. In this part of India, tobacco smoking among females is nonexistent. Past history of TIA and ischemic heart disease could not be reliably obtained. Disability status at 28th day was measured using Modified Rankin Scale obtained either by telephonic interview, or hospital or home visits by the medical social worker.
Stroke Types

CT brain was available in 344 (63.6%) and MRI in 33 patients (6.1%). We could categorize strokes into IS, ICH, and SAH in 372 (68.8%) patients, which were diagnosed in 83.6%, 11.6%, and 4.8%, respectively. The distribution of these stroke types did not differ between the urban and rural populations (Table 2). Stroke undetermined type was more in the rural population (rural 43.6% versus urban 28.1%, \( P < 0.003 \)) related to less frequent availability of brain imaging (rural 56.4% versus urban 71.9%, \( P < 0.018 \)). The incidence rates according to stroke types are shown in Table 3. Age adjusted incidence rates for the total (urban plus rural) population per 100 000 per year for IS, ICH, and SAH were 74.8, 10.1, and 4.2, respectively.

Risk Factor Distribution

The distribution of conventional stroke risk factors was remarkably similar among the urban and rural communities (Table 2). Hypertension was the most frequent and occurred in 450 (83.2%) patients. Seventy of 261 male patients (26.8%) smoked tobacco, whereas none of the female patients smoked. Compared to urban males, more rural males smoked tobacco (22.8% versus 39.3%, \( P < 0.013 \)). Half of the patients had diabetes mellitus and 26% had dyslipidemia. None of the risk factors was seen in only 28 (5%) patients. One risk factor was present 208 (38.4%) patients, two in 227 (42.0%), and three or more in 78 (14.4%) patients.

Patient Outcomes

Mortality

One hundred forty-seven patients did not survive beyond the 28th poststroke day - fatality rate 27.2% (24.5% for urban and 37.1% for rural population, \( P < 0.011 \); Table 2). One hundred six (72.1%) of these deaths occurred within 10 days of stroke onset.

Disability

For the 394 patients, who survived beyond the 28th day of stroke onset, functional outcome was available in 342 (86.8%) patients. Mild disability (Rankin score \( \leq 2 \)) was observed in 145 (42.4%) of them. Whereas 50 (14.6%) patients were bedridden (Rankin score 5), 147 (43%) were moderately disabled (Rankin score 3 or 4; Table 2). There was no significant difference in the functional outcome between males and females (\( P = 0.179 \)), between urban and rural patients (\( P = 0.515 \)), or across different age groups (\( P = 0.526 \)).

Table 1. Incidence Rates of Stroke per 100 000 Inhabitants per Year in Trivandrum, Kerala, India

<table>
<thead>
<tr>
<th>Age-Group (yr)</th>
<th>Urban Community</th>
<th>Rural Community</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>Population</td>
<td>Cases</td>
<td>Rate</td>
</tr>
<tr>
<td>&lt;15</td>
<td>94769</td>
<td>0</td>
</tr>
<tr>
<td>15–24</td>
<td>67205</td>
<td>1.32</td>
</tr>
<tr>
<td>25–34</td>
<td>60552</td>
<td>1.35</td>
</tr>
<tr>
<td>35–44</td>
<td>52015</td>
<td>2.88</td>
</tr>
<tr>
<td>45–54</td>
<td>41996</td>
<td>2.22</td>
</tr>
<tr>
<td>55–64</td>
<td>24737</td>
<td>4.55</td>
</tr>
<tr>
<td>65–74</td>
<td>15430</td>
<td>0.76</td>
</tr>
<tr>
<td>≥75</td>
<td>7001</td>
<td>0.48</td>
</tr>
<tr>
<td>All ages</td>
<td>363704</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Age adjusted rates (95% CI)

- IS indicates ischemic stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; NS, not significant, n, No. of patients.
Furthermore, there are marked differences between stroke and accessibility to medical care and imaging facilities. Factors) or apparent (attributable to differences in availability differences in genetic susceptibility and exposure to risk indices of stroke around the world can be real (related to death certificate diagnosis). We believe that the Trivandrum Stroke Registry to a great extent overcame these hurdles by the following means. First, we ascertained incident strokes from both urban and rural populations in a geographical region with well-developed primary and secondary medical care facilities. Second, in addition to intensive surveillance of all hospitals where stroke patients are likely to be admitted, we contacted medical practitioners, and brain imaging centers and physiotherapy facilities in the study area to ascertain nonhospitalized stroke events. It has been shown that these supplementary methods can lead to near-complete case ascertainment. Compared to other developing regions, chance of a patient from the highly literature and health conscious Kerala population, with stroke related symptoms lasting beyond 24 hours, not to seek medical consultation is very unlikely. Third, in the geographical region where nearly all deaths in the community get registered, through verbal autopsy, we could verify stroke related deaths in instances where death certificate diagnosis was uncertain. Fourth, at least 2 experienced neurologists reviewed the clinical and imaging data to achieve diagnostic accuracy of stroke and its type. All 3 incidence studies on stroke from India were undertaken in relatively small populations from northeastern part of the country. The methodology of 6-month house-to-house surveys used in 2 of these studies was more suited for prevalence estimation of stroke rather than incidence, and data were not presented in mid-decade age bands. Furthermore, only 10% of death certificates were available for investigators’ review in the most recently reported survey from the city of Kolkata, West Bengal.

The wide geographical variation in the epidemiological indices of stroke around the world can be real (related to differences in genetic susceptibility and exposure to risk factors) or apparent (attributable to differences in availability and accessibility to medical care and imaging facilities). Furthermore, there are marked differences between stroke epidemiological studies in definition of stroke, size of population surveyed, methods of case ascertainment, and quality of data ascertained and reported. Feigin et al reviewed 15 population-based incidence studies on stroke (hereafter called Feigin review) from 13 countries that more or less met the requirements of ideal epidemiological studies such as well-defined population denominator, diagnostic accuracy, and nearly complete case ascertainment. In Feigin review, age-standardized annual incidence of all types of stroke per 1000 population aged ≥55 years ranged from 4.2 to 6.5, and age-specific incidence of stroke increased progressively with each decade of life approaching rates of 12.0 to 20.0 for those aged 75 to 84 years. In Trivandrum, stroke occurred at rate of 7.1 per 1000 per year in people ≥55 years, and the rate escalated to 13.3 for the ≥75 years age-group. The mean age at stroke onset at Trivandrum of 65 years males and 67 years females is within the ranges of 60.8 to 75.3 years for males and 66.6 to 78.0 years for females cited in the Feigin review. Similarly, the frequency of IS, ICH, and SAH in Trivandrum of 83.6%, 11.6%, and 4.8%, respectively, are more or less within the ranges of 67.3% to 80.5%, 6.5% to 19.6%, and 0.8% to 7.0%, respectively, reported in Feigin review. Stroke undefined type (no brain imaging) was 31.2% in Trivandrum study compared to 2.0% to 14.5% in Feigin review. The case fatality of total strokes in Trivandrum of 27.2% did not vary beyond the range of 17% to 33% noted in Feigin review. Despite differences in methods of data collection, the 3 previous stroke incidence studies from eastern India have shown results more or less in agreement with ours. Nearly 60% of our patients were significantly disabled (Rankin score ≥3) 1 month poststroke, which is very similar to the outcome of patients from the Polish National Stroke Registry. Our inability to find more disability among older patients may be related to relatively small number of very old patients.

It is believed that the average age of patients with stroke in developing countries is 15 years younger than that in developed countries. In India, nearly one-fifth of patients with first ever strokes admitted to hospitals are aged ≤40 years. In a recent hospital-based study of stroke from sub-Saharan Africa, the mean age of patients was 58 years. High prevalence of stroke risk factors leading onto premature atherosclerosis, unreliability of hospital statistics in estimating the age distribution of stroke occurrences in the commu-

### Table 3. Incidence Rates per 100 000 per Year According to Stroke Type in Trivandrum, Kerala, India

<table>
<thead>
<tr>
<th>Age-Group (yr)</th>
<th>IS Cases</th>
<th>Rate 95% CI</th>
<th>ICH Cases</th>
<th>Rate 95% CI</th>
<th>SAH Cases</th>
<th>Rate 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤44</td>
<td>13</td>
<td>3.7 2.6–5.3</td>
<td>3</td>
<td>0.9 0.4–1.7</td>
<td>2</td>
<td>0.6 0.2–1.3</td>
</tr>
<tr>
<td>45–54</td>
<td>32</td>
<td>65.4 51.3–82.3</td>
<td>7</td>
<td>14.3 8.6–22.7</td>
<td>2</td>
<td>4.1 1.7–9.0</td>
</tr>
<tr>
<td>55–64</td>
<td>69</td>
<td>219.3 185.7–257.4</td>
<td>4</td>
<td>12.7 6.5–22.9</td>
<td>5</td>
<td>15.9 8.7–27.2</td>
</tr>
<tr>
<td>65–74</td>
<td>115</td>
<td>521.5 458.4–591.0</td>
<td>11</td>
<td>49.9 33.1–72.8</td>
<td>4</td>
<td>18.1 9.3–32.7</td>
</tr>
<tr>
<td>≥75</td>
<td>72</td>
<td>627.9 533.5–734.5</td>
<td>15</td>
<td>130.8 91.8–181.6</td>
<td>4</td>
<td>34.9 17.9–62.9</td>
</tr>
<tr>
<td>Total</td>
<td>301</td>
<td>65.0 59.8–70.2</td>
<td>40</td>
<td>8.6 6.8–10.5</td>
<td>17</td>
<td>3.7 2.4–4.9</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>74.8</td>
<td>66.3 63.2</td>
<td>10.1</td>
<td>7.0–13.2</td>
<td>4.2</td>
<td>2.2–6.1</td>
</tr>
</tbody>
</table>

IS indicates ischemic stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; CI, confidence interval.
nity, and population structure with smaller proportion of people ≥60 years have been implicated as reasons for the increased occurrence of stroke in the young in developing countries. In the Trivandrum Stroke Registry, only 3.8% of incident strokes occurred in people aged ≤40 years, 9.5% aged ≤50 years, and 18.1% aged ≤55 years; these data are very similar to that in another community-based study from northeastern India and those from developed countries. The reported occurrence of stroke in the young in developed countries, therefore, appears to be largely an artifact related to hospital-based case ascertaining.

It has been estimated that hypertension causes 54% of stroke mortality in low-income and middle-income countries, followed by high cholesterol (15%) and tobacco smoking (12%). Among our community-based stroke patients, nearly 85% had hypertension, half had diabetes mellitus, a quarter had dyslipidemia, and one-fifth of males smoked tobacco. Because we inquired only about current smoking, we could have underestimated the real contribution of this risk factor. In a case–control study from the same geographical region, compared to community-based controls, young stroke subjects were 8 times more likely to have had smoked tobacco. Only 5% of Trivandrum Stroke Registry patients did not have any modifiable risk factors, whereas more than half of them had two or more risk factors. Therefore, in the absence of reliable data on prevalence of above risk factors in the Trivandrum population, we are neither able to calculate the attributable risks nor able to comment on the causal role of these risk factors in our patient population.

Very few studies on stroke have focused on the urban-rural dichotomy. It is uncertain as to whether the urban-rural differences in the epidemiological indices of stroke observed in these studies are real or could be explained by the dissimilarities in the quality of the data, which are more difficult to obtain reliably in a rural setting compared to an urban setting. Studies from India on cardiovascular risk factors have shown a 2 to 3 times high prevalence of hypertension, hyperlipidemia, obesity, diabetes mellitus, and smoking (in males) in urban compared to rural communities. Because of the demographic transition occurring in majority of developing countries in recent years, the urban-rural difference in the risk factor distribution is fast disappearing. In Trivandrum, more rural males with stroke smoked tobacco. There were more strokes undetermined type in the rural community because of a lack of availability of imaging information. The stroke incidence did not differ between urban and rural communities. Significantly more of our rural patients compared to urban died within 1 month, probably reflecting inadequate facilities in the rural area to manage them during the early poststroke period.

We acknowledge the following limitations of our study. First, with the research fund allocated for this feasibility study, intensive surveillance was possible only for a 6-month period. We could not account for any seasonal variation in incidence of stroke, as our study did not run for a complete 1-year period. Second, patients with trivial strokes, particularly in the rural area, might not have been ascertained through any of the facilities we utilized. Third, to ensure a uniform data collection, we ascertained only selected consistently ascertaining risk factors and could not obtain reliable information on some of the important ones like ischemic and valvular heart diseases. Fourth, our incidence rates for the stroke types are likely to be underestimates because of the fact that one-third of patients had no brain imaging. Moreover, our inability to show any difference in the incidence rates of ICH and SAH between the urban and rural communities may be attributable to the small number of patients with these stroke types. Fifth, the questionnaire we used for verbal autopsy remains to be validated. Sixth, we used the 2001 census data to calculate stroke incidence rates in 2005. Because of very successful implementation of family planning measures, Kerala has achieved a near zero population growth in recent years. Therefore, it is unlikely that trivial change in the Kerala population demographics during the brief period of 2001 to 2005 would have affected our results. Last, as India is a vast country with marked socioeconomic diversity, our results cannot be extrapolated to other parts of the country, maybe not even to other southern regions. However, despite these limitations, as elaborated in the second paragraph of discussion, our incidence and mortality indices are in agreement with those from ideal stroke epidemiological studies from developed countries analyzed in Feigin review. The multi-center longitudinal population-based national stroke registry, which the Indian Council of Medical Research is planning to establish, may address the above listed deficiencies of the present study.

Conclusions
This epidemiological study illustrates that there are more similarities than differences between developing and developed countries in incidence, age distribution, types, mortality, and morbidity of stroke. We could not substantiate the usually held notion that stroke occurs more in the younger age group in low-income counties. Compared to urban stroke patients, rural ones were less likely to be optimally investigated and treated. Nearly 90% of stroke victims had one or more modifiable risk factors. The necessity for educating the people and health care professionals about implementing effective stroke preventive strategies cannot be overemphasized. The information that nearly two-thirds of stroke survivors were significantly disabled at 1 month after stroke demands better care during acute stage to minimize disability and long-term strategies to rehabilitate the disabled.

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Disclosures
None.

References
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