Risk Factors for Early Death in Acute Ischemic Stroke and Intracerebral Hemorrhage
A Prospective Hospital-Based Study in Asia

K.S. Wong, MD, for the Asian Acute Stroke Advisory Panel

Background and Purpose—In Asia, there has been no international study to investigate the risk factors for early death in patients with ischemic stroke and intracerebral hemorrhage.

Methods—We conducted a prospective study of consecutive patients with acute stroke who were admitted to 36 participating hospitals in China, India, Indonesia, Korea, Malaysia, the Philippines, Singapore, Taiwan, Thailand, and Vietnam. With the use of a simple identical data sheet, we recorded the demographics and cardiovascular risk factors of each patient. Early death was defined as death on discharge from the acute hospital.

Results—We enrolled 2403 patients with ischemic stroke and 783 patients with intracerebral hemorrhage. Among patients with ischemic stroke, previous use of antiplatelet drugs (adjusted odds ratio [OR] 0.53; 95% confidence interval [CI] 0.30 to 0.95) and relatively young age group 56 to 75 years (OR 0.65; 95% CI 0.42 to 1.00) were protective factors; atrial fibrillation (OR 2.23; 95% CI 1.40 to 3.57), ischemic heart disease (OR 2.03; 95% CI 1.37 to 3.05), diabetes (OR 1.52; 95% CI 1.04 to 2.22), and ex-smoker status (OR 2.18; 95% CI 1.18 to 4.05) were risk factors for early death. Among patients with intracerebral hemorrhage, hypertension (OR 0.56; 95% CI 0.38 to 0.82) and young age group 56 to 75 years old (OR 0.55; 95% CI 0.34 to 0.87) were associated with lower death rate, whereas diabetes (OR 1.74; 95% CI 1.01 to 2.98) was a risk factor for early death.

Conclusions—In Asian patients with stroke, previous use of antiplatelet drugs nearly halved the risk of early death in patients with ischemic stroke, whereas atrial fibrillation, ischemic heart disease, diabetes, and ex-smoker status were risk factors for early death. Among patients with intracerebral hemorrhage, diabetes was associated with early death, whereas young age group and hypertension were associated with lower death rates, though no clear explanation for the hypertension association could be discerned from the data available. (Stroke. 1999;30:2326-2330.)

Key Words: antiplatelet agents ■ hypertension ■ intracerebral hemorrhage ■ mortality ■ risk factors ■ stroke, ischemic

Stroke is one of the leading causes of death in the world. In Asia, the problem of stroke has a particularly strong impact, not only because more than half of the world’s population lives in Asia, but stroke is the predominant vascular disease in many parts of Asia.1 In 1990 alone, the World Health Organization estimated that there were 2.1 million people who died of stroke in Asian.2 The burden of stroke is likely to increase substantially in the future because of the aging population. Apart from implementing effective stroke prevention programs, identification of factors associated with more severe stroke may help to ease the burden of this coming epidemic.

Despite the importance of stroke in Asia, there have been very few prospective international studies of stroke within this region. Stroke is a heterogeneous disease. Ischemic and hemorrhagic strokes are the 2 main types of stroke, with very different pathogenesis and outcome. Ideally, the risk factors for death in each type of stroke should be studied separately, but limited data are available. We sought to investigate the risk factors for early death in patients with ischemic stroke or intracerebral hemorrhage (ICH) by performing a prospective international hospital-based study of consecutive patients with acute stroke in Asia.

Subjects and Methods

The Asian Acute Stroke Advisory Panel consisted of a group of neurologists who were interested in the study of acute stroke in Asia. For 3 months in 1996 to 1997, each participating hospital enrolled consecutive patients with acute stroke who were admitted within 1 week of onset of symptoms. Participating hospitals were located in China, India, Indonesia, Korea, Malaysia, the Philippines, Taiwan, Thailand, Singapore, and Vietnam (Figure). The names of the participating hospitals and the collaborators are listed in the Appendix. To ensure quality data, the coordinators of each country were experts on stroke in their own countries, and most of the participating hospitals were affiliated with local medical schools. We defined acute stroke as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or...
longer or leading to death, with no apparent cause other than of vascular origin," according to the World Health Organization criteria. We used a standardized data sheet to record the demographic variables including country, race, sex, and age. History of hypertension, diabetes mellitus, stroke or transient ischemic attack, ischemic heart disease, valvular heart disease, and rheumatic heart disease were also noted. We defined hypertension as a previous record of at least 2 blood pressure readings of >160/90 or the requirement of regular intake of antihypertensive drug(s). We defined diabetes as having a fasting plasma glucose level of >7.8 mmol/L (140 mg/dL), or a random glucose level of >11.1 mmol/L (200 mg/dL), or the requirement of regular hypoglycemic drugs. Because in many Asian countries the primary health care and screening program for cardiovascular risk factors were not as advanced as in the developed countries, some patients with hypertension and diabetes were not diagnosed before stroke. Therefore patients who required regular use of antihypertensive agents and hypoglycemic agents on discharge from the hospital (excluding the acute-phase changes) were also regarded as hypertensives and diabetics. Atrial fibrillation was defined by a positive history or the presence of atrial fibrillation on the ECG during hospital stay. History of ischemic heart diseases included previous known myocardial infarct and angina according to the patient’s medical record. History of cerebrovascular diseases included old stroke and transient ischemic attack. Patients were regarded as a nonsmoker if they never smoked, as an ex-smoker if they stopped smoking for >3 months, and as a current smoker if they still smoked within the last 3 months. Current regular uses of antiplatelet drugs or warfarin preceding the indexed stroke were also noted. Because aspirin constituted >99% of antiplatelet agents used in Asia (personal communications among members of our study groups), we decided not to register the names of other antiplatelet agents used in order to keep the data sheet simple. On discharge from acute hospitals, the length of stay and death were recorded. The discharge status, whether dead or alive, was used as the dependent variable for statistical analysis. Because a history of previous stroke could be a potential risk factor for early death and inclusion of recurrent stroke better reflected the true impact of stroke, patients with a history of stroke or transient ischemic attack were also included.3

Stroke types were classified into ischemic stroke, ICH, subarachnoid hemorrhage (SAH), and uncertain stroke type. Either computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain was required for the diagnosis of ischemic stroke and intracerebral and SAH. Patients without neuroimaging investigations were classified as having uncertain stroke type. Statistical analyses included only patients with neuroimaging that did not show SAH.

Statistical Analyses
Separated statistical analyses were performed for ischemic stroke and ICH. Univariate analysis was first performed with demographic characteristics and the risk factors of stroke by cross-tabulations with $\chi^2$ or Fisher’s exact tests for the unadjusted odds ratios (ORs). Then, a logistic multiple regression model was used4 because its

Results
We enrolled 3670 patients. The mean age was 62, and 2138 patients (58%) were male. The ethnic composition of the patients with stroke consisted of 1463 (40%) Chinese, 570 (16%) Koreans, 410 (11%) Indians, 353 (10%) Filipinos, 290 (8%) Indonesians, 240 (7%) Vietnamese, 234 (6%) Thais, 88 (2%) Malays, and 8 white subjects. Patient characteristics for type of stroke are summarized in Table 1. CT or MRI scans were performed in 93% of patients.

According to our classification, 2403 patients had ischemic stroke, 783 had ICH, 114 patients had SAH, and 370 had uncertain stroke type. Patients with SAH or uncertain stroke type were excluded from further analysis. Case fatality for ischemic stroke was 8.8% and for ICH, 29.8%. Death occurred after a mean of 12.9 days (median 6 days) after admission for ischemic stroke and 7.3 days (median 3 days) for ICH. The estimated ORs for early death obtained among patients with ICH and patients with ischemic stroke, together with the 95% CIs and probability values, are shown in Table 2. In summary, among patients with ischemic stroke, prior use of antiplatelet drugs before stroke (OR 0.53; 95% CI 0.30 to 0.95) and relatively younger age group 56 to 75 years (OR
TABLE 2. Risk Factors for Early Death Among Ischemic Stroke and ICH

<table>
<thead>
<tr>
<th></th>
<th>Ischemic Stroke (n=2403)</th>
<th></th>
<th>ICH (n=783)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted OR (95% CI)</td>
<td>P</td>
<td>Adjusted OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
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<tr>
<td>≥65</td>
<td>0.60 (0.30–0.92)†</td>
<td>0.02†</td>
<td>0.78 (0.46–1.34)</td>
<td>0.37</td>
</tr>
<tr>
<td>56–75</td>
<td>0.71 (0.50–1.00)†</td>
<td>0.06†</td>
<td>0.65 (0.42–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>≥76</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.82 (0.62–1.09)</td>
<td>0.17</td>
<td>0.72 (0.48–1.08)</td>
<td>0.11</td>
</tr>
<tr>
<td>Female</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.06 (0.79–1.43)</td>
<td>0.69</td>
<td>1.01 (0.69–1.49)</td>
<td>0.95</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.40 (1.04–1.90)</td>
<td>0.03</td>
<td>1.52 (1.04–2.22)</td>
<td>0.03</td>
</tr>
<tr>
<td>Smoking habit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1.98 (1.26–3.12)†</td>
<td>0.003†</td>
<td>2.18 (1.18–4.05)</td>
<td>0.01</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>1.05 (0.75–1.47)†</td>
<td>0.76†</td>
<td>1.29 (0.79–2.09)</td>
<td>0.30</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.41 (1.67–3.47)</td>
<td>&lt;0.000</td>
<td>2.23 (1.40–3.57)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>2.14 (1.56–2.93)</td>
<td>&lt;0.000</td>
<td>2.03 (1.37–3.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous cerebrovascular disease</td>
<td>0.79 (0.58–1.09)</td>
<td>0.15</td>
<td>1.08 (0.70–1.64)</td>
<td>0.74</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>2.20 (1.30–3.72)</td>
<td>0.003</td>
<td>1.72 (0.83–3.52)</td>
<td>0.14</td>
</tr>
<tr>
<td>Prosthetic heart disease</td>
<td>2.42 (0.92–6.38)</td>
<td>0.08*</td>
<td>0.43 (0.09–2.10)</td>
<td>0.30</td>
</tr>
<tr>
<td>Previous antiplatelet treatment</td>
<td>0.79 (0.49–1.27)</td>
<td>0.32</td>
<td>0.53 (0.30–0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous warfarin treatment</td>
<td>1.63 (0.80–3.33)</td>
<td>0.18</td>
<td>1.60 (0.60–4.21)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*By Fisher’s Exact test.
†By Fisher’s Exact test, with approximation of Woolf.
‡Prosthetic heart disease was excluded from the logistic multiple regression model in ICH because of the small number of cases.

Discussion

In general, the risk factors for early death after acute stroke in Asia mirror those in Europe and North America. For example, elderly and diabetic patients have a uniformly higher death rate regardless of the type of stroke in Asia. The detrimental effects of diabetes on the outcome of cerebrovascular disease are in accord with previous reports that diabetics have poorer outcome after stroke and coronary artery disease than nondiabetics.5–7 This observation may have important implications. For future estimation of the burden of stroke in elderly and diabetic patients, it would be important to take into account the excessive morbidity and mortality rates of these patients. The aging populations and the escalating number of diabetes in Asia add more significance to our observations.

In patients with ischemic stroke, our data show that atrial fibrillation and ischemic heart disease are independent risk factors for early death. Among different types of ischemic stroke, cardioembolic stroke tends to be more severe.8 In 2 population-based studies in Rochester and in Framingham, the ORs for stroke death were 1.7 and 2.0 for patients with atrial fibrillation.9,10 The magnitude of the hazard associated with atrial fibrillation is similar to our data, which show an OR of 2.23. The concurrence of our results with results from...
studies in other populations further strengthens the external validity of our study.

Our data also suggest that ex-smokers have a higher mortality rate compared with that of current smokers. We suspect that there are confounding variables such as malignancy and chronic lung diseases that might prompt patients to stop smoking. The presence of comorbidity may be the cause of the increased mortality rates. When we reclassify patients as "never-smoker" or "ever-smoker," there is no difference in mortality rates between these 2 groups (OR 0.97; 95% CI 0.64 to 1.48).

One important finding of this study was the observation that prior use of antiplatelet drugs, mainly aspirin, nearly halved the risk of early death among patients with ischemic stroke. The benefit of antiplatelet drugs in the secondary prevention of stroke and cardiovascular diseases is now firmly established. However, ischemic stroke may still occur in patients taking regular antiplatelet drugs. In this group of patients, it remains uncertain whether prophylactic use of aspirin reduces the severity of subsequent stroke. In other clinical situations in which acute arterial occlusion occurs, aspirin has been shown to abate the clinical manifestation. In cerebrovascular disease, Grotta and colleagues showed that patients who had a stroke while taking aspirin tended to have a less severe stroke. Recently, Karepov and colleagues observed a 34% reduction in risk of early death among 2113 patients with ischemic stroke. Although the risk reduction of early death was not statistically significant in this study, only 125 (6%) patients were taking aspirin and thus the interpretation might be subject to a type 2 error. In our AASAP Stroke Registry, 347 (14%) patients were taking aspirin. With improved statistical power, our data confirmed the protective effect of aspirin in reducing the risk of early death. Another important difference was that in Karepov and colleagues' study, only 78% of patients had CT scans done. Patients with ICH could have been included in the analysis, probably diluting the benefit of aspirin. In contrast, our analysis only included those patients with neuroimaging examinations. The mechanism of the protective effects of aspirin is presumably related to its antiplatelet effect. Inhibited platelet aggregation may reduce thrombus formation and propagation, resulting in a smaller brain infarct. Moreover, there has been recent interest in the neuroprotective effects of aspirin on ischemic brain.

Although ischemic stroke outnumbered ICH by 3 to 1, there were more deaths in the patients with ICH (233 vs 211 deaths) because of the high death rate of ICH. Our data suggest that hypertension is associated with significantly lower mortality rates in patients with ICH. This finding is intriguing and has not been well documented in the literature. It is likely that nonhypertensive patients had other underlying causes such as amyloid angiopathy or occult angioma, which might be more severe and cause worse outcomes. This observation needs to be replicated in future studies, which should include more detailed information regarding the blood pressure levels, types of antihypertensive drugs taken, whether blood pressures were acutely lowered, and evidence of end-organ damage from long-standing hypertension. Because this study was the first of its kind in this region and with limited resources, we did not record these variables in our data sheet.

A post hoc subgroup analysis showed that patients in Thailand had significantly higher death rates, whereas patients in Korea and India had significantly lower death rates irrespective of the stroke type. These findings should be viewed with caution because the criteria for hospital admission were different in different countries. For example, the Siriraj Hospital in Thailand is a center of excellence for stroke and therefore might attract patients with more severe stroke from other parts of Bangkok. These differences, however, should not overshadow the similarity of death rates among China, Indonesia, Malaysia, the Philippines, Singapore, Taiwan, and Vietnam.

There are several limitations of this study. Because this was a hospital-based study, patients with mild stroke who did not report to a hospital may have been excluded. However, our findings of some of the well-known prognostic factors such as atrial fibrillation are similar to other population-based studies. There may also be differences in the admitting policies among different participating hospitals. In some hospitals, patients with ICH were admitted to the surgical wards. We tried to overcome this problem by attempting to include all patients with stroke in different departments that we were able to trace. Stroke registries, nevertheless, have contributed substantially toward our understanding of stroke. Other limitations included lack of detailed clinical information of individual patients. For the individual patient, the best predictors for early death relate to the size and location of cerebral hematoma or infarct. Depressed level of consciousness and severe neurological deficits are well-documented poor prognostic factors. These variables, however, merely reflect the effect of stroke and provide limited information on the stroke mechanism. Risk factors such as diabetes and atrial fibrillation may provide better insight into the underlying cause of stroke in individual patients.

The strength of this study is the prospective design, uniform data acquisition form, and the ability to collect a large number of patients within a short time. More importantly, >93% of patients with stroke had confirmatory CT or MRI scans. Thus we were able to limit the analysis to those patients with neuroimaging while retaining statistical power to identify important risk factors for early death among patients with hemorrhagic and ischemic strokes separately. Subsequently, the observed statistical associations are robust.

In summary, our data suggest that prophylactic use of antiplatelet drugs before stroke reduce the risk of early death in patients with ischemic stroke. This benefit complements the mounting evidence in support of the use of antiplatelet drugs for patients at high risk of ischemic stroke. Advancing age, diabetes, and atrial fibrillation are not only risk factors for stroke but are risk factors for more severe stroke. Among patients with ICH, young age group and hypertension were associated with lower death rates, though no clear explanation for the hypertension association could be discerned from the data available. More importantly, our study shows that it is feasible to conduct a multicenter study on stroke in Asia with very limited resources. This may lay the foundation for further collaborative study of stroke in this region.
Appendix

Asian Acute Stroke Advisory Panel Members


Statisticians

J. Lau, LY Xu, A. Tang (The Chinese University of Hong Kong).

Participating Hospitals and Collaborators

China (817 Patients)

Prince of Wales Hospital, Hong Kong (K.S. Wong, W.W.M. Lam, A. Wong, R. Kay); Queen Elizabeth Hospital, Hong Kong (C.K. Wong, B. Yuen, P. Li); Pamela Youde Nethersole Eastern Hospital, Hong Kong (T.H. Tsoi, C.M. Cheung); Peking Union Medical College Hospital, Beijing (Y.N. Huang, S. Gao).

Korea (570 Patients)

Seoul National University Hospital, Seoul (S.B. Lee, J.K. Roh, B.W. Yoon, Y.S. Lee); Kyung Hee University Hospital, Seoul (K.C. Chung, D.I. Chang); Inha University Hospital, Incheon City (J.H. Rha); Chonbuk National University Hospital, Cheongju (Y.H. Kim, M.W. Seo); Seoul Borame City Hospital, Seoul (S.H. Park); Gyeongsang National University Hospital, Chinju (B.H. Lim); Dong-A University Hospital, Pusan (J.W. Kim); Dankook University Hospital, Cheonan (J.I. Kim); Chungbuk National University Hospital, Cheongju (S.H. Han); Eulji General Hospital, Seoul (B.A. Wie).

Taiwan (404 Patients)

National Taiwan University Hospital, Taipei (J.S. Jeng, P.K. Yip, T.K. Lee, Y.C. Chang, Z.S. Huang, S.K. Ng, R.C. Chen); Shin-Kong Wu Ho-Su Memorial Hospital, Taipei (H.C. Chiu, W.C. Hsu).

India (365 Patients)

Bhavnagar Hospital, Bhavnagar (A. Tipnis); Belle Vue Clinic, Calcutta (S.S. Nandi); Gauhati Medical College, Gauhati (A. Mahanta); Vijaya Health Center, Madras (D. Arjundas); Willingdon Hospital, Madras (G. Arjundas); Bombay Hospital, Mumbai (B.S. Singhal); Baheti Hospital, Nagpur (M. Baheti); Baroda Hospital, Vadodara (K.R. Buch); Mayo Hospital/Vadodara Hospital, Vadodara (C. Trivedi).

The Philippines (359 Patients)

Jose R. Reyes Memorial Medical Center, Manila (S. Marasigan, H. Gan); University of Santo Tomas, Manila (G. Gamez, J. Poblete, J. Navarro, B. Conde, R. Javier, I. David, R. Luzzo, E. Ong); Philippines General Hospital, Manila (E. Bitangda, F.E. Bacsal, R.M. Canlas, C. Chua, M. Dantes, M. Gose, P. Ramiro, J. Gutierrez, R. Libarnes, L. Lim, M. Perez, A. Roxas, M.G. Yusay, D. Lardizabal).

Indonesia (299 Patients)

Dr Ciptomangunkusumo, Jakarta (J. Misbach, W. Ali); RS Islam, Jakarta (J. Misbach, Syahrul).

Vietnam (242 Patients)

Bach Mai Hospital, Hanoi (L.D. Hinh, L.V. Tinh, P.H. Minh, D.B. Hou).

Thailand (237 Patients)

Siriraj Hospital, Bangkok (N. Poungvarin, V. Senanarong, R. Chaisevikul, N. Prayoonwivat).

Singapore (190 Patients)


Malaysia (187 Patients)

University Hospital, Kuala Lumpur (W.K. Ng); Pakar Perunding Perubatan, Hospital, Kelang (S.K. Chua, M.R. Usuh).

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References


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