

Asia Medical Forum, first in China



At yesterday's opening of the The Lancet Asia Medical Forum on Stroke, the first such Forum to be held in China, Dr Bill Summerskill, executive editor at *The Lancet*, said that he had great expectations for the future control, research and treatment of stroke in Asia. Describing the journal's commitment to Asia he said "during this year, *The Lancet* has published papers from 13 countries in the region, the quality and richness of these making *The Lancet*, the influential journal it is today". This year, *The Lancet* is publishing a series on Health System Reform in China, with plans for similar series focusing on other Asian countries in the near future. Dr Summerskill closed with a recent quote from the journal: "China has the opportunity to lead the world not only in research quantity, but also in quality".



The Forum has attracted in excess of 2000 delegates with most Asia-Pacific countries represented, including China, Hong Kong, Korea, Malaysia, Brunei, Thailand, Indonesia, India, Pakistan, Sri Lanka, Japan, Australia, and New Zealand. ■

Cost-effective interventions needed for global stroke prevention

by Yuzhou Guan

Tobacco control and salt reduction, two conventional population-based interventions, together with a multidrug regimen that uses off-patent drugs, are the most effective measures for global stroke prevention, according to Dr Ruth Bonita, from University of Auckland, New Zealand.



Dr Ruth Bonita

One in ten deaths worldwide is due to stroke, and the number of deaths from stroke each year will rise to 6.7 million by 2015 if no action is taken. In low-income and middle-income countries, four out of five deaths are due to stroke, and the cost of managing the consequences of stroke are least affordable. To prevent stroke, cost-effective and feasible interventions are available and needed to integrate with chronic disease prevention at a population-wide level and reducing risk in individuals. WHO's Global Goal for chronic diseases assumes an additional 2% annual reduction in chronic disease death rates worldwide, including stroke, over the next 10 years. Achieving this goal would avert or delay 36 million deaths over 10 years, including almost 6 million stroke deaths.

In an effort to meet this goal, Dr Bonita and her group approached three cost-effective interventions in 23 high burden countries, including two population-wide interventions (tobacco control and salt reduction), plus a clinical intervention (multidrug regime), and these methods proved to be highly effective and resulted in large economic savings. In the 23 countries involved, 32 million deaths (4.2 million stroke deaths) would be averted by 2015, exceeding the global goal. The project would only cost 1.5 USD per person and USD 5.8 billion per year. Applying these three interventions in just nine Asian countries (Bangladesh, China, India, Indonesia, Myanmar, Pakistan, Philippines, Thailand and Vietnam) would achieve half of the Global Goal, and total stroke deaths averted over 10 years would be 2.9 million by 2015.

Dr Bonita suggested a better balance between prevention (health promotion and public health approaches for the whole population) and clinical treatment (for individuals at high risk of disease) needs to be achieved. She listed tobacco control, salt reduction, and clinical intervention-treatment by off-patent drugs in populations with high risk factors including age, sex, smoking, systolic blood pressure and body mass index and previous history of CVD and other CVD risks. All risk factors should be balanced overall rather than focusing on the dominant risk, hypertension. The threshold of high blood pressure should be based on social values and available resources because patients in poor areas (Asia-Pacific countries) would rarely be willing to pay for the treatment of hypertension.

Dr Bonita mentioned that global stroke prevention will require a shift in thinking from the needs of people in high-income countries to the challenges of stroke in low- and middle-income countries. To achieve this goal, greater emphasis should be put on public health approaches and promotion of affordable drugs. ■

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A long way to go for stroke in Asia

by Yi Ma

“It’s time for us to start the journey and we have no time to wait”, said Yangfeng Wu, Professor of Epidemiology at the Peking University School of Public Health. “Firstly, risk factor profiles of stroke and the change in the profiles caused by socioeconomic development and lifestyle changes still remain largely unclear; secondly, the trends in major risk factors in developing countries like China and India are undoubtedly increasing” he said. Declining trends in incidence and mortality of stroke seen in many developed countries are not expected in China and other Asian countries (excluding Japan) in the near future.

According to the WHO World Health Statistics 2008, stroke is the second most common cause of death worldwide. The situation has improved in developed countries - Professor Wu quoted statistics from the UK that show the stroke mortality rate has decreased by more than 60% from 1979 to 2003 in 30-69-year-olds.

While stroke is still the single leading cause of death in China and many other Asian countries, a China MUCA study showed that from 1991 to 1999, there was almost no significant change in the trends of incidence of stroke in China.

“The changes in incidence and mortality of stroke between countries and between subtypes of stroke show a very diverse pattern in Asian countries,” he said. For example, data from Japan indicate an early decline in stroke mortality in Asia, whereas data for some other Asian countries suggest stable or increasing stroke mortality. Ischemic stroke is declining for the most part, yet intracranial cerebral stroke seems to be unchanged or even increased.

In China, different trends exist within different cities. “This may be due to the differences in risk factor profiles and the change of the profiles caused by socioeconomic development and lifestyle changes,” said Professor Wu.

Factors, like the CT scan rate increase from 50% in 1991 to 90% in 2000 may explain the trends in the proportion of different subtypes of stroke in China, for example, the decrease of undetermined stroke. But convincing explanations for the changes still remain largely unclear.

Professor Wu did not express optimism in the future, with the undoubted increasing trends in major risk factors in China, such as hypertension, hypercholesterolemia, diabetes, overweight and obesity, and the consistently high smoking rate in men. ■

Salt consumption and cardiovascular disease

by Larry Huang

High blood pressure is the major cause of stroke in China and the Asia-Pacific region, and the simplest approach to lower blood pressure (BP) is to reduce the dietary consumption of salt, according to Dr Rachel Huxley, Director of Nutrition and Lifestyle Division at the University of Sydney. This offers a low cost strategy for the prevention of stroke and other cardiovascular diseases.

“There is very good evidence in the past 30 years that the amount of salt we eat correlates very well with blood pressure. The higher the salt we take, the more likely we will develop high blood pressure,” she said.

Although substantial amounts of observational data supporting an association between reduced salt intake and lower BP exist, there is no large randomized trial to show the long-term effects of salt on cardiovascular disease outcomes to reach clear conclusions.

To reduce salt, there remain some obstacles, for example, dietary cations are hard for individuals to modify and there are commercial disincentives to change. She thinks a salt substitute might be appropriate to reduce consumption.

Dr Huxley described a pilot study in China, which demonstrated that among 600 individuals receiving a salt substitute in rural northern China, blood pressure lowering was impressive, with a maximum reduction of blood pressure of 5.4 mmHg at 12 months. The low-sodium, high-potassium salt substitute could reduce blood pressure to about the same extent as single drug therapy.

To further explore the relationship between salt consumption and CVD events, she designed the China Salt Reduction Trial, which plans to have 10,000 participants at high risk of CVD. The intervention will be a reduced-sodium, high-potassium salt substitute. Persons included will be randomized to a salt group and a salt substitute group. Follow-up is expected to be 3.5 years, after which she hopes there will be a substantial reduction in death, heart attack and stroke.

The salt substitute will provide an immediate, short-term CVD benefit in China and elsewhere where discretionary use of salt is high. Moreover, findings will provide definitive evidence that reducing dietary salt intake will substantially reduce CVD morbidity and mortality. ■

Stroke in Chinese women

by Yi Ma

Women have a relatively lower risk of stroke compared to men, due to a better risk profile, according to a speaker at the 10th International Symposium on Hypertension and Related Diseases. However, in women, female sex hormone does not appear to offer protection from stroke, unlike that demonstrated with ischemic heart disease.

Dr Xinhua Zhang (Department of Community and Family Medicine, Chinese University of Hong Kong) described how her team used individual participant data from cohort studies from populations in China to estimate the effect of major risk factors on stroke for women of different socioeconomic status. In total, more than one million person-years of follow-up and seven hundred stroke events were included in the analysis.

“Effects of common risk factors on the risk of stroke in the Chinese population include smoking, blood pressure, cholesterol and

other socioeconomic factors such as education, urban or rural living, manufacturing industry employees,” said Dr Zhang.

They found that women have a lower risk to develop stroke mainly due to a better risk profile.

After controlling for age, smoking and level of education, and stratifying by study centers, baseline systolic blood pressure (SBP) was significantly associated with the risk of total stroke, ischemic stroke and hemorrhagic stroke.

“The effect of elevated SBP on the risk of stroke is especially greater in the underprivileged female population” Dr Zhang said. The effect of smoking, whether active or passive, on the risk of stroke is much greater in women than in men.

Dr Zhang concluded that effective prevention of smoking and hypertension could produce a greater benefit in economically disadvantaged populations, especially in women. ■

Comprehensive interventions essential for fighting the stroke epidemic

by Larry Huang

Comprehensive interventions, including intensive prevention, regular education and health promotion activities focusing on blood pressure control in the hypertension population could dramatically reduce the incidence and mortality of stroke in China, according to the results of studies presented yesterday morning by Professor Wenzhi Wang (Beijing Neurosurgical Institute).

Professor Wang reviewed the current situation of stroke prevention in China. In contrast to western countries, the mortality of stroke is twice as high as coronary heart disease (CHD) in China, based on 1990 WHO statistics. The distribution of stroke has a distinct geographic variation. Mortality and morbidity of stroke in northern China are significantly higher than in the southern part.

He went on to introduce a large scale community-based intervention study from 1991 to 2000 in China where two natural populations were divided into an intervention group and control group. The intervention group reached a much higher knowledge and

practice (KAP) level than the control group. The morbidity and mortality of stroke decreased by 21.6% and 33.2% in the intervention group compared with 6.2% and 24.8% in the control group from 1992 to 1995. The same trend and pattern continued between 1996 and 2000. Another major finding was that, among patients with hypertension who also received follow-up between 1993 and 1995, the blood pressure control rate increased from 22.5% to 48.3%. The study demonstrates that multiple community-based interventions can play an important role in reducing stroke morbidity and mortality.

Professor Wang suggested that primary care should be the main force in stroke prevention. Today, large hospitals in China are overcrowded, and primary care appears oblivious to CVD prevention. However, it is the very lack of primary care that limits the improvement of diagnosis and treatment as a whole. He concluded that the best strategy to fight CVD is for neurologists and primary doctors to build a network to optimize medical resources. ■

Lancet Asia Medical Forum Poster Report

This year's Lancet Asia Medical Forum has attracted poster submissions from across the region. A selection of the submissions are summarized below. The posters can be viewed near the refreshment area outside Hall 1 on Level 2 of the Convention Center. The poster award ceremony will take place today at 13:30 in Ballroom 1.

ISS/WHO stroke survey in Mumbai, India

In order to plan stroke intervention and prevention programs, the International Stroke Society (ISS) and WHO have initiated a series of prospective population-based stroke surveys, including the community-based stroke registry for patients having first ever stroke (FES) conducted in Mumbai, India, by Dr Praful Dalal and colleagues at the LKMM Trust Research Centre at Lilavati Hospital in Mumbai.

The researchers collected data on annual incidence, stroke subtypes, and 28-day case fatality using the WHO STEP-wise approach to stroke surveillance (Version 2) as operating protocol to screen over 150,000 eligible persons aged ≥ 25 years.

Of 521 new cases of stroke, 456 had FES, or an annual incidence of 145 per 100,000 population and an annual age-standardized rate of 152 FES/100,000. At the time of stroke, women were older than men at 68.9 versus 63.4 years, with stroke diagnosis being supported by computed tomography in 89% (407/456) of FES cases, of which 366 (80.2%) were ischemic stroke, 81 (17.7%) hemorrhagic, and nine (1.9%) were of an unspecified stroke category. Hypertension, defined as blood pressure (BP) $>140/90$ mmHg, was present in 378 (82.8%). By 28 days, 136/456 (29.8%) FES patients had died, 82 (17.9%) of which were stroke deaths, with 54 (11.8%) deaths related to comorbidity. Among 320 survivors, 38.5% had moderate to severe disability (modified Rankin score 3-5). These results are similar to those reported from China and other industrialized cities, the researchers note, adding that similar studies from other Indian regions will help in planning intervention and prevention strategies.

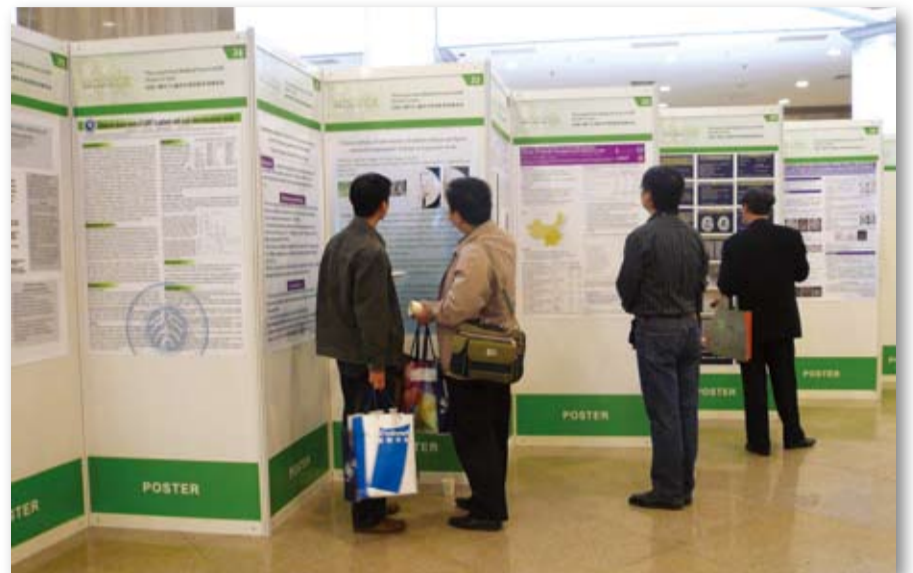


Determinants of post-stroke HRQoL in China

Determinants of health-related quality of life (HRQoL) after stroke in China, namely comorbid vascular disease, available money, disability level, and gender, are similar to those seen elsewhere, report the ChinaQUEST Investigators, who were led by Dr Candice Delcourt from the George Institute for International Health, Sydney, Australia.

Performed at 62 hospitals nationwide, the ChinaQUEST (Quality Evaluation of Stroke care and Treatment) Investigators used a China-specific 35-item questionnaire (QoL35) to assess determinants of HRQoL in patients surviving 12 months after stroke, with multivariate stepwise logistic regression used to develop a predictive model of low HRQoL, with proxy responses for those unable to complete QoL35.

Among 4,283 survivors assessed after 12 months, most (59.6%) were proxy responders, who were more likely to be female, have a lower income, be less educated manual workers, to have had severe stroke (Glasgow Coma Scale [GCS] < 8) at onset, and be dependent at discharge (modified Rankin scale ≥ 3). Baseline factors predicting low QoL35 scores in proxy responders included older age, living with others, lack of a high level of medical insurance, being dependent,



having diabetes, history of prior stroke or transient ischemic attack (TIA), and being disabled at discharge, with similar predictive factors seen in self-responders.

Health insurance role after acute stroke in China

Another team of ChinaQUEST Investigators studied the role of health insurance in averting the considerable economic hardship of families after acute stroke in China, where there are few data on the economic effects of stroke, despite it being a major health burden.

In a prospective nationwide 62-hospital registry study, the investigators, headed by the George Institute's Dr Emma Heeley, gathered data on demographics, clinical features, socioeconomic factors, management, and healthcare costs of acute stroke in China, where recent attempts to provide health insurance to relieve the potentially catastrophic economic burden of stroke in urban populations have had mixed success. Data on health expenditure were obtained for stroke survivors at 3 and 12 months of follow-up, with 'catastrophic' economic burden defined as $\geq 30\%$ of total household annual income.

Among 4,739 stroke survivors with 3 months of complete outcome data, mean healthcare costs were 16,525 yuan (US\$2,361), with out-of-pocket expenses a further 14,478 yuan (\$2,068). Overall, 71% experienced catastrophic out-of-pocket expenses, with those without health insurance being seven times more likely to experience catastrophic payments than those with insurance.

Because healthcare costs are high relative to income in China, the researchers conclude that families face considerable economic hardship after stroke. However, health insurance protects against such costs, highlighting the need to accelerate establishment of comprehensive health insurance schemes in both rural and urban areas.

MicroRNA markers of cerebral ischemic stroke

Researchers have identified several microRNAs in the peripheral blood of stroke patients that can be used as biomarkers in the diagnosis and prognosis of the disease, and differentiate between lacunar and large artery strokes.

MicroRNAs are 19- to 21-nucleotide non-coding RNAs that regulate gene expression, with both chronic and acute dysregulation being involved in the pathogenesis of several human diseases. Studies in animal models of stroke performed by Professor Kandiah Jeyaseelan and co-workers at the Department of Biochemistry, National University of Singapore, and the Departments of Medicine and Molecular Medicine, University of Malaya, Kuala Lumpur, have shown that blood microRNAs are temporally regulated during cerebral ischemic conditions and could serve as early biomarkers of the disease.

The researchers used microarrays to investigate microRNAs in the peripheral blood of stroke patients being followed at University Hospital, Malaysia. Patients with lacunar stroke had different patterns of microRNA expression than those with large artery stroke. In addition, the expression of microRNAs implicated in endothelial or vascular function, erythropoiesis, angiogenesis, and neural function differed from that seen in healthy controls. Several microRNAs involved in hypoxia, apoptosis and inflammation were also identified. ■

SPEAKERS IN FOCUS



Thrombolysis and the medical management of acute ischaemic stroke

Geoffrey A Donnan, National Stroke Research Institute, Melbourne, Australia

Intravenous thrombolysis is the most biologically effective intervention to improve outcome after acute stroke onset. With an absolute risk–benefit of 10–14% for little or no disability, and a number needed to treat of 7–10, the benefits of intravenous thrombolysis are significant. However, during the somewhat restrictive 3 hour therapeutic time window within which we work, there are some factors that could substantially improve clinical outcomes. Time to treatment is the most important factor affecting stroke outcome, with a direct association shown by meta-analyses of existing trials; clear benefits are seen up to 4.5 hours after stroke onset. There is some evidence that age greater than 80 years is associated with poor outcome, although this notion is far from conclusive. Similarly, patients in whom early ischaemic changes are present on CT are likely to have unfavourable outcomes. Those with internal carotid occlusion might also have worst functional outcomes.

It is unclear whether selection of patients on the basis of the presence of penumbra documented by either MR DWI/PWI mismatch or similar CT perfusion parameters within 3 hours is clinically useful. The possibility that the time window for thrombolysis may be extended beyond 3 hours is also being investigated.

These issues must all be placed within the context of which factors result in the greatest community improvements as a consequence of thrombolysis. Here, management of thrombolysis in the setting of a stroke unit, and perhaps the use of telemedicine to increase the number of patients able to receive therapy, are factors that could be even more important.



Antithrombotic therapy: rationale, evidence, and issues

Graeme J Hankey, Royal Perth Hospital, Perth, Australia

The rationale for antithrombotic therapy after ischaemic stroke is to reduce the otherwise high risk of subsequent atherothromboembolism and cardiac embolism.

The evidence from systematic reviews of randomised trials indicate that immediate treatment of acute ischaemic stroke with aspirin 300 mg daily, compared with controls, reduces the odds of recurrent stroke by 13% (95% CI 4–22%) and death and dependency by 5% (2–9%). Intravenous abciximab is more hazardous than helpful. The benefits of heparin for the prevention of recurrent ischaemic stroke are also offset by the risks of haemorrhagic stroke. However, the short term (3 months) use of clopidogrel and aspirin combined shows promise in patients with acute atherothromboembolic transient ischaemic attack and minor ischaemic stroke.

In the longer term, aspirin reduces the relative risk (RR) of atherothromboembolic ischaemic events by 13% (6–19%), ticlopidine reduces this risk by 23% (1–40%), and cilostazol by 39% (9–59%) compared with placebo. In comparison with aspirin, clopidogrel reduces the RR by 9% (0.3–16%), cilostazol reduces RR by 38% (-26 to 70%), and the combination of aspirin and dipyridamole by 18% (9–26%). Warfarin (hazard ratio 1.02; 95% CI 0.77–1.35), triflusal (1.02; 0.83–1.26), and the combination of clopidogrel and aspirin (RR 0.93; 0.83–1.05) are not more effective than aspirin. Clopidogrel and the combination of aspirin and dipyridamole share similar efficacy and safety (RR 1.01; 0.92–1.11) and are first-line drugs. Ongoing trials are comparing the safety and efficacy of terutroban (a platelet thromboxane receptor antagonist) with aspirin, and the effect of adding SCH530348 (an antagonist of the action of thrombin on the platelet protease activated receptor-1) to optimum ‘background’ antiplatelet therapy.

For long-term prevention of cardioembolic ischaemic events associated with atrial fibrillation, aspirin reduces the RR by 22% (6–35%) and warfarin reduces the RR by 64% (49–74%). The combination of clopidogrel and aspirin, and once weekly subcutaneous idraparin, are not as safe and effective as warfarin. Ongoing trials will determine whether parenteral factor Xa inhibitors (subcutaneous biotinylated idraparin), oral factor Xa inhibitors (rivaroxaban, apixaban), and oral direct thrombin inhibitors (dabigatran) are safe and non-inferior to warfarin.

Current challenges are to externally validate some of the above evidence among Asian populations, translate the evidence into practice, and keep to a minimum the risk of haemorrhagic complications of antithrombotic therapy. Genetic factors, such as polymorphisms of apolipoprotein E ($\epsilon 2$ or $\epsilon 4$ alleles), P450 cytochrome CYP2C9, and vitamin K epoxide reductase complex 1 (VKORC1), might identify some patients who are sensitive to bleeding complications.

Welcome Gala Dinner



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