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## Referral Bias May Underestimate Number of Very Elderly Patients Eligible for rtPA

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# Letters to the Editor

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## Has Stroke Shifted From Hemorrhagic to Ischemic in China?

To the Editor:

In China, which has the largest population and greatest number of stroke victims in the world, data concerning stroke epidemiology are very limited. Guidelines of stroke prevention and management designed for Chinese were tailored, to a considerable degree, according to the epidemiological, etiological and clinical profiles mirrored from western populations. The higher morbidity and mortality of stroke in Chinese further bulks the need of nationwide epidemiological data for establishing population specialized strategies for stroke prevention and management.

We read with great interest the study by Jiang et al concerning the stroke incidence and trends in 3 large cities in China.<sup>1</sup> It was shown that incidence of intracranial hemorrhage (ICH) decreased significantly at an annual rate of 12.0% in Beijing, 4.4% in Shanghai, and 7.7% in Changsha; at the time, incidence of ischemic stroke (IS) increased in Beijing (5.0% per year) and Shanghai (7.7%) during the 1990s. As reasoning this opposite trends of ischemic and hemorrhagic stroke, the authors wrote:

These (lifestyle) changes may have resulted in increased prevalence of obesity, hypertension, diabetes, and hypercholesterolemia in Chinese populations and may also help explain the increasing trend of IS as observed in this study. Uncontrolled hypertension and high prevalence of smoking might partially explain the hemorrhagic stroke predominance among Chinese in the past, and the increasing awareness of hypertension control and decrease in cigarette smoking may have contributed to its decrease in the past decade.

These explanations are ridiculous because it means hypertension and other risk factors were increasing when interpreting the trends of IS, while these risk factors were controlled and decreasing when interpreting the trends of ICH. Furthermore, well-designed large epidemiological studies indicated prevalence of cigarette smoking was increasing in the 1980s and 1990s,<sup>2</sup> and percentage of smokers contemplating quitting was low in China.<sup>3</sup> The incidence of hypertension and diabetes mellitus were also increased throughout the 1990s in China.<sup>4,5</sup> Under these circumstances, it is rather arbitrary to interpret the 12% annual decrease of ICH incidence detected in this study as a result of some underlying changes of risk factors in Chinese population.

On the other hand, the results that IS increased and ICH decreased during 1990s can be more reasonably explained by the misclassification of stroke patients, especially during the early days of this study when CT and MRI scans were less available. In the absence of neuroimaging results, IS may be misclassified as ICH and vice versa. This study did not provide substantive classification criteria applied at time of stroke onset. The Atherosclerosis Risk in Communities (ARIC) criteria for stroke diagnosis and classification used in this study were published many years after the initiation of the study.<sup>6</sup> In the ARIC study, the rate of cases with CT scan is higher (84%), and stroke patients were possibly classified as definite cerebral infarction or definite ICH only when autopsy results or CT/MRI scans were available. For stroke patients without neuroimaging or autopsy results, a probable classification was made. When a stroke case was equivocal, it was classified following the hierarchy of ICH, subarachnoid hemorrhage, embolic brain infarction and thrombotic brain infarction. This indicates that equivocal cases were more probably classified as ICH than as IS. This arbitrary

allocation will undoubtedly increase the possibility of IS being misclassified as ICH especially in patients without CT or MRI scans. Many patients who had been diagnosed in the early days of this study (eg, >50% of the patients diagnosed in 1991 in Shanghai) did not have a CT or MRI scan. For these patients ICH may be overdiagnosed.

In a large multicenter collaborative study which included Beijing and Shanghai as this study did, Zhang and colleagues showed proportion of clinically diagnosed<sup>7</sup> ICH in total stroke was increased gradually during the early years of the 1990s (which are contrary to the results of this study), a time when clinical application of CT and MRI was booming in mainland China. But when ratio of patients with CT scan reached a satisfying 85% after 1996, proportion of ICH kept considerably equivalent over years. These results indicate that inconsistency in stroke classification related to increasing use of CT/MRI scan may be a prominent obstruction in evaluating the temporal trends of strokes components.

This article provides valuable information of stroke incidence in urban China. However, because of significant design flaw and lack of valid criteria for stroke classification, the conclusion that the decreased ICH and increased IS was caused by underlying changes of risk factors in Chinese populations is misleading.

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## Response:

We thank Drs Xu and Liu for their interest in our recent publication on the stroke trends in 3 cities of China,<sup>1</sup> and we reply to clarify their questions about our stroke diagnostic criteria and classification in our study and provide some further information regarding our study that we could not include in the original report because of the space limitation. However, we believe what we observed in our study was real, and our inference of the shift from hemorrhage to ischemic stroke pattern in China was correctly drawn.

The criteria for stroke diagnosis and classification were similar to those used in the Atherosclerosis Risk in Communities (ARIC) Study, both of which were adapted from published criteria from the National Survey of Stroke.<sup>2</sup> Minor modifications were made to facilitate the field data collection in China. The major differences between the criteria used in these 2 studies,<sup>1,3</sup> other than languages, included: (1) "unilateral numbness of 2 or more body parts" was regarded as a major symptom in our study but a minor symptom in the ARIC study; (2) in the ARIC Study, a hierarchical case definition was used for the rare situation where the cases met criteria for 2 different diagnostic categories. In our study, we defined such cases as "undetermined", even for cases with CT/MRI information. Conversely, cases only with neuroimaging data without clinical symptoms and signs were excluded. As in many other epidemiological studies, misclassifications were expected, but diagnostic errors should be few.

We shared Dr Xu et al's concern that >10% of the stroke subtypes were classified based on clinical examinations. This was true for the first several years of follow-up. CT/MRI technologies have become readily available in Beijing and Shanghai (>90%) since mid-1990s. Further, the high hospitalization rate and high quality medical service in these large cities should have to some extent alleviated such a concern. As noted by Dr Xu et al, ICH in total stroke gradually increased in the study by Zhang et al in early 1990s.<sup>4</sup> However, CT use was slightly lower in that study compared to ours, and the increasing trend of ICH in total stroke stopped since 1996 when CT was used in 85% of their case diagnoses.<sup>1,4</sup>

We believe that the trend we observed in our study reflects the changes of stroke incidence and composition in our study populations. Further, our observation was consistent with the findings from the MONICA study in Beijing during 1984 to 1999.<sup>5</sup> However, our potential explanations are speculative and we have made it clear in our discussion. More studies are needed to confirm our findings in both urban and rural Chinese populations and to find out the reasons underlying these changes.

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## Referral Bias May Underestimate Number of Very Elderly Patients Eligible for rtPA

To the Editor:

We read with interest the article by Berrouschot and colleagues on the outcome and complications of intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rtPA) in stroke patients aged ≥80 years.<sup>1</sup> Although randomization of patients in this age group into the ongoing IST-3 trial will expand the evidence base for treatment in patients aged >80

years, both within 3 hours and 3 to 6 hours of onset, most active thrombolysis centers receive referrals for older patients who currently fall outside licensing restrictions in Europe on the basis of age alone. Treatment is felt by many to be justified on the basis of observational data and the small amount of randomized controlled trial data.<sup>2</sup> There is sparse information on numbers and source of referral for the elderly in the thrombolysis literature.

We undertook a prospective log of all referrals to our unit for thrombolysis over a 12-month period (July 2004 through June 2005). Of 188 referrals, 43/188 (23%) were patients aged ≥80 years. Excluding 7 patients aged 80, who would be eligible for thrombolysis on the basis of current licensing, 36/188 (19%) would have been ineligible for treatment only on the basis of age. Our unit has no age limit on treatment within 3 hours provided all other criteria are satisfied, the patient or their representative is in agreement with a treatment decision, and with the proviso that all treated patients are registered with Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). Eight patients aged >80 years received IV rtPA (median age 84, IQR: 83, 87). Of 312 patients with confirmed acute ischemic stroke admitted to the unit over the 12-month study period, IV rtPA was given to 8/67 (12%) aged >80 years, compared with 41/245 (17%) of patients aged ≤80 years. Those over 80 years of age were not significantly less likely to be treated (Odds ratio 0.67, 95% CIs 0.23 to 1.52, P=0.45 [Fisher exact test]).

Our stroke unit provides both a local comprehensive stroke service to around 350 000 population, and is a regional neurosciences center covering 2.5 million people over a wide geographical area. For patients aged >80, the majority of referrals came from primary care and already hospitalized patients (30.5% each). Local and regional emergency departments accounted for 28% and 11% of referrals, respectively. This differed from patients aged ≤80 years, where the referral sources were emergency departments (72%), primary care (23%) and inpatients (5%) ( $\chi^2$  test; P<0.001). Of patients referred but having contraindications to treatment based on the European product license, 22/33 (67%) had only age as a contraindication for referrals from primary care or inpatients, whereas age was the only factor in 13/49 (26.5%) referred from emergency departments (P<0.001).

Based on our experience, a high proportion of patients may be excluded from IV rtPA on grounds of age alone. Referral bias is present, but treatment rates did not differ significantly from the under 80s in our service for those assessed. The bias against referral by emergency departments that we saw may reflect a harsher judgment of functional status in the very elderly, but does not appear to reflect knowledge or application of current license criteria. Discrepancies in baseline functional status between patients aged >80 and those ≤80 may explain higher mortality and reduced favorable outcome in the elderly population. Failure to control for baseline differences may underestimate the benefit of thrombolysis with the recognition that hemorrhage rates do not differ significantly.

The outcomes reported by Berrouschot et al are consistent with the Canadian Alteplase for Stroke Effectiveness Study (CASES) series,<sup>3</sup> and reflect our own experience. Using prestroke modified Rankin Scale to adjust for baseline discrepancies, the CASES series found a 16% relative increase in patients achieving an excellent outcome.<sup>3,4</sup> Continued registration of patients older than 80 in SITS-ISTR will allow wider analysis.

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- Berrouschot J, Rother J, Glahn J, Kucinski T, Fiehler J, Thomalla G. Outcome and severe hemorrhagic complications of intravenous thrombolysis with tissue plasminogen activator in very old ( $\geq 80$  years) stroke patients. *Stroke*. 2005;36:2421–2425.
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**Response:**

We thank Drs McCormick and Muir for their comments on our article and the report of their practice with acute stroke treatment in very old patients, which is very much in line with our own proceeding. Their results further strengthen the main conclusion of our study: the outcome of intravenous thrombolysis may be worse in very old patients, but this is not related to thrombolysis, but to worse stroke outcome in elderly in general, and to a more severe initial neurological deficit in the very old patients. Because the risk of severe hemorrhagic complications is not increased in very old patients, and even in the very old a notable number of patients reaches a favorable outcome after thrombolysis (26% in our study), thrombolytic therapy seems justified in this increasing stroke population.

In this context, 2 recently published studies are of interest. The analysis of stroke patients treated with intravenous tPA from a Swiss databank showed a higher mortality in patients  $\geq 80$  years (32% versus 12%), whereas the percentage of patients with a favorable 3-month outcome was comparable between very old and younger patients (29% versus 37%).<sup>1</sup> Moreover, logistic regression did not identify age as an independent predictor of outcome in this sample. In another patient series from Texas, the results were similar with a higher mortality, but comparable rates of improvement and symptomatic intracerebral hemorrhage in patients aged 80 years and over.<sup>2</sup>

In their letter Drs McCormick and Muir addressed the problem of a potential bias leading to lower referral rates of very old patients to thrombolysis centers. Such a bias might further contribute to the lower tPA treatment rates in patients aged 80 and over. In the European BIOMED study of stroke care 30% of all strokes occurred in the group aged 80 and over.<sup>3</sup> In contrast to this, in the group of tPA treated patients, the proportion of patients  $\geq 80$  years ranges somewhat lower, between 12% in the Swiss databank<sup>1</sup> and 16% in our study.<sup>4</sup> A higher incidence of contraindications against tPA, such as anticoagulation or severe comorbidity in older patients, may contribute to lower rates. However, neither in our study nor in the sample reported by McCormick and Muir, those aged 80 and older were less likely to be treated with tPA than younger patients.

To conclude, in a substantial number of patients, age is the only contraindication against thrombolysis with tPA. A growing

number of studies reported on intravenous thrombolysis in old and very old patients, and none of these studies provides evidence to exclude patients from tPA treatment, only because they have trespassed an arbitrary age limit. Hopefully, results from ongoing randomized controlled trials will provide more evidence. Until then, carefully selected very old stroke patients should not be deferred from intravenous tPA, which is the only effective acute ischemic stroke therapy.

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**Economic Benefit of Increasing Utilization of Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke in the United States**

*To the Editor:*

We read with interest the sensitivity analysis on the US economic benefit possible from increasing utilization of tissue plasminogen activator in acute stroke by Demaerschalk et al.<sup>1</sup>

While there are several issues of concern affecting its validity, we believe their analysis seriously under-represented the present dollar value of the savings by using a reference value of (-)\$600 per patient from 1996. After adjusting for the annual effect of inflation using US Bureau of Labor Statistics Consumer Price Index data, the actual per treated patient savings is 24% greater, or (-)\$745 per patient, in 2005. Using this figure, the best estimate of cost savings in the first year poststroke ranges from 9 to  $>90$  million dollars, with similar changes in the 95% CI limits, depending on the proportion of patients receiving tissue plasminogen activator (see Table below for cost savings per treatment %).

**Estimated US First-Year Post-Stroke Cost Savings by Proportion of Patients Receiving tPA**

2%	4%	6%	8%	10%	15%	20%
\$9 176 411	\$18 352 822	\$27 529 233	\$36 705 644	\$45 882 055	\$68 823 083	\$91 764 110

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- Demaerschalk BM, Yip TR. Economic benefit of increasing utilization of intravenous tissue plasminogen activator for acute ischemic stroke in the United States. *Stroke.* 2005;36:2500–2503.

**Response:**

Drs Scott and Silbergelit are correct that our estimates of economic benefit of increasing utilization of intravenous tissue plasminogen activator (tPA) for acute stroke in the US<sup>1</sup> do not reflect current day savings because our reference values came from 1996 cost data published in 1998.<sup>2</sup> Unfortunately, this remains the most current US cost-effectiveness study available for tPA in stroke.

By using the US Department of Labor Bureau of Labor Statistics Consumer Price Index (CPI) inflation calculator ([www.bls.gov](http://www.bls.gov)) to adjust for inflation (reference year 1996 and recent year 2005), the net cost after the first year post-tPA treatment estimate increases to -\$756 (95% CI -\$4384 to \$2524) of savings per treated patient.<sup>3</sup> As you have pointed out, this change would result in \$9 314 000 best estimate of cost savings for every additional 2% of ischemic stroke patients who are thrombolysed nationwide (see the Table below). Regardless, the inflation-based revised estimates, to which you refer, remain well within the published 95% CI.

Unfortunately, this inflation-based correction does not overcome the fact that the 1998 cost-effectiveness study is becoming outdated. The values corrected to the annual general inflation rates assume that the healthcare costs associated with thrombolysis for stroke have inflated at the same rate. A more accurate estimate could be derived from gathering updated cost data associated with the care of acute stroke patients receiving tPA in 2005 to 2006.

Although we agree that the anticipated cost savings is probably closer to \$9 million, not \$7 million, per additional 2% increase in the national proportion of thrombolysed patients, the main message remains the same: using tPA for stroke results in a net cost savings to our healthcare system. This combined with the clearly favorable health outcomes among tPA-treated patients supports the continuing efforts to treat a higher proportion of stroke patients with this drug.

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- Demaerschalk BM, Yip TR. Economic benefit of increasing utilization of intravenous plasminogen activator for acute ischemic stroke in the united states. *Stroke.* 2005;36:2500–2503.

**Best Estimates of US Cost Savings in the First Year After Ischemic Stroke by Varying Proportions of Patients Receiving Intravenous tPA**

2%	4%	6%	8%	10%	15%	20%
\$9 314 000	\$18 628 000	\$27 942 000	\$37 256 000	\$46 570 000	\$69 855 000	\$93 140 000

Adjusted for annual effect of inflation.

- Fagan SC, Morgenstern LB, Petita A, Ward RE, Tilley BC, Marler JR, Levine SR, Broderick JP, Kwiatkowski TG, Frankel M, Brott TG, Walker MD. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. NINDS rt-PA stroke study group. *Neurology.* 1998;50: 883–890.
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**Hyperglycemia and Hyperinsulinemia in Circulatory Disorder After Subarachnoid Hemorrhage**

*To the Editor:*

We read with great interest the recent article by Dr Frontera and colleagues<sup>1</sup> dealing with the relationship between hyperglycemia and complications after subarachnoid hemorrhage (SAH). The results of their study demonstrated that hyperglycemia (the average peak daily glucose level >105 mg/dL) after SAH was associated with serious hospital complications, such as congestive heart failure, increased intensive care unit length of stay, and an increased risk of death or severe disability. The authors proposed that strict normoglycemic management in patients with SAH might be important.

Numerous studies have shown that hyperglycemia may actively participate in the regulation of cellular functions. Barbagallo et al<sup>2</sup> showed that hyperglycemia elevated cytosolic free calcium (Ca) both in myocardial and vascular smooth muscle cells, suggesting that glucose-related excess intracellular Ca might be a fundamental lesion in diabetes that contribute to the elevated blood pressure and cardiac mass in this disease. On the other hand, it is well recognized that hyperglycemia may be associated with hyperinsulinemia. Evidence indicates that hyperinsulinemia might actively participate in the regulation of circulatory disorders. Sela et al<sup>3</sup> demonstrated that polymorphonuclear leukocytes (PMN) in essential hypertension showed increased level of intracellular Ca content correlating positively with the individual's blood pressure and plasma insulin. They proposed that, because PMN priming may lead to oxidative stress and inflammation, intracellular Ca and insulin are involved in the pathogenesis of hypertension-induced vascular injury. In a study we presented earlier, a relationship between membrane fluidity (a reciprocal value of membrane microviscosity) of erythrocytes and insulin was investigated in essential hypertension by means of an electron paramagnetic resonance method.<sup>4</sup> It was demonstrated that the higher the plasma insulin level, the lower the membrane fluidity of erythrocytes, which might indicate that hyperinsulinemia might be involved in the regulation of membrane fluidity of erythrocytes. In an in vitro study, we showed that insulin alone and in combination with Ca decreased the membrane fluidity of erythrocytes.<sup>5</sup> The decreased membrane fluidity of erythrocytes might cause a disturbance in the blood rheologic behavior and the microcirculation, which could contribute, at least in part, to the pathophysiology of circulatory disorders. One hypothesis is that insulin might accelerate abnormalities in intracellular Ca-metabolism and membrane function in blood cells, such as PMN and erythrocytes, which could partially explain the cardiovascular complications in subjects with hyperinsulinemia.

In this context, we speculate that abnormal membrane functions associated with hyperglycemia and hyperinsulinemia might

partially explain the increased complications in patients with SAH. Therefore, we would like to know whether hyperinsulinemia might be related to the complications after SAH. Further studies should be performed to assess more precisely the mechanisms by which hyperglycemia could induce complications in patients with SAH.

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#### Response:

Dr Tsuda postulates that elevated plasma insulin levels lower erythrocyte membrane fluidity leading to adverse rheologic effects and microcirculatory complications. Erythrocyte rigidity and plasma and whole blood viscosities are higher in animal models of non-insulin-dependent diabetes mellitus,<sup>1</sup> but insulin itself may further exacerbate these effects by altering intracellular calcium metabolism. Furthermore, intensive insulin therapy has been shown to have deleterious effects on retinopathy by increasing vascular endothelial growth factor gene expression.<sup>2</sup>

In contrast, since van den Berghe's landmark article,<sup>3</sup> in which intensive insulin therapy led to substantially reduced mortality and lowered hospital complications in critically ill patients, speculation has arisen over whether glycemic control alone was responsible for these effects or if insulin therapy confers its own protective benefit. Local administration of insulin has been shown to increase the availability of  $\gamma$ -aminobutyric acid

(GABA) and the sensitivity of post-synaptic GABA receptors. Increased GABA-ergic inhibitory effects may be neuroprotective<sup>4</sup> and indeed, in a separate study, van den Berghe found that intensive insulin therapy reduced the incidence of seizure in patients with isolate brain injury.<sup>5</sup> Similarly, other nonglycemic effects of insulin include partial correction of abnormal lipid profiles and attenuation of the catabolic state present in critical illness.<sup>6</sup>

In our recent article<sup>7</sup> we did not find an association between hyperglycemia and vascular complications, such as vasospasm or cerebral infarction, though others have.<sup>8</sup> We were, however, unable to quantify the amount of insulin our patients received and cannot directly address the effect of insulin on these vascular complications. Thus, though it is clear that hyperglycemia is detrimental in the critically ill, the effects of insulin on endothelial and rheologic function warrant further investigation.

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