

Editorial

## Benefit or harm: Does age matter in stroke outcome after thrombolysis?



In the past several decades, stroke has been the second most common cause of mortality worldwide.<sup>1</sup> Currently, it is the third leading cause of global disease burden estimated by disability-adjusted life years.<sup>2</sup> Stroke remains the leading cause of disability in elderly individuals.<sup>3</sup> Therefore, stroke is a substantial public health concern and poses a tremendous socioeconomic burden. Stroke prevention should be a major focus of health care. However, in the absence of effective preventive programs, a complementary acute stroke care policy, especially for acute stroke management, is critically important.

In excess of 80% of strokes are of the ischemic type. Intravenous (IV) administration of recombinant tissue plasminogen activator (rt-PA) within 3 hours of symptom onset is the only approved medical therapy for patients with acute ischemic stroke.<sup>4,5</sup> However, there are currently few proven treatment options for very elderly people, and only 42 patients over 80 years of age have been recruited in randomized controlled trials (RCTs) for rt-PA.<sup>5</sup> With the ever-growing elderly population, stroke risk is expected to increase, together with life expectancy.<sup>6</sup> An estimated 30% of strokes occur in patients over 80 years of age, but the safety and efficacy profiles of IV rt-PA in this age group remain unclear.<sup>4,7</sup> The European Cooperative Acute Stroke Study (ECASS) trial specifically excluded this age group for fear of excessive symptomatic intracranial hemorrhage.<sup>7</sup> Advancing age is associated with increased in-hospital mortality<sup>8</sup> and hemorrhage risk<sup>9</sup> in stroke patients treated with rt-PA. However, older stroke patients also demonstrate higher stroke mortality without rt-PA treatment, and are less likely to recover than younger stroke patients. Thus, older age should not be a contraindication in thrombolytic therapy.

Unfortunately, as stated above, RCT data on the safety and efficacy of thrombolysis in patients over 80 years of age are limited, although this age group accounts for nearly one-third of stroke admissions in developed countries. Therefore, reliable data are needed to ensure that therapy is provided to appropriately selected older patients and to improve poor outcomes from stroke in this aging segment of the population. Because there is a lack of RCT-based data regarding the efficacy of rt-PA within 3 hours of symptom onset in elderly stroke patients, other sources of data may be used to judge the appropriateness of thrombolytic therapy in this population.

Recent cohort studies and meta-analyses comparing treatment with IV rt-PA in stroke patients aged >80 years with

younger ( $\leq 80$  years of age) stroke patients showed inconsistent findings.<sup>10–12</sup> Chen et al retrospectively analyzed a cohort of 183 patients receiving thrombolytic therapy, of whom 56 were in the aged group (>80 years).<sup>10</sup> There were no significant differences in stroke risk factors between these two groups, except that the aged group contained more female patients. However, the baseline National Institute of Health Stroke Scale (NIHSS) score was insignificantly higher in the aged group. In addition, there was a trend toward a lower percentage of aged patients returning home after stroke. Despite these differences, this study showed similar recanalization rates, symptomatic intracranial hemorrhage rates, and short-term outcomes between patients over 80 years of age and younger patients.

The largest prospective observational study of thrombolytic outcomes to date (the Safe Implementation of Treatment in Stroke International Stroke Thrombolysis Register, SITS-ISTR)<sup>11</sup> included 1831 patients aged >80 years and 19,411 patients aged  $\leq 80$  years. Compared to the younger age group, the aged group demonstrated greater stroke severity, a lower level of pre-stroke independence, and included a larger proportion of women. After 3 months, the aged group exhibited a higher rate of mortality and poorer functional outcomes (as determined by a score  $>2$  on the modified Rankin Scale). Similar conclusions were also reached in a recent meta-analysis.<sup>12</sup>

Therefore, which factors may be used to predict 3-month functional outcome? In addition to baseline NIHSS score, hemorrhagic transformation (HT), and age, early neurologic improvement (ENI) may play a role in stroke outcome.<sup>10,11,13,14</sup> A *post-hoc* explorative analysis of the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA trial showed that minor degrees of NI ( $\leq 3$  points on the NIHSS) were seen frequently in both the patient and placebo groups.<sup>4</sup> Greater degrees of NI ( $\geq 4$  points on the NIHSS or an NIHSS score of 0 at 24 hours after thrombolytic therapy) should be regarded as ENI. Dramatic early improvement also might be a marker of recanalization after thrombolytic therapy and predictive of good functional outcomes, irrespective of age group.<sup>10</sup> Lack of ENI was also associated with poor outcomes and death at 3 months.<sup>13</sup> However, another study showed that age and time to treatment were predictors of major neurological improvement after thrombolysis.<sup>14</sup> So, whether older age may be associated with lack of ENI is still controversial.

In the current issue of the *Journal of the Chinese Medical Association*, Ong et al<sup>15</sup> report on ENI in an aged ( $\geq 80$  years) population. From January 2007 to December 2012, a total of 157 patients with acute ischemic stroke received IV rt-PA therapy; of these patients, 17 were  $\geq 80$  years of age. Seventy-eight aged patients received no thrombolytic therapy. The rates of ENI, NI at discharge, HT, and symptomatic HT were similar between the treated older and younger groups. Of the aged population, the NI at discharge rate was significantly higher in the thrombolytic group than in the nonthrombolytic group. The authors suggested that thrombolytic therapy may be feasible in the older patients.

From February 2009 to October 2013, a total of 103 acute ischemic stroke patients received IV rt-PA therapy in Taipei Veterans General Hospital, of whom 23 were aged  $>80$  years (9 women; mean age:  $84.6 \pm 3.4$  years, range: 81–95 years). NIHSS scores at baseline ( $12.2 \pm 7.8$  vs.  $12.4 \pm 6.9$ ) and 24 hours after thrombolytic therapy ( $10.4 \pm 7.5$  vs.  $9.8 \pm 6.8$ ) were similar between the two groups. Therefore, patients over 80 years of age and younger patients had similar recanalization, short-term improvement, and HT rates after IV rt-PA. Large-scale RCTs are needed to test the safety and efficacy profiles in this particular patient population.

### Conflicts of interest

The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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Li-Chi Hsu

Jong-Ling Fuh\*

Department of Neurology, Neurological Institute,  
Taipei Veterans General Hospital, Taipei, Taiwan, ROC  
National Yang-Ming University School of Medicine, Taipei,  
Taiwan, ROC

\*Corresponding author. Dr. Jong-Ling Fuh,  
Department of Neurology, Neurological Institute,  
Taipei Veterans General Hospital, 201, Section 2,  
Shih-Pai Road, Taipei, 112, Taiwan, ROC.  
E-mail address: jlfuh@vghtpe.gov.tw (J.-L. Fuh)