

The Safety and Effectiveness of Low-Dose Recombinant Tissue Plasminogen Activator (0.6 mg/kg) Therapy for Elderly Acute Ischemic Stroke Patients (≥ 80 Years Old) in the Pre-endovascular Era

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Abstract

There are still few studies of low-dose recombinant tissue plasminogen activator (rtPA) therapy (0.6 mg/kg) for acute ischemic stroke (AIS) patients ≥ 80 years old, though most strokes occur in elderly people. The safety and effectiveness of this form of thrombolysis without endovascular therapy were evaluated in AIS patients ≥ 80 years old at our hospital. The data were collected from August 2006 to April 2010, before approval of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) retriever in Japan. Intravenous rtPA was administered to patients within 3 hours of stroke onset. The incidence of intracerebral hemorrhage (ICH), the recanalization rate of the occluded artery, and the modified Rankin Scale (mRS) score 3 months after stroke were examined. The patients who received rtPA therapy were stratified into two age groups: a younger group (< 80 years) and an older group (≥ 80 years). Of the 87 patients who received rtPA therapy, 17 (19.5%) were ≥ 80 years old. The incidence of symptomatic ICH was not significantly different between the younger (4.3%) and older (0%) groups ($p = 0.61$). The recanalization rate of the occluded artery was not significantly different between the younger (54%) and older (50%) groups ($p = 0.78$). The rate of an mRS score of 0–2, 3 months after stroke was significantly higher in the younger (44.3%) than in the older group (11.8%) ($p = 0.013$). Low-dose rtPA therapy appears to be as safe and feasible for AIS patients ≥ 80 years old as it is for younger people. This therapy should not be withheld because of age.

Key words: recombinant tissue plasminogen activator therapy, acute ischemic stroke, elderly people

Introduction

In Japan, intravenous recombinant tissue plasminogen activator (rtPA) therapy (0.6 mg/kg) for acute ischemic stroke (AIS) patients within 3 hours of onset was approved by the Ministry of Health, Labor, and Welfare of Japan in 2005. Since then, several multicenter studies have been conducted to analyze low-dose rtPA therapy, and it has been proven to offer clinical safety and effectiveness compatible with the 0.9 mg/kg-dose rtPA therapy.^{1–4}

Most previous randomized, controlled trials of rtPA therapy for AIS patients excluded people older than 80 years because the elderly had been believed to have a greater risk of symptomatic intracerebral hemorrhage (ICH).^{5,6} However, most strokes occur in elderly people, and their life expectancy is increasing,

so the benefits and risks of thrombolytic treatment are worth evaluating in this group.^{7,8} A number of recent observational studies compared the outcomes of rtPA (0.9 mg/kg) therapy in patients older than 80 years with their younger counterparts, and the recent systematic review suggested that the risks of symptomatic ICH did not increase among elderly patients, despite the higher 3-month mortality and the less favorable outcome.^{9–17} However, there are still few studies of the safety and effectiveness of low-dose rtPA therapy (0.6 mg/kg) for AIS patients aged > 80 years old. In Japan, the MERCI retriever was first approved in 2010 for endovascular therapy in AIS patients. In the future, the number of AIS patients treated by rtPA therapy plus endovascular therapy is expected to increase, so it will be more and more difficult to evaluate the safety and effectiveness of low-dose rtPA therapy (0.6 mg/kg) for AIS patients without endovascular therapy.

Received August 2, 2013; Accepted December 16, 2013

Therefore, in this study, the safety and effectiveness of this thrombolytic therapy for AIS patients ≥ 80 years old were analyzed and compared to the younger people at our hospital in the pre-endovascular therapy era.

Materials and Methods

I. Patients

Consecutive patients with AIS who received intravenous rtPA therapy at Aizu Chuo Hospital from August 2006 to April 2010, before approval of the MERCI retriever in Japan, were retrospectively reviewed.

II. Clinical/imaging data

The data collected for each patient contained information on demographics, severity of neurologic deficits on admission, onset-to-treatment time, stroke subtype, and the occluded artery confirmed by magnetic resonance angiography (MRA). Stroke severity and neurological impairment at admission were measured using the National Institutes of Health Stroke Scale (NIHSS). Stroke subtype was diagnosed based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.¹⁸⁾

III. Protocol and inclusion/exclusion criteria for thrombolysis

For suspected stroke patients in the emergency room, non-enhanced head computed tomography (CT) was first performed to exclude intracranial hemorrhage. If intracranial hemorrhage was excluded, head magnetic resonance imaging (MRI) was next conducted to screen for rtPA therapy. The acute stroke MRI protocol consisted of T_2 -weighted imaging (T_2 WI), diffusion-weighted imaging (DWI), and MRA of the head and neck. Perfusion imaging and T_2^* -weighted imaging was not included in the protocol. MRI exclusion criteria for thrombolysis included definite hyperintensity areas larger than 33% of the middle cerebral artery (MCA) territory on DWI.^{19–21)} Clinical eligibility criteria for thrombolysis were applied according to the National Institute of Neurological Disorders and Stroke (NINDS) trial¹³⁾ criteria and “The Guidelines” prepared by the Japan Stroke Society.²²⁾ Age is not a contraindication for this treatment. Clinical exclusion criteria for thrombolysis were: the patient or family who refused thrombolysis; patients who were disabled in activities of daily living (ADL) [e.g., modified Rankin Scale (mRS) score ≥ 3]; or the patients who had severe chronic disease (severe heart failure, severe cancer, etc.). Based on the Japan Alteplase Clinical Trial (J-ACT) criteria,⁴⁾ intravenous rtPA (0.6 mg/kg, alteplase, 10% of the dose as a bolus and the remainder over 60 min)

was administered to patients within 3 hours of stroke onset.

IV. Outcome measures

To evaluate the safety of rtPA therapy, the incidence of ICH after thrombolysis, mortality, and the cause of death were analyzed. According to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST),²³⁾ symptomatic ICH was defined as ICH on CT performed within 36 hours after onset with an increase of ≥ 4 points from the baseline NIHSS score. In this study, both the late phase mortality more than 3 months after stroke and the early phase mortality were examined.

To evaluate the effectiveness of rtPA therapy, the recanalization rate of the occluded artery and clinical outcomes at 3 months after stroke were analyzed. To analyze the recanalization of the occluded artery, head MRA was performed within 72 hours after initiation of rtPA therapy. Clinical outcome was determined by the mRS score 3 months after stroke.

V. Statistical analysis

The patients who received rtPA therapy were stratified into two age groups: the younger group (< 80 years) and the older group (≥ 80 years). Baseline characteristics, ICH, recanalization rate of the occluded artery, mortality, and 3-month mRS scores were compared between the two groups. Univariate comparisons were performed using the Mann-Whitney U test and the chi-square test. All calculations were performed using JMP 9 software (SAS Institute Inc., Cary, North Carolina, USA). A probability value < 0.05 was considered significant.

Results

I. Baseline characteristics

From August 2006 until April 2010, 1,744 stroke patients [including 626 patients (35.9%) ≥ 80 years old] were admitted to our hospital, of whom 87 (4.5%) received rtPA therapy after MRI screening. Of the 87 treated patients, 17 (19.5%) were ≥ 80 years old. The rate of thrombolysis-treatment was lower in patients ≥ 80 years old than in younger patients. The baseline characteristics of both the younger and older groups are summarized in Table 1. There were significantly fewer men in the older group than in the younger group ($p = 0.04$). The median admission NIHSS score was significantly higher in the older group ($p = 0.002$). Onset-to-treatment time, the distribution of stroke subtype, and the distribution of the occluded artery were not significantly different between the two groups.

Table 1 Baseline characteristics of the younger and older groups

	Age < 80	Age ≥ 80	p value
Patients n (%)	70 (80.5)	17 (19.5)	
Mean age ± SD (year)	68.6 ± 10.7	84.4 ± 3.2	< 0.001*
Male, n (%)	44 (62.9)	6 (35.3)	0.04*
NIHSS on admission Mean ± SD	15.4 ± 8.6	22.8 ± 9.2	0.002*
Onset-to-treatment time (minute)	142.0 ± 32.2	145.2 ± 19.6	0.71
Stroke subtype (%)			
Cardioembolic	37 (52.9)	12 (70.6)	0.28
Atherothrombotic	26 (37.1)	4 (23.5)	0.40
Other (lacunar/not differentiated)	7 (10.0)	1 (5.9)	0.69
Occluded artery (%)			
AC	2 (2.9)	0 (0)	1.00
BA	7 (10.0)	4 (23.5)	0.21
IC	19 (27.1)	2 (11.8)	0.22
M1	28 (40.0)	8 (47.1)	0.78
M2	7 (10.0)	2 (11.8)	1.00

*p < 0.05. AC: anterior cerebral artery, BA: basilar artery, IC: internal carotid artery, M1: the proximal branch of middle cerebral artery, M2: the distal branch of middle cerebral artery, NIHSS: National Institutes of Health Stroke Scale, SD: standard deviation.

Table 2 Intracranial hemorrhage of the younger and older groups

n (%)	Age < 80	Age ≥ 80	p value
Asymptomatic ICH	15 (21.4)	1 (5.9)	0.17
Symptomatic ICH	3 (4.3)	0 (0)	0.61
All	18 (25.7)	1 (5.9)	0.10

ICH: intracranial hemorrhage, mRS: modified Rankin Scale.

II. ICH

The incidence rate of symptomatic ICH was not significantly different between the younger patients (< 80 years, 4.3%) and the older patients (≥ 80 years, 0%) (p = 0.61, Table 2). The incidence rate of all ICH was not significantly different between the two groups.

III. Mortality and causes of death

The late phase mortality at 3 months after stroke was significantly higher in the older group (35.3%) than in the younger group (11.4%; p = 0.03, Table 3).

Table 3 Mortality and causes of death in the younger and older groups

n (%)	Age < 80	Age ≥ 80	p value
Mortality after 3 months	8 (11.4)	6 (35.3)	0.03*
Mortality within 7 days	3 (4.3)	0 (0)	0.61
Causes of death n (%)			
ICH or infarction	5 (62.5)	0 (0)	0.03*
Infection (pneumonia, etc.)	2 (25)	5 (83.3)	0.10
AMI	0 (0)	1 (16.7)	0.43
Renal dysfunction	1 (12.5)	0 (0)	1.00

*p < 0.05. AMI: acute myocardial infarction, ICH: intracranial hemorrhage, mRS: modified Rankin Scale.

Table 4 Recanalization rates of the younger and older groups

n (%)	Age < 80	Age ≥ 80	p value
AC	0 (0)	NA	NA
BA	5 (71.4)	1 (25.0)	0.24
IC	5 (26.3)	0 (0)	1.00
M1	20 (71.4)	6 (75)	1.00
M2	4 (57.1)	1 (50)	1.00
All	34 (54.0)	8 (50)	0.78

AC: anterior cerebral artery, BA: basilar artery, IC: internal carotid artery, M1: the proximal branch of middle cerebral artery, M2: the distal branch of middle cerebral artery, NA: not available.

However, the early phase mortality at 7 days after stroke was 4.3% in the younger group and 0% in the older group, with no significant difference (p = 0.61). There were significantly fewer patients in the elderly group whose causes of death were related to cerebral hemorrhage or infarction (0 vs. 5; p = 0.03), and there tended to be more whose causes of death were related to infection (e.g., pneumonia) compared to the younger group (5 vs. 2; p = 0.10).

IV. Rate of recanalization

The recanalization rate for all occluded arteries was 54% in the younger patients and 50% in the older patients (Table 4). In particular, the recanalization rate of the proximal branch of the MCA (M1) was high, 71.4% in the younger patients and 75% in the older patients. The recanalization rate of each occluded artery was not significantly different between the two groups.

Table 5 Outcomes of the younger and older groups

n (%)	Age < 80	Age ≥ 80	p value
mRS 0–1	19 (27.1)	2 (11.8)	0.22
mRS 0–2	31 (44.3)	2 (11.8)	0.013*
mRS 3–5	31 (44.3)	9 (53.0)	0.593

*p < 0.05. mRS: modified Rankin Scale.

V. Clinical outcome

The rate of a favorable outcome (mRS score 0–1) 3 months after stroke was higher in the younger (27.1%) than in the older group (11.8%), but the difference was not significant (p = 0.22, Table 5). The rate of an mRS score of 0–2, 3 months after stroke was significantly higher in the younger (44.3%) than in the older group (11.8%) (p = 0.013).

Discussion

The present analysis showed that very elderly patients do not have an increased risk of intracranial hemorrhage after low-dose rtPA therapy compared to young patients. In addition, the present study demonstrated that the rate of favorable outcome 3 months after stroke was significantly lower in the older than in the younger group, and the mortality 3 months after stroke was significantly higher in the older than in the younger group. This result was similar to other studies²⁴⁾ of low-dose (0.6 mg/kg) and high-dose (0.9 mg/kg) rtPA therapy.^{9–17)}

The natural history of stroke in very elderly people is associated with a poor prognosis.^{25–27)} Elderly patients have higher rates of complicating medical conditions such as heart failure, hypertension, and atrial fibrillation. Therefore, there are several reasons unrelated to a hemorrhagic complication of the thrombolysis that could explain the poor outcome of elderly patients. In fact, the present study showed that there were fewer patients in the elderly group whose causes of death were related to cerebral hemorrhage or infarction, and more whose causes of death were related to infection compared with those in the younger group. Referring to the paper of Uyttenboogaart et al.,¹⁷⁾ early mortality (within 7 days after stroke) was also not different between the two groups. This means that the poor outcome at 3 months was not related to acute thrombolytic therapy, but to factors that occurred in the chronic stage. In brief, low-dose (0.6 mg/kg) therapy may be almost as safe for the elderly as it is for younger patients.

The results of the present study showed that the rate of an mRS score of 0–2, 3 months after

stroke was significantly lower in the older than in the younger group (p = 0.013). The rate of an mRS score of 0–2, 3 months after stroke in AIS patients ≥ 80 years old who underwent thrombolysis in the present study (11.8%) was not higher than that in AIS patients > 80 years old who did not undergo thrombolysis in another study (21.3%), which was a collaborative registry of stroke trials, Virtual International Stroke Trials Archive (VISTA).¹¹⁾ However, one cannot conclude that the low-dose rtPA therapy was ineffective for elderly people, because the median admission NIHSS score of the older group in the present study (22.8) was much higher than that of the younger group in the present study (15.4) or that of the elderly group in VISTA (14). To confirm the effectiveness of low-dose rtPA therapy with respect to the mRS score of elderly people, a median admission NIHSS score-controlled study should be conducted.

This study demonstrated that the recanalization rate of very elderly patients with low-dose rtPA therapy was not significantly different from that of young patients. In particular, the recanalization rate of the proximal branch of the MCA was not poor compared with that of J-ACT II (69.0%).¹⁾ In addition, this rate was not poor compared with that of 0.9 mg/kg-dose rtPA therapy.²⁸⁾ In brief, the effectiveness of low-dose (0.6 mg/kg) rtPA therapy for the elderly might be almost equal to that of 0.9 mg/kg-dose rtPA therapy for younger patients.

In Japan, the MERCI retriever was first approved in 2010, and the Penumbra System was approved in 2011 for endovascular therapy in AIS patients. In the future, the number of AIS patients treated by rtPA therapy plus endovascular therapy is expected to increase. However, a recent randomized, controlled study showed that endovascular therapy was not superior to rtPA therapy.²⁹⁾ In that study, the outcome of endovascular therapy was poorer than that of rtPA therapy for the older group (> 67 years, but not including > 80 years). According to that study, the reason for the poor outcome in the endovascular therapy group might have been a delay in the initiation of therapy. Therefore, urgent low-dose (0.6 mg/kg) rtPA monotherapy without endovascular therapy may be appropriate in the elderly. To confirm these findings, a randomized study should be conducted in the future.

Some limitations are present in our study. The study data did not come from a randomized, controlled study of intravenous low-dose rtPA therapy for patients ≥ 80 years old, but from a retrospectively observed cohort of patients in only one institution. In this study, the rate of thrombolysis treatment was lower in patients ≥ 80 years old than in younger

patients, and we presume that the reason for this was that there might be more patients who were not treated with thrombolysis because of the clinical exclusion criteria. Because of the lack of a control group and the relatively small number of patients (especially patients ≥ 80 years old), the present study could not offer definitive evidence of the usefulness of this thrombolysis therapy. A prospective, controlled study involving a large cohort in many medical institutions is needed.

In conclusion, intravenous rtPA therapy (0.6 mg/kg) for AIS patients ≥ 80 years old appears to be as safe and feasible as it is for younger patients. This therapy should not be withheld because of age.

Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices in the article. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

References

- Mori E, Minematsu K, Nakagawara J, Yamaguchi T, Sasaki M, Hirano T; Japan Alteplase Clinical Trial II Group: Effects of 0.6 mg/kg intravenous alteplase on vascular and clinical outcomes in middle cerebral artery occlusion: Japan Alteplase Clinical Trial II (J-ACT II). *Stroke* 41: 461–465, 2010
- Nakagawara J, Minematsu K, Okada Y, Tanahashi N, Nagahiro S, Mori E, Shinohara Y, Yamaguchi T; J-MARS Investigators: Thrombolysis with 0.6 mg/kg intravenous alteplase for acute ischemic stroke in routine clinical practice: the Japan post-Marketing Alteplase Registration Study (J-MARS). *Stroke* 41: 1984–1989, 2010
- Toyoda K, Koga M, Naganuma M, Shiokawa Y, Nakagawara J, Furui E, Kimura K, Yamagami H, Okada Y, Hasegawa Y, Kario K, Okuda S, Nishiyama K, Minematsu K; Stroke Acute Management with Urgent Risk-factor Assessment and Improvement Study Investigators: Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients: general outcomes and prognostic factors from the SAMURAI register. *Stroke* 40: 3591–3595, 2009
- Yamaguchi T, Mori E, Minematsu K, Nakagawara J, Hashi K, Saito I, Shinohara Y; Japan Alteplase Clinical Trial (J-ACT) Group: Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). *Stroke* 37: 1810–1815, 2006
- Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, Boysen G, Bluhmki E, Höxter G, Mahagne MH: Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS) *JAMA* 274: 1017–1025, 1995
- Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, Larrue V, Bluhmki E, Davis S, Donnan G, Schneider D, Diez-Tejedor E, Trouillas P: Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet* 352: 1245–1251, 1998
- Manton KG, Vaupel JW: Survival after the age of 80 in the United States, Sweden, France, England, and Japan. *N Engl J Med* 333: 1232–1235, 1995
- Saposnik G, Black SE, Hakim A, Fang J, Tu JV, Kapral MK; Investigators of the Registry of the Canadian Stroke Network (RCSN); Stroke Outcomes Research Canada (SORCan) Working Group: Age disparities in stroke quality of care and delivery of health services. *Stroke* 40: 3328–3335, 2009
- Berrouschot J, Röther J, Glahn J, Kucinski T, Fiehler J, Thomalla G: Outcome and severe hemorrhagic complications of intravenous thrombolysis with tissue plasminogen activator in very old ($>$ or $=$ 80 years) stroke patients. *Stroke* 36: 2421–2425, 2005
- Meseguer E, Labreuche J, Olivot JM, Abboud H, Lavalley PC, Simon O, Cabrejo L, Echeverria A, Klein IF, Mazighi M, Amarenco P: Determinants of outcome and safety of intravenous rt-PA therapy in the very old: a clinical registry study and systematic review. *Age Ageing* 37: 107–111, 2008
- Mishra NK, Ahmed N, Andersen G, Egidio JA, Lindsberg PJ, Ringleb PA, Wahlgren NG, Lees KR; VISTA collaborators; SITS collaborators: Thrombolysis in very elderly people: controlled comparison of SITS International Stroke Thrombolysis Registry and Virtual International Stroke Trials Archive. *BMJ* 341: c6046, 2010
- Mishra NK, Diener HC, Lyden PD, Bluhmki E, Lees KR: Influence of age on outcome from thrombolysis in acute stroke: a controlled comparison in patients from the Virtual International Stroke Trials Archive (VISTA). *Stroke* 41: 2840–2848, 2010
- Pundik S, McWilliams-Dunnigan L, Blackham KL, Kirchner HL, Sundararajan S, Sunshine JL, Tarr RW, Selman WR, Landis DM, Suarez JJ: Older age does not increase risk of hemorrhagic complications after intravenous and/or intra-arterial thrombolysis for acute stroke. *J Stroke Cerebrovasc Dis* 17: 266–272, 2008
- Tanne D, Gorman MJ, Bates VE, Kasner SE, Scott P, Verro P, Binder JR, Dayno JM, Schultz LR, Levine SR: Intravenous tissue plasminogen activator for acute ischemic stroke in patients aged 80 years and older: the tPA stroke survey experience. *Stroke* 31: 370–375, 2000
- Tanne D, Kasner SE, Demchuk AM, Koren-Morag N, Hanson S, Grond M, Levine SR: Markers of increased risk of intracerebral hemorrhage after intravenous recombinant tissue plasminogen activator therapy

- for acute ischemic stroke in clinical practice: the Multicenter rt-PA Stroke Survey. *Circulation* 105: 1679–1685, 2002
- 16) Toni D, Lorenzano S, Agnelli G, Guidetti D, Orlandi G, Semplicini A, Toso V, Caso V, Malferrari G, Fanucchi S, Bartolomei L, Prencipe M: Intravenous thrombolysis with rt-PA in acute ischemic stroke patients aged older than 80 years in Italy. *Cerebrovasc Dis* 25: 129–135, 2008
 - 17) Uyttenboogaart M, Schrijvers EM, Vroomen PC, De Keyser J, Luijckx GJ: Routine thrombolysis with intravenous tissue plasminogen activator in acute ischaemic stroke patients aged 80 years or older: a single centre experience. *Age Ageing* 36: 577–579, 2007
 - 18) Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE: Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 24: 35–41, 1993
 - 19) Larrue V, von Kummer R, del Zoppo G, Bluhmki E: Hemorrhagic transformation in acute ischemic stroke. Potential contributing factors in the European Cooperative Acute Stroke Study. *Stroke* 28: 957–960, 1997
 - 20) The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group: Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 333: 1581–1587, 1995
 - 21) Schellinger PD, Fiebich JB, Hacke W: Imaging-based decision making in thrombolytic therapy for ischemic stroke: present status. *Stroke* 34: 575–583, 2003
 - 22) The Japan Stroke Society: The guidelines for appropriate intravenous rtPA treatment. *Jpn J Stroke* 27: 327–354, 2005
 - 23) Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Kuelkens S, Larrue V, Lees KR, Roine RO, Sooinne L, Toni D, Vanhooren G; SITS-MOST investigators: Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet* 369: 275–282, 2007
 - 24) Kono S, Deguchi K, Morimoto N, Kurata T, Yamashita T, Ikeda Y, Narai H, Manabe Y, Takao Y, Kawada S, Kashihara K, Takehisa Y, Inoue S, Kiriyama H, Abe K: Intravenous thrombolysis with neuroprotective therapy by edaravone for ischemic stroke patients older than 80 years of age. *J Stroke Cerebrovasc Dis* 22, 1175–1183, 2013
 - 25) Di Carlo A, Lamassa M, Pracucci G, Basile AM, Trefoloni G, Vanni P, Wolfe CD, Tilling K, Ebrahim S, Inzitari D: Stroke in the very old: clinical presentation and determinants of 3-month functional outcome: a European perspective. European BIOMED Study of Stroke Care Group. *Stroke* 30: 2313–2319, 1999
 - 26) Kammersgaard LP, Jørgensen HS, Reith J, Nakayama H, Pedersen PM, Olsen TS; Copenhagen Stroke Study: short- and long-term prognosis for very old stroke patients. The Copenhagen Stroke Study. *Age Ageing* 33: 149–154, 2004
 - 27) Mayo NE, Neville D, Kirkland S, Ostbye T, Mustard CA, Reeder B, Joffres M, Brauer G, Levy AR: Hospitalization and case-fatality rates for stroke in Canada from 1982 through 1991. The Canadian Collaborative Study Group of Stroke Hospitalizations. *Stroke* 27: 1215–1220, 1996
 - 28) Derex L, Nighoghossian N, Hermier M, Adeleine P, Berthézène Y, Philippeau F, Honnorat J, Froment JC, Trouillas P: Influence of pretreatment MRI parameters on clinical outcome, recanalization and infarct size in 49 stroke patients treated by intravenous tissue plasminogen activator. *J Neurol Sci* 225: 3–9, 2004
 - 29) Ciccone A, Valvassori L, Nichelatti M, Sgoifo A, Ponzio M, Sterzi R, Boccardi E; SYNTHESIS Expansion Investigators: Endovascular treatment for acute ischemic stroke. *N Engl J Med* 368: 904–913, 2013

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