Effectiveness and Safety of Thrombolysis in Ischemic Stroke Patients Aged 80 Years or Older

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Introduction

Age is a strong independent risk factor of stroke. Stroke incidence doubles with every decade after 55 years, and in those aged >80 years the incidence reaches 21 per 1,000.1 In addition, the population of very elderly individuals is rapidly growing worldwide.2 Optimizing the treatment and prevention of stroke in these much older people will increasingly be a priority for health-care providers, research funding agencies, and policy makers in years to come.3

Thrombolysis is a standard treatment option in acute ischemic stroke (AIS) patients. However, the evidence supporting its use in the very elderly with stroke is still lacking, mainly because they are excluded from most randomized controlled trials for thrombolysis.4-9 Observational studies comparing patients aged ≥80 years with those <80 years reported inconsistent findings.
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with respect to the effect of intravenous (IV) or intra-arterial (IA) thrombolysis.\textsuperscript{10,15} Most of studies showed that the elderly treated with thrombolysis have higher mortality than the younger, and they tend to have worse outcome. The risk of symptomatic hemorrhagic transformation (sHT) is not different between the elderly and younger patients, although there are persistent concerns that advanced age increases the risk of sHT related to thrombolysis.\textsuperscript{11,12,16,17} By including only the patients received thrombolysis, most of previous studies made a comparison between the old, thrombolysis-treated patients and the young, also thrombolysis-treated ones. Because the elderly patients have more disabling stroke and an increased mortality across a similar spectrum of stroke severity,\textsuperscript{18} it is natural that we expect worse outcome in the elderly compared to the younger when both are treated with thrombolysis.

Without clear evidences, many physicians decide to do thrombolysis in the elderly with acute ischemic stroke.\textsuperscript{19,21} For making evidence, a randomized controlled trial for thrombolysis to the elderly stroke patients is the best choice, but it has not been reported yet.

This study aimed to investigate whether the effectiveness and safety of thrombolysis (IV, IA or combined) for acute ischemic stroke differ by age, by comparing the thrombolysis-treated patients and the thrombolysis-untreated.

**Subjects and Methods**

**Study population**

A consecutive series of patients with ischemic stroke, who were admitted to Seoul National University Bundang Hospital between January 2004 and February 2009, were identified retrospectively using the prospective stroke registry database.\textsuperscript{22} Patients hospitalized within 12 hours from symptom onset and having relevant lesions on computed tomography (CT) or magnetic resonance imaging (MRI) were included in this study. Those who received thrombolytic treatment prior to our institution were excluded.

During the study period, all patients, who arrived within 12 hours from symptom onset, were treated according to our institution thrombolysis protocols. The principles of protocols were as follows: 1) If patients were candidates for IV thrombolysis by the current stroke guideline,\textsuperscript{23} IV thrombolysis was considered after brain CT. 2) If patients were not candidates, they underwent brain MRI and MR angiography including diffusion weighted image (DWI) and perfusion images, and then IV, IA, or combined IV-IA thrombolysis was chosen according to the presence and magnitude of perfusion-diffusion mismatch, stroke severity, DWI lesion volume, prestroke functional status, the presence of major arterial occlusion, changes on fluid-attenuated inversion recovery (FLAIR) imaging, and other clinical or radiological parameters. 3) We used IV tissue plasminogen activator (tPA) dose of 0.6 mg/kg, 15% of those as a bolus and the remainder over 30 min, when considering the combined thrombolysis. When the additional IA thrombolysis was not considered, we used the IV tPA with dose of 0.9 mg/kg, 10% of the dose as a bolus and the remainder over 60 minutes.

**Data collection**

Medical history, clinical profiles and risk factors for stroke, acute managements including thrombolysis, and laboratory findings were available in the prospective stroke registry database or were supplemented by reviewing electronic medical records. The severity of neurologic deficits at presentation was assessed with the NIH stroke scale (NIHSS).\textsuperscript{24} Stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.

For assessing the effectiveness of thrombolysis, the modified Rankin scale (mRS) at 3 months was used. The mRS scores were obtained as follows; patients were contacted at 3 months after stroke onset for telephone interview as part of an institutional quality-of-care monitoring program for hospitalized stroke patients. An experienced stroke nurse (M.H.Y.) blinded to whether patients were treated by thrombolysis or not was responsible for administering the mRS. Stroke deaths were verified by contact of family members and by obtaining information from a national death certificate system.

The safety of thrombolysis was evaluated by the presence of sHT, which was defined as any neurological deterioration in NIHSS that was accompanied with HT and considered to be caused by HT according to clinical judgment.\textsuperscript{25} The sHT was retrospectively captured by stroke neurologists through independent review of medical records and brain images (Y.K., J.H.P.; kappa value=0.833). When there was a disagreement between the two examiners, a decision was reached by consensus after joint review.
Statistical analysis

All values are presented as a mean±standard deviation (SD) or a median (interquartile range, IQR) for continuous variables and as a number of subjects (%) for categorical variables. Age was categorized into ≥80 years and <80 years. The mRS was dichotomized into 0 to 2 (favorable) and 3 to 6 (unfavorable).

Patients who received thrombolysis were compared to those without thrombolysis with respect to clinical characteristics, functional outcomes and the presence of sHT. Pearson’s chi-square test or Fisher’s exact test was used for categorical variables, and Mann-Whitney’s U test or Student’s t-test was for continuous variables. Similar comparisons were made between patients aged 80 years or more and less than 80 years.

For the effectiveness of thrombolysis, multivariable logistical regression analysis was performed on patients who met the eligibility criteria and in whom mRS at 3 months was available. The safety of thrombolysis was examined in all patients who met the eligibility criteria. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for the favorable outcome at 3 months (mRS≤2) and the presence of sHT, respectively. Variables for adjustments were selected as follows. First, we selected variables that have been reported to be associated with functional outcome after stroke according to previous reports.26-28 Second, among them, variables of P<0.25 in association with thrombolysis were chosen finally for adjustments. The similar process was repeated for safety outcome and sHT. To investigate whether the

| TABLE 1. Baseline characteristics of study subjects according to thrombolysis (n=1,195) |
|-----------------------------------------------|-----------------------------------------------|------------------|
|                                              | Thrombolysis (n=271)                         | No thrombolysis (n=924) | P value* |
| Age, yr                                       | 68.0±12.9                                   | 67.8±12.8            | 0.81     |
| Age<80                                        | 225 (83.0)                                  | 751 (81.3)           | 0.51     |
| Age≥80                                        | 46 (17.0)                                   | 173 (18.7)           |          |
| Male                                          | 154 (56.8)                                  | 554 (60.0)           | 0.36     |
| TOAST classification                           |                                              |                   |
| SVO                                           | 4 (1.5)                                     | 190 (20.6)           |          |
| LAD                                           | 102 (37.6)                                  | 318 (31.8)           |          |
| CE                                            | 115 (42.4)                                  | 210 (22.7)           |          |
| Other                                         | 7 (2.6)                                     | 28 (3.0)             |          |
| Undetermined                                  | 43 (15.9)                                   | 178 (19.3)           |          |
| NIHSS                                         | 13 (7-18)                                   | 4 (2-7)              | <0.001   |
| FAT to arrival time, min                      | 65 (38-120)                                 | 248 (120-441)        | <0.001   |
| SBP, mmHg                                     | 155.6±27.8                                  | 159.7±28.3           | 0.04     |
| DBP, mmHg                                     | 84.3±17.3                                   | 85.7±16.5            | 0.24     |
| Initial Blood Glucose, mg/dL                  | 134.0±1.3                                   | 137.3±1.4            | 0.25     |
| Prestroke antiplatelet                         | 79 (29.2)                                   | 312 (33.8)           | 0.15     |
| Prestroke anticoagulant                        | 28 (10.3)                                   | 57 (6.2)             | 0.02     |
| DM                                            | 63 (23.3)                                   | 264 (28.6)           | 0.08     |
| Hypertension                                  | 160 (59.0)                                  | 547 (59.2)           | 0.96     |
| Hyperlipidemia                                 | 34 (12.5)                                   | 160 (17.3)           | 0.06     |
| Atrial fibrillation                            | 43 (15.9)                                   | 45 (4.9)             | <0.001   |
| History of stroke                              | 60 (22.1)                                   | 206 (22.3)           | 0.96     |
| Smoking                                       | 89 (32.8)                                   | 343 (37.1)           | 0.2      |
| Prestroke mRS                                  |                                              |                   |
| 0 to 2                                        | 248 (91.5)                                  | 823 (89.1)           |          |
| 3 to 6                                        | 23 (8.5)                                    | 101 (10.9)           |          |

Values are mean±SD or median (interquartile range) for continuous variables, and absolute number (percentages) for categorical variables. *P values were calculated by Person’s chi-square test, Student’s t-test, or Mann-Whitney’s U test when appropriate. SVO: small vessel occlusion, LAD: large artery disease, CE: cardioembolism, NIHSS: NIH stroke scale, FAT: first abnormal time, SBP: systolic blood pressure, DBP: diastolic blood pressure, FBS: fast blood sugar, DM: diabetes mellitus, mRS: modified Rankin scale.
Effectiveness of thrombolysis was age-dependent or not, we introduced an interaction term (thrombolysis × age group) into the multivariable models.

As a sensitivity analysis, the stratified analysis using propensity score was performed. With the use of a multivariable logistic regression model that includes basic clinical parameters as the independent variables, the probability of a patient’s being assigned to thrombolysis was determined. The goodness-of-fit of the propensity score model was obtained by c statistics and the Hosmer and Lemeshow Test. The population was then divided into quintiles according to the propensity score. Using these quintile groups, we performed conditional logistic regression and compared outcomes.

All statistical analyses were performed with SAS 9.2 (SAS Institute, Cary, NC). A two-sided P value <0.05 was considered as the minimum level of statistical significance. This study was approved by the local institutional review board.

Results

One-thousand two-hundred twelve patients were hospitalized due to ischemic stroke within 12 hours after symptom onset during the study period and 1195 (98.6%) met the eligibility criteria. Ten patients who received thrombolysis prior to our institution and 7 who did after 12 hour from symptom onset were excluded from the study. Those 1195 patients were used for the analysis of the baseline characteristics and the safety analysis. The effectiveness analysis was performed on 1,143 subjects after excluding 52 (4.4%) in whom mRS at 3 months was not available.

Among the safety analysis dataset (n=1,195), 271 (22.6%) received thrombolysis. Among them, 94 (34.7%) were treated with IV thrombolysis only, 80 (29.5%) with IA thrombolysis only, and 97 (35.8%) with combined thrombolysis (See the Appendix 2). Patients who were treated with tPA dose of 0.6 mg/kg were 177 (92.7%) of 191 with IV or combined thrombolysis. Median intervals from first admission time (FAT) to starting thrombolysis were 135 minutes in all patients with IV thrombolysis only, 285 minutes in those with IA thrombolysis only, and 119 minutes in those with combined thrombolysis. There was no difference in thrombolysis-related factors between patients aged ≥80 and <80 years except interval from FAT to starting treatment in the combined thrombolysis group.

Comparison of baseline characteristics according to whether thrombolyzed or not were presented in Table 1. The thrombolysis group had higher initial NIHSS score, shorter interval from FAT (first abnormal time, when stroke symptoms were first detected) to arrival, lower systolic BP, more frequently anticoagulants prior to stroke, atrial fibrillation, and cardioembolic stroke, and less frequently small vessel occlusion (P<0.05).

Two-hundred nineteen patients (18.3%) were aged ≥80 years. These elderly patients were more likely to have female sex, cardioembolism, atrial fibrillation, and worse prestroke mRS, and were less likely to have DM, hyperlipidemia, and smoking (See the Appendix 1). Baseline NIHSS was higher, and diastolic BP and initial blood glucose were lower in the elderly.

Among the effectiveness analysis dataset (n=1,143), the proportion of patients with a favorable outcome was lower with thrombolysis group than without thrombolysis group (Table 2). The mortality during the first 3 months was 14.3% in the thrombolysis group and 6.2% in the no thrombolysis group. Among the safety analysis dataset (n=1,195), sHT developed in

| TABLE 2. Effectiveness and safety outcomes according to age group |
|---------------------------------------------------------------|
| mRS at 3 months | mRS at 3 months | P value* |
|----------------|----------------|----------|
| (0-2)          | (3-6)          |          |
| Total (n=1,143)| <0.001         |          |
| Thrombolysis   | 117 (45.4)     | 141 (54.7)|          |
| No thrombolysis| 565 (63.8)     | 320 (36.2)|          |
| Age≥80         | 0.09           |          |
| Thrombolysis   | 9 (21.4)       | 33 (78.6) |
| No thrombolysis| 58 (35.4)      | 106 (64.6)|          |
| Age<80         | <0.001         |          |
| Thrombolysis   | 108 (50.0)     | 108 (50.0)|          |
| No thrombolysis| 507 (70.3)     | 214 (29.7)|          |

| Symptomatic hemorrhage transformation | Yes | No |
|---------------------------------------|-----|----|
| Total (n=1,195)                      | <0.001 |
| Thrombolysis                         | 26 (9.6) | 245 (90.4) |
| No thrombolysis                      | 12 (1.3)  | 912 (98.7) |
| Age≥80                                | <0.001  |
| Thrombolysis                         | 7 (15.2)  | 39 (84.8)  |
| No thrombolysis                      | 3 (1.7)   | 170 (98.3) |
| Age<80                                | <0.001  |
| Thrombolysis                         | 19 (8.4)  | 206 (91.6) |
| No thrombolysis                      | 9 (1.2)   | 742 (98.8) |

Values are number of patients (%).
P values were calculated by Pearson’s chi-square test or Fisher’s exact test when appropriate.
38 (3.2%); 26 (9.6%) in the thrombolysis group and 12 (1.3%) in the no thrombolysis group. Those associations of thrombolysis with unfavorable functional outcome and sHT were unchanged with stratification by age (Table 2).

The effectiveness of thrombolysis using mRS≤2 at 3 months as an outcome variable was examined with adjustments for baseline NIHSS, prestroke mRS, stroke subtype, SBP, blood glucose, DM, atrial fibrillation, and FAT to Arrival (Table 3). The adjusted OR was 1.70 in all age group and 95% CI was 1.08 to 2.68 (data not shown). The P value for the interaction term of thrombolysis and age group was 0.91. The estimated OR of thrombolysis for each age group was 1.61 (95% CI, 0.58-4.49) in the aged ≥80 and 1.71 (1.05-2.78) in the aged <80. The results of safety analysis were similar to those of effectiveness analysis (Table 3). The adjusted OR in all age group was 4.72 (1.94 to 11.45, data not shown) with no significant interaction between thrombolysis and age group (P=0.86).

The sensitivity analysis using the stratification by propensity score showed also that there were no significant interaction with respect to both effectiveness (P=0.88) and safety (P=0.83) (See the Appendix 3).

**Discussion**

With respect to the effectiveness, our patients receiving thrombolysis had lesser favorable outcome (45.4%) than those in national institute of neurological disorders and stroke (NINDS) trial (50%) and safe implementation of thrombolysis in stroke monitoring (SITS-MOST) registry (55%). However, comparing with them, our patients had more often a previous stroke history, had more severe neurological deficits at presentation, were more disabled before stroke, and were hospitalized later. Furthermore,
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The prolyse in acute cerebral thromboembolism II (PROACT-II) trial showed that patients attaining independency at 3 months were only 40% despite IA thrombolysis. According to researches separating age group, the rate of independency at 3 month was 58% to 63% in younger patients with only IV thrombolysis, which was 16% to 36% in elderly. Korea single center pilot study showed that the favorable outcome at 3 month was 68% in younger patients but 29% in the elderly. Recently, based on the SITS-ISTR dataset, it was reported that the very elderly were functionally less independent than the young. Compared with past reports, independency of our study was slightly lower in both young and elderly patients due to the reasons mentioned above.

However, our analysis demonstrated that thrombolytic treatments for acute ischemic stroke were associated with better functional outcomes (OR, 1.70; 95% CI, 1.08 to 2.68), and then there was no difference in the effectiveness of thrombolytic treatments between the aged ≥80 and <80 (OR, 1.61 vs. 1.71; the P value of the interaction term was 0.91). Our findings could be reinforced by the sensitivity analysis using propensity and by the very recent report from the Virtual International Stroke Trials Archive (VISTA) group. They gathered the individual patient data on 5,817 subjects from the various neuroprotection trials conducted from 1998 to 2007 and analyzed and compared the effect of IV thrombolysis between the aged ≤80 and >80. For mRS 0 to 2, the ORs adjusting for age and baseline NIHSS were 1.54 for the aged ≤80 and 1.52 for the aged >80.

With respect to the safety, the development of sHT in the thrombolysed patients was not infrequent in our study (9.6% in all, 15.2% in ≥80 years and 8.4% in <80) compared to previous thrombolysis trials. The rate of sHT in patients with IV thrombolysis was reported 1.7% in the SITS-MOST and 6.4% in the NINDS tPA trial (1% in placebo). Unlike the SITS-MOST, we defined that sHT was hemorrhage associated with any neurologic deterioration in NIHSS during hospitalization. The rate of sHT was 7.3% when applying the criteria of any deterioration in NIHSS within 7 days on the SITS-MOST subjects.

In PROACT II, the sHT developed in 10% of the IA thrombolysis group (2% in the placebo group). A recent observational

| TABLE 4. Multivariable analysis: safety of thrombolysis (symptomatic hemorrhagic transformation) |
|---------------------------------------------------------------------------------------------------------------|
| Variables | Adjusted OR | 95% CI | P value |
|-----------------------|-------------|----------|--------|
| TOAST classification |             |          |        |
| LAD                    | 1           |          |        |
| CE                     | 1.02        | 0.45 to 2.31 | 0.96 |
| SVO+Other+UD          | 0.77        | 0.30 to 1.96 | 0.58 |
| Baseline NIHSS        | 1.09        | 1.05 to 1.14 | <0.01 |
| FAT to arrival time   | 1.00        | 1.00 to 1.00 | 0.80 |
| SBP                    | 1.01        | 0.99 to 1.02 | 0.15 |
| Prestroke antiplatelet |             |          |        |
| No                     | 1           |          |        |
| Yes                    | 2.14        | 1.06 to 4.31 | 0.03 |
| Prestroke anticoagulant |            |          |        |
| No                     | 1           |          |        |
| Yes                    | 2.25        | 0.83 to 6.15 | 0.11 |
| DM                     |             |          |        |
| No                     | 1           |          |        |
| Yes                    | 1.06        | 0.48 to 2.34 | 0.89 |
| Thrombolysis (age≥80)  |             |          |        |
| No                     | 1           |          |        |
| Yes                    | 5.27        | 1.18 to 23.61 | 1.54 |
| Thrombolysis (age<80)  |             |          |        |
| No                     | 1           |          |        |
| Yes                    | 4.52        | 1.67 to 12.25 | 1.52 |

P value is 0.86 for an interaction term between thrombolysis and age group.
study on IA thrombolysis comprising a significant proportion of patients aged ≥80 (28.9%) reported the rate of sHT as 15.8%. Despite using more strict definition of sHT (intracerebral hematoma or hemorrhagic infarction with clinical deterioration likely to result in permanent disability or death within 36 hours), the rate of sHT was 9.9% in the Interventional Management of Stroke (IMS) II trial, which tested the feasibility and safety of combined thrombolysis within 3 hours of onset.

Therefore, the high rate of sHT in this study could be attributed to the different definition of sHT and the inclusion of patients treated with IA thrombolysis and combined thrombolysis. In addition, higher incidence of sHT to thrombolytic treatments in Asian population could be suggested based on recent Japanese and Chinese studies. Although the sHT rate in the elderly who were given thrombolysis was higher than in the younger in our study, as previously reported, neither the adjusted ORs were apparently different (5.27 in the aged ≥80 and 4.52 in the aged <80), nor there was significant interaction between age group and thrombolysis (P=0.86). The VISTA group did not report the analysis results about sHT.

In most cases (92.7%), the low dose tPA (0.6 mg per kg) was used, even in patients treated with IV thrombolysis only (87.2%). The Japan alteplase clinical trial (J-ACT) and another retrospective multicenter observational study conducted in Japan (the SAMURAI register) reported that the proportion of good outcome through low dose IV tPA therapy was comparable to that from the western postmarketing surveys using 0.9 mg/kg alteplase. In our study, the proportion of favorable outcome at 3 months (mRS 0-2) was 45.4%, which was not different from that of the SAMURAI register (47.6%).

Thrombolysis was not performed to the elderly patients for different reasons from young patients. Korea multicenter study reported that a smoking, prestroke history, prestroke disability and NIHSS at admission were associated with receiving thrombolysis in patients over 80 years and the most common cause for rejecting thrombolysis was minor stroke and rapid improvement. Comparing with patients less than 80 years in our data, elderly patients had a lesser smoking, higher NIHSS at admission, more AF and more disability before stroke but similar FAT to arrival time, rate of past stroke and rates of thrombolysis (Appendix 1 or 2). Although we could not find why no thrombolysis did in each case, selection bias by age may be little effect to our final results due to following reasons: 1) all thrombolysis have been decided by trained stroke specialist in our hospital, 2) thrombolysis rates (in IV, IA or combined) were not different between two age groups, 3) effectiveness and safety were not different between both groups after adjustment for the different factors.

This study has some limitations. First, this is the single center observation study. A randomized controlled trial is the best way to look into the efficacy of treatment. Although the NINDS study included patients aged >80, the proportion of the elderly was small. Two large clinical trials are ongoing and we should wait for the results of these trials to get the final answer to our question. Second, we should admit that the heterogeneity in thrombolytic treatments may limit the generalization of the study results. Unfortunately, insufficient sample size did not allow us to analyze separately the modalities of thrombolysis, although they were not statistically different between both age groups (See the Appendix 2). Third, this study certainly possesses limitations of a retrospective cohort study, such as selection bias. However, since the prospective stroke registry was used, we are certain that almost all of sHT cases had been captured, and functional outcome was obtained prospectively in 98% of the study subjects.

In Korea, the use of IV tPA is not reimbursed in patients aged more than 80 years by the health insurance, mostly due to the current tPA labeling in EU. However, the results of this study are strongly supporting that thrombolysis is relatively safe and effective even in the aged 80 years or more. Age should not be the only determinant in deciding whether to do thrombolysis or not in the very elderly with acute ischemic stroke.

Conflicts of Interest

The authors have no financial conflicts of interest.

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APPENDIX 1. Baseline characteristics according to age group (n=1195)

|                | ≥80 years (n=219) | <80 years (n=976) | P value |
|----------------|------------------|------------------|---------|
| Age            | 84.3±3.94        | 64.1±11.02       | <0.001  |
| Male           | 102 (46.6)       | 606 (62.1)       | <0.001  |
| TOAST          |                  |                  | <0.001  |
| SVO            | 24 (11)          | 170 (17.4)       |         |
| LAD            | 61 (27.9)        | 359 (36.8)       |         |
| CE             | 88 (40.2)        | 237 (24.3)       |         |
| Other          | 1 (0.5)          | 34 (3.5)         |         |
| Undetermined   | 45 (20.5)        | 176 (18)         |         |
| NIHSS          | 6 (3-15)         | 4 (2-10)         | <0.001  |
| FAT to arrival time, minutes | 156 (91-332) | 191 (66-381) | 0.79   |
| SBP, mmHg      | 161.7±28.9       | 158.0±28.0       | 0.08    |
| DBP, mmHg      | 82.00±16.2       | 86.12±16.7       | 0.01    |
| Blood Glucose, mg/dL | 134.45±38.6 | 148.80±66.5 | 0.02   |
| Prestroke antiplatelet | 70 (32) | 321 (32.9) | 0.79   |
| Prestroke anticoagulant | 15 (6.8) | 70 (7.2) | 0.87   |
| DM             | 36 (16.4)        | 291 (29.8)       | <0.001  |
| Hypertension   | 141 (64.4)       | 566 (58)         | 0.08    |
| Hyperlipidemia | 19 (8.7)         | 175 (17.9)       | 0.01    |
| Atrial fibrillation | 34 (15.5) | 54 (5.5) | <0.001  |
| History of stroke | 57 (26) | 209 (21.4) | 0.14   |
| Smoking        | 49 (22.4)        | 383 (39.2)       | <0.001  |
| Prestroke mRS  |                  |                  | <0.001  |
| 0 to 2         | 174 (79.5)       | 897 (91.9)       |         |
| 3 to 6         | 45 (20.5)        | 79 (8.1)         |         |

Values are mean±SD or median (interquartile range) for continuous variables, and absolute number (percentages) for categorical variables. 

*P values are calculated by Pearson chi-square test for categorical variables, and by Mann-Whitney’s U test or Student’s t-test for continuous variables when appropriate.
APPENDIX 2. Summary of thrombolysis procedures (n=271)

| Variables                        | ≥80 years | <80 years | P value* |
|----------------------------------|-----------|-----------|----------|
| Type of thrombolysis             |           |           | 0.29     |
| IV only                          | 14 (30.4) | 80 (35.6) |          |
| IA only                          | 18 (39.1) | 62 (27.6) |          |
| Combined                         | 14 (30.4) | 83 (36.9) |          |
| IV tPA dose (n=191)              |           |           | 0.41     |
| 0.6 mg/kg                        | 27 (96.4) | 150 (92.0)|          |
| 0.9 mg/kg                        | 1 (3.6)   | 13 (8.0)  |          |
| FAT to thrombolysis starting time|           |           | 0.17     |
| ≤ 3 hr                           | 26 (56.5) | 151 (67.1)|          |
| > 3 hr                           | 20 (43.5) | 74 (32.9) |          |
| FAT to starting IV thrombolysis, min | 137 (110-177) | 135 (105-178) | 0.99 |
| Arrival to starting IV thrombolysis, min | 73 (59-81) | 69 (50-98) | 0.69 |
| FAT to starting IA thrombolysis, min | 258 (193-312) | 300 (194-356) | 0.26 |
| Arrival to starting IA thrombolysis, min | 119 (102-146) | 114 (88-156) | 0.55 |
| FAT to starting combined thrombolysis, min | 161 (109-198) | 115 (90-150) | 0.01 |
| Arrival to starting combined thrombolysis, min | 69 (57-90) | 59 (47-78) | 0.06 |

Values are a median [interquartile range] or an absolute number [percentage].

*P values are calculated by Pearson chi-square test for categorical variables, and by Mann-Whitney’s U test or Student’s t-test for continuous variables when appropriate.

APPENDIX 3. Sensitivity analysis using propensity score

| Variables                        | Adjusted OR | 95% CI  |
|----------------------------------|--------------|---------|
| Effectiveness of thrombolysis*: mRS≤2† |              |         |
| Thrombolysis (age≥80)            |              |         |
| No                               | 1            |         |
| Yes                              | 1.61         | 0.57 to 4.49 |
| Thrombolysis (age<80)            |              |         |
| No                               | 1            |         |
| Yes                              | 1.75         | 1.05 to 2.91 |
| Safety of Thrombolysis*: sHT§     |              |         |
| Thrombolysis (age≥80)            |              |         |
| No                               | 1            |         |
| Yes                              | 4.95         | 1.10 to 22.28 |
| Thrombolysis (age<80)            |              |         |
| No                               | 1            |         |
| Yes                              | 4.14         | 1.56 to 10.95 |

*P value is 0.88 for an interaction term between thrombolysis and age group, †Adjusted forBaseline NIHSS, prestroke mRS, Stroke Subtype, SBP, Blood Glucose, DM, Atrial fibrillation, and FAT to Arrival, §P value is 0.83 for an interaction term between thrombolysis and age group, †Adjusted for baseline NIHSS, stroke subtype, SBP, DM, prestroke antiplatelet, prestroke anticoagulant, and FAT to Arrival.