Influence of Age on Thrombolysis Outcome in Wake-Up Stroke

Dulka Manawadu, MRCP; Shankaranand Bodla, MD; Jeff Keep, FCEM; Lalit Kalra, PhD

Background and Purpose—Thrombolysis in patients >80 years remains controversial; we hypothesized that >80-year-old patients with wake-up ischemic stroke (WUIS) will benefit from thrombolysis despite risks because of poor outcomes with no treatment.

Methods—The study included 68 thrombolysed patients with WUIS (33 [48%] >80 years), 54 nonthrombolysed patients with WUIS (21 [39%] >80 years), and 117 patients (>80 years old) thrombolysed within 4.5 hours of symptom onset (reference group). Mortality and modified Rankin Scale (mRS) were assessed at 90 days.

Results—Baseline characteristics of thrombolysed and nonthrombolysed >80 and ≤80-year-old patients with WUIS were comparable. Thrombolysis outcomes in >80-year-old patients with WUIS were better than in nonthrombolysed >80-year-old patients with WUIS (90-day mortality: 24% versus 47%, \( P=0.034 \); mRS 0–2: 30% versus 5%, \( P=0.023 \); mRS 0–1: 15% versus 5%, \( P=0.24 \)) and comparable with thrombolysed ≤80-year-old patients with WUIS. Thrombolysis was associated with odds ratio 0.27 (95% confidence interval, 0.05–0.97) for mortality and odds ratio 28.6 (95% confidence interval, 1.8–448) for mRS 0 to 2 at 90 days in >80-year-old patients with WUIS after adjusting for stroke severity and risk factors.

Conclusions—Thrombolysis may be associated with greater benefit in >80-year-old patients with WUIS but a selection bias favoring thrombolysis in those most likely to benefit may significantly reduce interpretability of these findings. (Stroke. 2013;44:2898-2900.)

**Key Words:** aging ■ outcomes ■ stroke management ■ thrombolysis ■ wake-up stroke

Patients who are >80 years old constitute a third of strokes but are excluded from clinical trials and recombinant tissue-type plasminogen activator license. Although >80-year-old patients with stroke have 2-fold higher mortality and morbidity even with thrombolysis compared with ≤80-year-old patients, pooled results of thrombolysis and neuroprotection trials suggest potential for benefit with thrombolysis in >80-year-old patients. This may be important for patients wake-up ischemic stroke (WUIS), who are significantly older, constitute 14% of acute presentations, and 36% may be eligible for thrombolysis. We have shown that thrombolysis improves outcomes in patients with WUIS and hypothesize that >80-year-old patients with WUIS benefit more from thrombolysis than ≤80-year-old patients because of worse outcomes without treatment.

**Methods**

We compared outcomes in thrombolysed and nonthrombolysed >80- and ≤80-year-old patients with WUIS, sampled consecutively from a prospective register between January 2009 and December 2010. Selection criteria were the following: (1) last seen normal <12 but ≥4.5 hours from symptom onset; (2) persistent deficits with National Institute of Health Stroke Scale (NIHSS) score ≥5; (3) no or early ischemic changes in <1/3 middle cerebral artery territory on noncontrast CT scan (4) meet thrombolysis criteria apart from time. The decision to thrombolysed was based on the treating physician’s judgment on patients’ potential to benefit. Of the qualifying patients with WUIS, 68 were thrombolysed and 54 were not thrombolysed. A reference group of 117 patients, who were >80 years old, thrombolysed within 4.5 hours of stroke onset was recruited for comparison.

Patient data were extracted from the register and verified against source data. The primary outcome was the modified Rankin Scale (mRS) assessed at 90 days and defined as excellent (mRS 0–1) or favorable (mRS 0–2). Symptomatic intracerebral hemorrhage was defined by European Cooperative Acute Stroke Study (ECASS-II) criteria at 24 hours. All analyses were prespecified; data are presented and compared using appropriate parametric and nonparametric tests. Logistic regression with forward selection was used to assess the independent association between thrombolysis and mRS 0 to 2 at 90 days and mortality to adjust for baseline NIHSS score, diabetes mellitus, and atrial fibrillation, which also showed significant associations in univariate analyses. Two-sided values of \( P<0.05 \) were considered significant. IBM-SPSS version 20 was used for analyses.

**Results**

Of the 68 thrombolysed patients with WUIS, 33 (48.5%) were >80 years old, and 35 patients (51.5%) were ≤80 years old. Atrial fibrillation and cardioembolic stroke were more common in patients >80 years old compared with those ≤80 years old (Table). There were no significant differences in other...
baseline variables between the groups. Favorable functional outcomes at 90 days and bleeding rates were comparable between >80- and ≤80-year-old patients with WUIS and the reference group. The reference group had higher mortality but also higher NIHSS score and Alberta Stroke Program Early CT Score (ASPECTS).

Twenty-one patients (39%) of the 54 nonthrombolysed patients with WUIS were >80 years old and comparable with nonthrombolysed ≤80-year-old patients with WUIS and thrombolysed >80-year-old patients with WUIS (Table). Nonthrombolysed >80-year-old patients with WUIS had significantly worse functional outcomes and mortality compared with younger patients (Table).

Thrombolysed >80-year-old patients with WUIS had lower mortality (24% versus 47%; \( P = 0.034 \)), better mRS 0 to 2 (30% versus 5%; \( P = 0.023 \)) and mRS 0 to 1 (15% versus 5%; \( P = 0.24 \)) at 90 days than nonthrombolysed patients >80 years old (Table). There were no significant differences in outcomes between thrombolysed and nonthrombolysed ≤80-year-old patients with WUIS. Thrombolysis was associated with an odds ratio of 0.27 (95% confidence interval, 0.05–0.97), \( P = 0.034 \) for mortality and 28.6 (95% confidence interval, 1.8–448), \( P = 0.017 \) of mRS 0 to 2 at 90 days in >80-year-old patients with WUIS (n=54), after adjusting for baseline NIHSS score, diabetes mellitus, and atrial fibrillation. Thrombolysis was not an independent predictor of mortality or mRS 0 to 2 at 90 days in ≤80-year-old patients with WUIS (n=68).

**Discussion**

Patients with stroke, who were >80 years old, have higher morbidity and mortality because of prestroke disability or comorbidities and may have more to gain with thrombolysis despite the risks (Figure). This study showed that >80-year-old patients with WUIS who are eligible but not thrombolysed...
had significantly worse outcomes than nonthrombolysed patients ≤80 years, and the benefits of thrombolysis were greater in this age group (Figure). The independent association between thrombolysis and good outcomes in >80-year-old patients with WUIS persisted after adjusting for stroke severity and other prognostic covariates in multiple logistic regression. The bleeding risk with thrombolysis in >80-year-old patients with WUIS was comparable with ≤80-year-old patients with WUIS and the reference group.

The study is a nonrandomized comparison in a small sample, and thrombolytic therapy in WUIS is not proven. The sample consisted of consecutive patients meeting predefined criteria for thrombolysis but selection bias in thrombolysis favoring those likely to benefit reduces interpretability. The potential effect of baseline differences in covariates was accounted for in the multiple logistic regression; the effect of thrombolysis was statistically significant in patients ≥80 but not ≤80 years. Although baseline data did not show any statistical difference between the groups, the findings of this study need to be interpreted cautiously because subjective bias in selection for thrombolysis and unmeasured age-related confounders remain unknown.

Sources of Funding
This work was funded by Research and Development, King’s College Hospital.

References

Disclosures
None.
Influence of Age on Thrombolysis Outcome in Wake-Up Stroke
Dulka Manawadu, Shankaranand Bodla, Jeff Keep and Lalit Kalra

Stroke. 2013;44:2898-2900; originally published online August 1, 2013;
doi: 10.1161/STROKEAHA.113.002273

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/44/10/2898

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/