Impact of Obesity on Stroke Outcome After Intravenous Thrombolysis

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Background and Purpose—Obesity is an established risk factor for stroke and has reached epidemic proportions. However, its impact on intravenous thrombolysis applied for acute ischemic stroke is not well known. We aimed to compare the clinical outcome and safety after intravenous thrombolysis in obese (body mass index $\geq 30$ kg/m²) and nonobese (body mass index $<30$ kg/m²) patients with ischemic stroke.

Methods—Data of 304 consecutive patients with stroke (251 nonobese and 53 obese) treated with intravenous thrombolysis were studied. We assessed the rate of favorable outcome (modified Rankin Scale score 0 or 1), mortality, and symptomatic intracranial hemorrhage in the 2 groups.

Results—Obese patients presented more often with diabetes mellitus (30.2% versus 12.4%, $P<0.01$) and arterial hypertension (77.4% versus 61.4%, $P=0.03$) as compared with their nonobese counterparts. At 3 months, the rate of favorable outcome was lower in obese compared with nonobese patients (50.9% versus 68.1%, $P=0.02$). More obese than nonobese patients died (13.2% versus 4.0%, $P=0.01$), whereas the rate of symptomatic intracranial hemorrhage was similar in the 2 groups (1.9% versus 1.6%, $P=1.0$). After multivariable adjustment, obesity still remained an independent predictor of unfavorable outcome ($P=0.04$) and mortality ($P=0.04$).

Conclusions—Our data indicate that obesity is an independent predictor of unfavorable clinical outcome and mortality in acute ischemic stroke treated with intravenous thrombolysis. (Stroke. 2011;42:2330-2332.)

Key Words: ischemia ■ obesity ■ outcome ■ thrombolysis

Obesity is an established vascular risk factor with increasing prevalence and a huge impact on public health worldwide. It has been shown to be an independent predictor for ischemic stroke with an 4% risk increase for each unit augmentation in body mass index. Thus, obese patients will constitute an increasing subgroup of candidates for intravenous thrombolysis (IVT). However, little is known about the impact of obesity on outcome in patients with stroke treated with IVT. Therefore, we aimed to assess the clinical outcome and safety in obese and nonobese patients undergoing IVT for acute ischemic stroke.

Methods
We studied prospectively collected data of consecutive patients with acute ischemic stroke who underwent IVT with alteplase but no other or additional thrombolytic treatment at the University Hospital of Zurich between January 1, 2005, and November 30, 2008. Routine baseline investigations and definition of variables have been reported in a previous study. Body mass index was calculated as weight in kilograms divided by height squared in meters. Body weight and height were either obtained from the patient or the accompanying relatives at admission or measured by a nurse during the hospital stay. Patients were classified as obese when body mass index was $\geq 30$ kg/m². Intravenous thrombolysis was performed according to current guidelines except the use of extended time window up to 4.5 hours, the latter based on a pooled analysis presented at the 27th International Stroke Conference in February 2002 (San Antonio, TX). Patients and relatives were informed about the off-label use of alteplase beyond the 3-hour time window and informed consent was obtained before IVT. All patients were monitored in our stroke unit for at least 24 hours after thrombolysis. The study is approved by the local ethics committee.

Outcome Measurements
Symptomatic intracranial hemorrhage was defined as neurological deterioration causing a $\geq$4-point worsening on the National Institutes of Health Stroke Scale causally related to intracranial hemorrhage detected by cerebral computed tomography within 36 hours after initiation of IVT. Asymptomatic intracranial hemorrhage was defined as any intracranial hemorrhage without neurological deterioration. Clinical outcomes were mortality and the modified Rankin Scale score at 3 months, the latter dichotomized into favorable (0 to 1) and unfavorable (2 to 6).

Statistical Analysis
Statistical analysis was performed with SPSS 10.0 for MacIntosh statistical software (SPSS Inc). Statistical significance for intergroup differences was assessed by the $\chi^2$ or Fisher exact test (the latter if some expected counts in the $2\times2$ table were too low) for categorical variables and the Mann-Whitney $U$ test for continuous variables.

Received August 10, 2010; final revision received January 21, 2011; accepted February 10, 2011.

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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.110.599613

2330
| Table. Baseline Characteristics in Patients With BMI ≥30 kg/m² Versus BMI <30 kg/m² |
|-------------------------------|-------------------------------|-----------------|
|                              | BMI ≥30                       | BMI <30         | P   |
|                              | kg/m² | kg/m² | (n=53) | (n=251) |     |
| Mean age±SD, y               | 63.6±13.6 | 63.6±14.7 | 0.99 |
| Male sex                     | 62.3 (33) | 66.1 (166) | 0.63 |
| Hypertension                 | 77.4 (41) | 61.4 (154) | 0.03 |
| Diabetes mellitus            | 30.2 (16) | 12.4 (31) | <0.01 |
| Coronary artery disease      | 15.1 (8) | 17.1 (43) | 0.84 |
| Current smoking              | 28.3 (15) | 26.7 (67) | 0.87 |
| Total cholesterol SD, mmol/L | 5.2±1.2 | 5.1±1.2 | 0.52 |
| Prestroke antiplatelet treatment | 35.8 (19) | 32.3 (81) | 0.63 |
| Admission systolic blood pressure SD, mm Hg | 154.6±23.1 | 154.1±26.4 | 0.90 |
| Admission diastolic blood pressure SD, mm Hg | 87.8±13.9 | 88.9±14.2 | 0.66 |
| Admission blood glucose SD, mmol/L | 7.2±2.6 | 6.6±2.3 | 0.12 |
| Baseline NIHSS score SD      | 10.7±5.9 | 10.0±5.5 | 0.37 |
| Stroke onset to treatment time SD, min | 161.3±38.6 | 158.4±43.0 | 0.65 |
| Stroke subtype (TOAST classification) | 49.1 (26) | 53.0 (133) | 0.09 |
| Cardioembolism               | 49.1 (26) | 53.0 (133) | 0.09 |
| Large-artery atherosclerosis | 17.0 (9) | 6.4 (16) | 0.66 |
| Small-vessel disease         | 9.4 (5) | 6.4 (16) | 0.66 |
| Other determined etiology    | 3.8 (2) | 5.2 (13) | 0.66 |
| Undetermined etiology        | 20.7 (11) | 29.0 (73) | 0.66 |

Values are percent (no.) unless noted otherwise. BMI indicates body mass index; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

Backward stepwise logistic regression analyses were performed to assess an independent association between obesity and the predefined endpoints. The variables included were age, gender, hypertension, diabetes mellitus, smoking status, baseline National Institutes of Health Stroke Scale score, time from stroke onset to treatment, and prestroke treatment with antiplatelet agents. Significance was declared at the 2-sided P<0.05 level.

Results

A total of 304 patients were eligible for this study; 53 (17%) of them were obese (mean body mass index 33.2 kg/m²) and 251 (83%) nonobese (mean body mass index 25.1 kg/m²). Obese patients presented more often with arterial hypertension and diabetes mellitus as compared with their nonobese counterparts, whereas age, stroke severity, time to treatment, and other baseline characteristics were similar in both cohorts (Table). At 3 months, 27 of 53 (50.9%) obese and 171 of 251 (68.1%) nonobese patients experienced a favorable outcome (P=0.02), whereas 7 of 53 obese (13.2%) and 10 of 251 (4.0%) nonobese patients died (P=0.01; Figure). Symptomatic intracranial hemorrhage occurred in 1 of 53 (1.9%) obese and 4 of 251 (1.6%) nonobese patients (P=1.0), whereas asymptomatic intracranial hemorrhage was observed in 7 of 53 (13.2%) obese and 35 of 251 (13.9%) nonobese patients (P=0.62). Logistic regression analyses identified a higher baseline National Institutes of Health Stroke Scale score (P<0.01) and obesity (P=0.04) as independent predictors of unfavorable clinical outcome, whereas baseline National Institutes of Health Stroke Scale score (P<0.01), age (P=0.01), time to treatment (P=0.02), and obesity (P=0.04) predicted mortality independently.

Discussion

Our study suggests an adverse influence of obesity on IVT in ischemic stroke. Obese patients had less often a favorable outcome and were at higher mortality risk as compared with their nonobese counterparts. Logistic regression analyses suggest that the poor outcome in the obese cohort is independent from the associated vascular risk factors such as hypertension or diabetes mellitus.

Several reasons might explain the unfavorable clinical outcome in obese patients with stroke treated with IVT. First, obesity has been shown to be associated with a proinflammatory and prothrombotic state,6,7 thus potentially hampering the clot-dissolving effect of alteplase. Plasminogen activator inhibitor-1 is a main inhibitor of fibrinolysis and seems to be consistently overexpressed in adipose tissue.8 Furthermore, obesity is closely associated with the metabolic syndrome,9 and the rate of middle cerebral artery recanalization is lower.

Figure

Proportion of obese (body mass index [BMI] ≥30 kg/m²) and nonobese (BMI <30 kg/m²) patients according to the modified Rankin Scale (mRS) scores at 3 months.
in patients as compared with those without metabolic syndrome.\textsuperscript{10} Second, body weight was $>100$ kg in 13 (25\%) obese patients; thus, the dose of alteplase might have been insufficient in these patients because the maximum dose is limited at 90 mg. In line with this, increased body weight in patients with acute myocardial infarction was associated with lower probability of coronary artery recanalization after IVT.\textsuperscript{11} Because pretreatment status of cerebral arteries and recanalization were unknown in our study, however, we have no means to support this hypothesis. Third, obese patients might be prone to more in-hospital complications such as venous thromboembolism.\textsuperscript{12} In our study, obesity was associated with a higher mortality rate. This finding is in line with a previous study that reported a greater risk of all-cause and cardiovascular death among patients with stroke with higher body mass index.\textsuperscript{13} The symptomatic intracranial hemorrhage risk in the obese cohort was similar compared with the nonobese patients. However, the low number of symptomatic intracranial hemorrhage precludes any definite conclusions on hemorrhage risk of IVT in obese patients with stroke.

This study has some limitations. The cohort size of obese patients is small and does not allow us to generalize our findings. Thus, our observation should be interpreted with caution and needs to be confirmed by further studies. Metabolic syndrome and hyperglycemia, both associated with obesity and higher resistance to IVT,\textsuperscript{10,14} might have contributed to the effect of obesity. Another limitation of this study is that body weight and height were self-reported by patients or caregivers in part, although the validity of self-reported measurements of body weight has been shown.\textsuperscript{15} Finally, the outcomes were measured in clinical routine and thus were not necessarily obtained by blinded assessors.

In conclusion, our study suggests that obesity is an independent predictor of unfavorable clinical outcome and mortality in patients with stroke treated with IVT. This observation might have a practical consequence because obesity may indicate a subgroup of patients with poor response to IVT, who may benefit from more aggressive treatment and monitoring strategies.

**Disclosures**

None.

**References**


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*Stroke*. 2011;42:2330-2332; originally published online July 14, 2011;
doi: 10.1161/STROKEAHA.110.599613

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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World Wide Web at:
http://stroke.ahajournals.org/content/42/8/2330

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