Is the Maximum Dose of 90 mg Alteplase Sufficient for Patients With Ischemic Stroke Weighing >100 kg?

Jennifer Diedler, MD; Niaz Ahmed, MD, PhD; Jörg Glahn, MD; Martin Grond, MD; Svetlana Lorenzano, MD; Miroslav Brozman, MD, PhD; Marek Sykora, MD, PhD; Peter Ringleb, MD

**Background and Purpose**—Intravenous alteplase for acute ischemic stroke has a maximum dose limit of 90 mg. Consequently, patients >100 kg body weight receive a lower per-kilogram dose compared with those ≤100 kg. We investigated if the lower per-kilogram dose is associated with poor early neurological improvement and worse outcome after thrombolysis.

**Methods**—Of 27 910 patients registered in Safe Implementation of Treatment in Stroke–International Stroke Thrombolysis Register (SITS-ISTR; 2002 to 2009), 1190 (4.3%) weighed >100 kg. Major neurological improvement was used to estimate recanalization (National Institutes of Health Stroke Scale improvement ≥8 points or score of 0 at 24 hours). Outcome measures included symptomatic intracerebral hemorrhage (National Institutes of Health Stroke Scale deterioration ≥4 points within 24 hours and Type 2 parenchymal hemorrhage), functional independence (modified Rankin Scale 0 to 2), and mortality at 3 months.

**Results**—Patients >100 kg received a lower per-kilogram alteplase dose (0.82 versus 0.90, \( P<0.001 \)), were younger (62 versus 70 years, \( P<0.001 \)), had a lower baseline National Institutes of Health Stroke Scale (10 versus 12, \( P<0.001 \)), but more frequently had cardiovascular risk factors. Major neurological improvement at 24 hours occurred in 27.7% in both groups. Symptomatic intracerebral hemorrhage occurred in 2.6% versus 1.7% (\( P=0.03 \)) in >100 kg versus ≤100 kg. Functional independence was 59.7% versus 53.6% (\( P<0.001 \)) and mortality was 14.4% versus 15.1% (\( P=0.54 \)). After adjustment for baseline characteristics, there was no significant difference for major neurological improvement or functional independence between >100 kg and ≤100 kg, but >100-kg patients had a higher odds ratio for symptomatic intracerebral hemorrhage (OR, 1.6; 95% CI, 1.06 to 2.41; \( P=0.02 \)) and mortality (OR, 1.37; 95% CI, 1.08 to 1.74; \( P=0.01 \)).

**Conclusions**—Our results support the current upper dose limit. There was a higher incidence of symptomatic intracerebral hemorrhage in patients >100 kg despite the lower per-kilogram recombinant tissue plasminogen activator dose. Major neurological improvement and functional independence were similar.

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**Key Words:** stroke ■ thrombolysis ■ weight

Fibrinolytic therapy has a weight-based dose of 0.9 mg/kg with a maximum dose limit of 90 mg according to the European licensing criteria for the application of alteplase for ischemic stroke in the 3-hour timeframe. Consequently, patients >100 kg body weight receive lower doses of alteplase per kilogram body weight compared with those ≤100 kg. However, overweight and obesity have been independently associated with the risk for ischemic stroke and their incidence is increasing in industrialized countries.1-4 Hence, the percentage of patients exceeding 100 kg is expected to rise. So far, there are only limited data available on the success of recanalization therapies in patients >100 kg.5 6 and it is unclear whether the lower dose per kilogram will result in less effective recanalization and poorer outcome in these patients.

Based on the patients registered within the Safe Implementation of Treatment in Stroke (SITS) International Stroke Thrombolysis Register (ISTR; https://sitsinternational.org), we investigated the hypothesis that the maximal alteplase dose of 90 mg may not be sufficient for people >100 kg as measured by major neurological improvement after thrombolysis and/or worse functional outcome.

**Methods**

**Study Population and Design**

The SITS database is a worldwide prospective, open, multinational, multicenter audit of thrombolysis. Details of data collection and management have been published previously.7 8 Data sets comprise information on baseline and demographic characteristics, including body weight, risk factors and medication history, baseline and follow-up stroke severity measured by National Institutes of Health Stroke Scale...
Baseline and follow-up (at 22 to 36 hours) imaging data, and information on functional outcome as assessed by modified Rankin Scale (mRS) at 3 months. The current analysis is based on patients undergoing thrombolysis for acute ischemic stroke and recorded within the SITS-ISTR registry. Recruitment of patients opened on December 25, 2002; the cutoff for the current analysis was November 2, 2009.

Outcome Measures
Outcome measures included major neurological improvement, incidence of symptomatic intracerebral hemorrhage (SICH), and functional outcome and mortality at 3 months.

Major neurological improvement (MNI) was used to estimate recanalization success and defined as improvement of 8 points on the NIHSS or a NIHSS of 0 at either (1) 2 hours; or (2) 24 hours after treatment. Incidence of SICH was assessed according to the SITS Monitoring Study (SITS MOST) criteria (local or remote parenchymal hemorrhage Type 2 on the 22 to 36 hours post-treatment imaging scan combined with a neurological deterioration of 4 points compared with baseline NIHSS or the lowest NIHSS value between baseline and 24 hours) and the European–Australasian Acute Stroke Study (ECASS) II definition (any hemorrhage with neurological deterioration, as indicated by an NIHSS score >4 than the value at baseline or the lowest value within 7 days, or any hemorrhage leading to death). mRS at 3 months was dichotomized into 0 to 2 versus 3 to 6 for independence and 0 to 1 versus 2 to 6 for excellent recovery.

Statistical Analysis
For comparison between patients >100 kg versus ≤100 kg, Pearson χ² and Mann-Whitney U tests were used where appropriate. For categorical variables, percentage proportions were calculated by dividing the number of events by the total number of patients, excluding missing or unknown cases. ORs for the different outcome parameters were calculated by comparing patients weighing >100 kg compared with those ≤100 kg. Adjusted ORs were calculated to account for substantial baseline differences between the 2 groups using logistic regression analysis. All variables that were significant (P < 0.05) in univariate analysis as shown in Table 1 were included in the multivariable model. All statistical analyses were performed using the STATISTICA software (Version 8.0).

Results
Between December 2002 and November 2009, 28,136 patients were registered in SITS-ISTR and information on body

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<tr>
<th>Table 1. Demographic and Clinical Characteristics of Patients Weighing &gt;100 kg Compared With Those ≤100 kg</th>
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<tr>
<td><strong>Baseline Variables</strong></td>
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<td>Alteplase dose, mg</td>
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<td>Lacunar</td>
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<td>Others*</td>
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Data are median (interquartile) or no./No. (%). mRS indicates modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NS, nonsignificant. *Others includes unusual causes and stroke mimics.
weight was available for 27,910 (99.2%) patients. Of these, 14.6% (n = 4,100) had measured and 84.6% (n = 23,810) had estimated weight. A total of 1190 (4.2%) patients were ≤100 kg (median, 110 kg; interquartile range, 13). The median weight of patients ≤100 kg was 75 kg (interquartile range, 18). Figure 1 shows the distribution of body weight in the SITS population.

Baseline Characteristics
Baseline characteristics of patients >100 kg as compared with those ≤100 kg are shown in Table 1. Patients >100 kg predominantly were male (79.9% versus 57.3%, P<0.001), they were significantly younger (62 versus 70 years, P<0.001), and had lower baseline NIHSS scores than patients ≤100 kg (10 versus 12, P<0.001). In contrast, they more frequently had cardiovascular risk factors such as hypertension (73.3% versus 62.6%, P<0.001), diabetes (29.3% versus 16.8%, P<0.001), and hyperlipidemia (45.8% versus 34.8%, P<0.001). Moreover, they had significantly higher baseline glucose levels (127 versus 117, P<0.001) and systolic blood pressure on admission (155 versus 150 mm Hg, P<0.001). Overall, stroke etiology was similar for patients with >100 and ≤100 kg (P=0.16 for the overall group). However, lacunar stroke slightly more often occurred in >100-kg group than ≤100 kg (11% versus 9%, P=0.02).

The median alteplase dose for those >100 kg was 0.82 mg/kg as compared with 0.90 mg/kg for patients ≤100 kg (P<0.001). Onset-to-treatment time did not differ significantly between groups (median, 145 minutes for both groups).

Neurological Improvement After Thrombolysis
At 2 hours, MNI had occurred in 12.4% of patients >100 kg and in 14.0% of those ≤100 kg (OR, 0.86; 95% CI, 0.72 to 1.04; P=0.12; Table 2). At 24 hours, MNI had occurred in 27.7% in both groups (OR, 1.00; 95% CI, 0.87 to 1.15; P=0.99).

<table>
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<th>Table 2. Main Outcomes for Patients Weighing &gt;100 kg Compared With Those ≤100 kg</th>
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<td>Excellent recovery at 3 mo (mRS 0 to 1)</td>
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SITS-ISTR indicates Safe Implementation of Treatment in Stroke–International Stroke Thrombolysis Register; MNI, major neurological improvement; SICH, symptomatic intracerebral hemorrhage; SITS MOST, SITS Monitoring Study; ECASS, European–Australasian Acute Stroke Study; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

*ORs were calculated by comparing patients weighing >100 kg compared with those ≤100 kg.
†Adjusted for variables which were statistically significant (P<0.05) in the univariate analysis: age, sex, history of hypertension, diabetes mellitus, hyperlipidemia, smoking, stroke subtypes (lacunar versus other), baseline NIHSS, baseline blood glucose, blood pressure, and alteplase dose (mg/kg).
The adjusted OR for MNI at 24 hours for patients >100 kg as compared with those ≤100 kg was 1.12 (95% CI, 0.97 to 1.30; P=0.13; Table 2). After adjustment for baseline imbalances, there were no significant differences between the groups with respect to functional outcome at 3 months: the adjusted OR for independence was 0.99 (95% CI, 0.84 to 1.17; P=0.93) and 1.01 (95% CI, 0.87 to 1.18; P=0.87) for excellent recovery. However, despite the absolute lower mortality of patients >100 kg, adjusted ORs for mortality were significantly increased for those >100 kg (OR, 1.37; 95% CI, 1.08 to 1.74; P=0.01).

The adjusted OR for SICH per SITS MOST definition was 1.60 (95% CI, 1.06 to 2.41; P=0.02) and 1.08 (95% CI, 0.81 to 1.43; P=0.60) per ECASS II.

**Discussion**

In the present study, we have analyzed the so far the largest cohort (n=1190) of patients with ischemic stroke weighing >100 kg who were treated with intravenous thrombolysis. One previous small study including only 20 patients has shown a nonsignificant trend for an association between lower doses of recombinant tissue plasminogen activator and unfavorable 3-month outcomes. In our study, we found that although patients >100 kg received a lower per-kilogram alteplase dose, the major neurological improvement at 2 and 24 hours is equal compared with patients ≤100 kg. Furthermore, there was no significant difference in functional outcome at 3 months between the >100-kg and ≤100-kg groups. However, we found a significantly increased rate of SICH according to the SITS MOST definition but not according to the ECASS II definition in patients >100 kg. Although there was no significant difference in the univariate mortality rates between the groups, surprisingly, the adjusted OR for mortality was significantly higher in the >100-kg group than the ≤100-kg group.

Solid evidence from transcranial Doppler studies and a study based on SITS data supports the close association between successful recanalization and MNI. The threshold of ≥8-points improvement on the NIHSS score was chosen in accordance with the literature, suggesting that lower thresholds may be too insensitive to the effects of alteplase. Reanalyzing data from the National Institute of Neurological Disorders and Stroke (NINDS) trial, Brown and colleagues investigated predictors for MNI within 24 hours, including weight >100 kg among other variables. Seven percent (n=27) of the patients were weighing >100 kg compared with 4.3% (n=1190) in our study. Comparable to our data, the overall percentage of MNI was 32.5%, and MNI was found to be predictive for favorable functional outcome at 3 months. In this previous study, only age and stroke onset-to-treatment time were independently associated with MNI. Weight >100 kg did not exert a significant negative
effect on MNI. This result was confirmed in our current study.

However, another reanalysis of the NINDS data including 20 recombinant tissue plasminogen activator (rtPA)-treated patients >100 kg reported a nonsignificant trend for an association between lower doses of rtPA and unfavorable 3-month outcomes. Furthermore, weight >100 kg was a predictor of poor outcome and neurological deterioration after rtPA treatment. In contrast, including a by far larger population, we did not find a significant difference in odds for favorable functional outcome at 3 months between the 2 groups after adjustment for baseline imbalances. This finding again points toward sufficient efficacy of the maximum dose of 90 mg rtPA in patients >100 kg. The unadjusted analysis surprisingly showed a higher proportion of patients >100 kg achieving a favorable functional outcome compared with patients ≤100 kg. This finding most likely could be attributed to the fact that patients >100 kg were 8 years younger and had 2 points less severe strokes as measured by NIHSS score, age, and stroke severity being among the strongest predictors of outcome after ischemic stroke.

Interestingly, at the same time, the incidence of SICH per SITS MOST definition was significantly higher in patients >100 kg despite the significantly lower alteplase dose, the younger age, and less severe stroke. ORs for SICH per SITS definition remained significantly higher after adjustment for baseline imbalances. This finding is in line with a recently published analysis of the SITS MOST cohort including 6483 patients, identifying body weight as an independent predictor of SICH per SITS MOST definition (by 1 SD of 13.9; OR, 1.32; 95% CI, 1.09 to 1.60). In the same analysis, it was observed that a lower per-kilogram alteplase dose was associated with higher mortality, which was also confirmed in the current analysis. Although the point estimate for mortality at 3 months was lower in patients >100 kg than in patients ≤100 kg in the unadjusted analysis, there was a significantly increased odds of mortality for those weighing >100 kg in the multivariable analysis. Although the causes for this increase in mortality remain unclear, it is unlikely that lower per-kilogram dose causes higher mortality in the >100-kg group than in the ≤100-kg group.

Considering earlier studies using higher doses of rtPA or dose escalation studies of the newer generation thrombolytic agents, the comparable efficacy of thrombolytic therapy in terms of MNI, the equal odds for favorable functional outcome, and finally the increase in odds for SICH even under a lower per kilogram for patients >100 kg, the current study in summary confirmed the upper dose limit in clinical practice based on a large population.

Limitations of SITS data have been intensively discussed previously. A particular limitation of our current analysis is that most of the data on body weight were based on estimated weight, including weight indicated by the patients or the family or the attending physician. Only 14.5% of the patients had measured weight. Although according to previous studies, the patients’ own estimations seem to be accurate with reported differences of approximately 2.7 kg. Physicians’ estimations frequently seem to be more unreliable. This represents a possible source of bias in the current study.

Conclusions

The lower per-kilogram body weight alteplase dose in patients >100 kg did not result in less successful thrombolysis compared with patients ≤100 kg as assessed by MNI, a surrogate marker of recanalization. Likewise, functional outcome did not differ between the groups after adjustment for baseline variables. Considering these findings and the higher incidence of SICH in patients >100 kg, our results support the current practice of the upper dose limit for rtPA.

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Disclosures

None.

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Abstract 10

100 kg이 넘는 헬혈뇌졸중 환자에서 alteplase의 최대 용량 90 mg은 충분한가?

Is the Maximum Dose of 90 mg Alteplase Sufficient for Patients With Ischemic Stroke Weighing > 100 kg?

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(Stroke. 2011;42:1615-1620.)

Key Words: stroke ■ thrombolysis ■ weight

배경과 목적
급성 헬혈뇌졸중(acute ischemic stroke)에서 정맥내 alteplase 두어는 최대 90 mg으로 제한되어 있다. 그 결과 100 kg 이상의 환자는 알테플라세가 상대적으로 적을 수 밖에 없다. 저자들은 100 kg 이상의 환자를 대상으로 초기 alteplase 사용을 추천하였다. 24시간 내에 최소한의 신경학적 두려움이 발생한 환자가 100 kg 초과의 환자에서 2.6%였으며, 100 kg 이하 환자에서 1.7% 발생하였다 (P=0.03). 기능적 독립성은 59.7% vs. 53.6% (P<0.001)이었으며, 사망률은 14.4% vs. 15.1% (P=0.54)였다. 초기 독성은 보존한 결과, 100 kg 초과 및 이하군에서, 주요 신경학적 회복 및 기능적 독립성 측면에서 유의한 차이는 관찰되지 않았다. 그러나 100 kg 초과 환자군은 증상성뇌내출혈이 발생한 경우가 많았다 (odds ratio, OR)가 1.6, 95% CI, 1.06~2.41 (P=0.02), 사망률도 높았다 (OR, 1.37, 95% CI, 1.08~1.74, P=0.01).

방법
Safe Implementation of Treatment in Stroke – International Stroke Thrombolysis Register (SITS–ISTR; 2002~2009년)에 등록된 환자 27,910명 중 1,190명(4.3%)이 100 kg을 초과하였다. 주요 신경학적 회복(National Institutes of Health Stroke Scale)의 8점 이상 양상 혹은 24시간 내에 회복을 평가하였다. 결과 변수는 증상성뇌내출혈(symptomatic intracerebral hemorrhage)(24시간 이내 National Institutes of Health Stroke Scale)의 4점 이상 악화 및 2형 뇌실질내출혈(parenchymal hemorrhage), 기능적 독립성(modified Rankin Scale) 0~2점 및 3개월 시점에서의 사망률을 사용하였다.

결과
100 kg을 초과하는 환자들은 kg당 alteplase 용량이 낮았으 며 (0.82 vs. 0.90, P<0.001) 더 적었고 (62세 vs. 70세, P<0.001), 초기 National Institutes of Health Stroke Scale이 낮았으며 (10 vs. 12, P<0.001) 더 많은 혈관 조영활성을 가지고 있었다. 24시간 시점에서의 주요 신경학적 회복은 두 군 모두 27.7%에서 발생하였다. 증상성뇌내출혈은 100 kg 초과군에서 2.6%였으며, 100 kg 이하군에서 1.7% 발생하였다 (P=0.03). 기능적 독립성은 59.7% vs. 53.6% (P<0.001)이었으며, 사망률은 14.4% vs. 15.1% (P=0.54)였다. 초기 독성은 보존한 결과, 100 kg 초과 및 이하군에서, 주요 신경학적 회복 및 기능적 독립성 측면에서 유의한 차이는 관찰되지 않았다. 그러나 100 kg 초과 환자군은 증상성뇌내출혈이 발생한 경우가 많았다 (odds ratio, OR)가 1.6, 95% CI, 1.06~2.41 (P=0.02), 사망률도 높았다 (OR, 1.37, 95% CI, 1.08~1.74, P=0.01).

결론
저자들의 결과는 현재의 용량 제한을 지지한다. 100 kg 초과 환자군에서 재조합조직플라스민성분제(recombinant tissue plasminogen activator) 용량이 kg당 더 낮을수록 불구하고 증상성뇌내출혈 발생이 증가하였다. 주요 신경학적 회복 및 기능적 독립성 동등하였다.