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Outcome of intravenous thrombolysis in stroke patients weighing over 100 kg

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Abstract: **BACKGROUND:** Intravenous thrombolysis with alteplase for ischemic stroke is fixed at a maximal dose of 90 mg for safety reasons. Little is known about the clinical outcomes of stroke patients weighing >100 kg, who may benefit less from thrombolysis due to this dose limitation. **METHODS:** Prospective data on 1,479 consecutive stroke patients treated with intravenous alteplase in six Swiss stroke units were analyzed. Presenting characteristics and the frequency of favorable outcomes, defined as a modified Rankin scale (mRS) score of 0 or 1, a good outcome (mRS score 0-2), mortality and symptomatic intracranial hemorrhage (SICH) were compared between patients weighing >100 kg and those weighing 100 kg. **RESULTS:** Compared to their counterparts (n = 1,384, mean body weight 73 kg), patients weighing >100 kg (n = 95, mean body weight 108 kg) were younger (61 vs. 67 years, p < 0.001), were more frequently males (83 vs. 60%, p < 0.001) and more frequently suffered from diabetes mellitus (30 vs. 13%, p < 0.001). As compared with patients weighing 100 kg, patients weighing >100 kg had similar rates of favorable outcomes (45 vs. 48%, p = 0.656), good outcomes (58 vs. 64%, p = 0.270) and mortality (17 vs. 12%, p = 0.196), and SICH risk (1 vs. 5%, p = 0.182). After multivariable adjustment, body weight >100 kg was strongly associated with mortality (p = 0.007) and poor outcome (p = 0.007). **CONCLUSION:** Our data do not suggest a reduced likelihood of favorable outcomes in patients weighing >100 kg treated with the current dose regimen. The association of body weight >100 kg with mortality and poor outcome, however, demands further large-scale studies to replicate our findings and to explore the underlying mechanisms.

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Outcome of Intravenous Thrombolysis in Stroke Patients Weighting Over 100 kg

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Background. Intravenous thrombolysis with alteplase for ischemic stroke is fixed at 90 mg for safety reasons. Little is known about clinical outcome in stroke patients >100 kg who may benefit less from thrombolysis due to this dose limitation.

Methods. Prospectively collected data of 1479 consecutive stroke patients treated with intravenous alteplase in six Swiss stroke units were analyzed. Presenting characteristics and the frequency of favorable outcome defined as modified Rankin scale (mRS) score 0 or 1, good outcome (mRS score 0-2), mortality and symptomatic intracranial hemorrhage (SICH) were compared between patients >100 kg and ≤100 kg.

Results. Patients >100 kg (n=95, mean body weight 108 kg) differed from their counterparts (n=1384, mean body weight 73 kg) by younger age (61 vs. 67 years, $p<0.001$), more frequent male gender (83% vs. 60%, $p<0.001$) and a higher rate of diabetes mellitus (30% vs. 13%, $p<0.001$). As compared with control group, patients >100 kg had similar rates of favorable outcome (45% vs. 48%, $p=0.656$), good outcome (58% vs. 64%, $p=0.270$), mortality (17% vs. 12%, $p=0.196$) and SICH risk (1% vs. 5%, $p=0.182$). After multivariable adjustment, body weight >100 kg was strongly associated with mortality ($p=0.007$) and bad outcome ($p=0.007$).

Conclusion. Our data do not suggest a reduced likelihood of favorable outcome in patients >100 kg treated with the current dose regimen. The association of body weight>100 kg with mortality and bad outcome, however, demands further large-scale studies to replicate our findings and to explore the underlying mechanisms.

1 INTRODUCTION

2 Intravenous thrombolysis (IVT) with alteplase is currently the only approved treatment for
3 acute ischemic stroke. The international stroke guidelines recommend a weight adapted
4 dose (0.9 milligram (mg) alteplase per kilogram (kg) body weight) and a maximum dose of 90
5 mg for safety reasons [1,2], meaning that no further dose adjustment is permitted in patients
6 >100 kg. However, this recommendation is rather based on few small dose escalation
7 studies [3,4], On the other hand, obesity has recently risen to epidemic levels and the World
8 Health Organization estimates that by 2015, approximately 2.3 billion adults will be
9 overweight and more than 700 million will be obese [5]. Keeping in mind that obesity is an
10 independent predictor for ischemic stroke [6,7], obese patients will constitute an increasing
11 group of candidates for IVT. Furthermore, several studies reported an elevated level of
12 plasminogen activator inhibitor-1 and impaired fibrinolysis in obese patients [8,9], Thus,
13 stroke patients >100 kg may benefit less from IVT which may have major therapeutic
14 implications in clinical practice. We present the outcomes of patients >100 kg compared with
15 those $\leq$ 100 kg after IVT for acute ischemic stroke.

17 METHODS

18 We studied prospectively collected data of consecutive patients with acute ischemic
19 stroke who underwent IVT at six Swiss stroke centers up to December 31, 2008. The
20 Appendix provides detailed data about the number of patients and the study period for each
21 center. Baseline investigations included neurologic and physical examination, assessment of
22 stroke severity by using the National Institutes of Health Stroke Scale (NIHSS) [10], routine
23 blood analysis, 12-lead electrocardiography (ECG), brain computed tomography (CT) and/or
24 magnetic resonance imaging (MRI). Following variables were ascertained: age, gender,
25 baseline NIHSS score, vascular risk factors according to predefined criteria [11], history for
26 coronary heart disease, antithrombotic medication, time to treatment, stroke etiology
27 according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [12], blood
28 pressure and blood glucose values. Body weight was either measured by the unit nurse at

admission or, when not feasible, obtained verbally from the patient or caregiver. Thrombolysis was applied according to current guidelines by using intravenous alteplase 0.9 mg/kg to a maximum of 90 mg, ten percent of the total dose given as a bolus and the remaining dose in the next hour [1,2]. All patients treated with IVT were admitted to intermediate or intensive care units for at least 24 hours. Follow-up CT or MRI were obtained 24 to 48 hours after IVT and additional scans in case of clinical deterioration. Functional outcome was assessed by outpatient visits or structured telephone interviews using the modified Rankin Scale (mRS) [13].

Outcome measurements

The primary outcome measure was the incidence of favorable outcome at three months, defined as a mRS score of 0 or 1. We additionally evaluated the incidence of good outcome, defined as mRS score 0-2. Secondary, we assessed the rate of mortality at three months and the rate of symptomatic intracranial hemorrhage (SICH) by using both the NINDS and ECASS II criteria [14,15].

Statistical analysis

Non-normally distributed data were expressed as median and interquartile range (IQR) and compared by using Mann-Whitney U-test. Distribution of frequencies was examined by using chi-square or Fisher's exact test where appropriate (the latter if some expected counts in the two-by-two table were less than 5). Influence of body weight (>100 kg vs. ≤100 kg) on the outcomes was examined by using univariate analysis. Multivariable logistic regression analyses were performed to assess joint effects of body weight and other predictors on the outcomes. Selection of parameters was based on clinical reasons and were derived from SITS-MOST registry evaluating outcome predictors [16]. Thus, following variables were forced into the model: baseline NIHSS score, age and blood glucose for all 3 outcome measures; additionally gender and diastolic blood pressure for favorable outcome and

mortality, and antiplatelet medication and systolic blood pressure for SICH. Significance was declared at $p < 0.05$ level.

RESULTS

Study population

Among 1503 stroke patients treated with IVT, 1479 (98%) were eligible for this study; 24 patients (2%) were excluded because of lacking body weight data. Of the included 1479 patients, 95 (6.4%) had a body weight > 100 kg (range 101-150 kg, mean 107.5 ± 9.3 kg, median 103.0 kg [95% CI 105.6-109.4], IQR 103-110 kg) and 1384 (93.6%) a body weight ≤ 100 kg (range 36-100 kg, mean 73.1 ± 11.6 kg, median 74.0 kg [95% CI 72.4-73.7], IQR 66-80 kg). The maximum dose of alteplase applied in patients was 90 mg.

As compared with their counterparts, patients > 100 kg were younger (61 vs. 67 years of age, $p < 0.001$) and more often men (83% vs. 60%, $p < 0.001$) with a higher rate of diabetes mellitus (30% vs. 13%, $p < 0.001$) (Table 1). Stroke severity assessed by baseline NIHSS score, time to treatment, blood pressure, antithrombotic medication and stroke causes were comparable in the two cohorts (Table 1).

Outcome

At three months, clinical outcome was available in 1462 (99%) and classification of SICH in 1454 (98%) of the included 1479 patients. All patients who were lost to follow-up and all but one with undefined hemorrhage classification had a body weight ≤ 100 kg.

A favorable outcome was observed in 694 of 1462 (47%) patients. The rate of patients with favorable outcome at three months were comparable between the two groups (45.3% of patients > 100 kg and 47.6% of patients ≤ 100 kg, $p = 0.656$). After multivariable adjustment, age ($p < 0.001$), baseline NIHSS score ($p < 0.001$) and blood glucose ($p < 0.001$) predicted favorable outcome, while no association with body weight > 100 kg was evident ($p = 0.213$) (Table 2). Good outcome was observed at similar frequency in patients ≤ 100 kg and those > 100 kg (63.9% vs. 57.9%, $p = 0.270$). However, multivariable adjustment revealed

an independent association between good outcome and body weight ≤ 100 kg ($p=0.007$) (Table 2).

Death within the three-month follow-up occurred in 184 of 1462 (13%) patients with a tendency to disadvantage of patients >100 kg (16.8% vs. 12.3%, $p=0.196$). Multivariate logistic regression analyses identified body weight >100 kg as an independent predictor of mortality ($p=0.007$), along with age ($p<0.001$), baseline NIHSS score ($p<0.001$), blood glucose ($p<0.001$) and diastolic blood pressure ($p=0.029$) (Table 2). Sixteen patients >100 kg died during 3-month follow-up (median at day 6 after stroke onset): 15 of 16 patients were male, median age 66 years and median baseline NIHSS score 15. Following causes of death were identified in these 16 patients: malignant middle cerebral artery infarct ($n=6$), cardiopulmonary arrest ($n=5$), extensive basilar artery infarct ($n=1$), second ischemic stroke ($n=1$) and aspiration pneumonia ($n=1$). The remaining two patients died in external rehabilitation centers and the exact causes of death were not identifiable.

Seventy-four of 1454 (5%) patients experienced a SICH according to NINDS criteria, 1.1% in patients >100 kg and 5.4% in the counterpart group ($p=0.084$) (Table 2). The rate of SICH by using the ECASS II criteria did not significantly differ between the two groups, either (1.1% vs. 4.6%, $p=0.182$) (Table 2). Multivariate logistic regression analyses identified baseline NIHSS score as independent predictors of SICH according to NINDS criteria ($p=0.045$) and ECASS II criteria ($p=0.020$), but not body weight >100 kg ($p=0.243$ and $p=0.336$, respectively) (Table 2).

DISCUSSION

This study aimed to assess the clinical outcomes in patients >100 kg receiving intravenous alteplase fixed at 90 mg in comparison to patients ≤ 100 kg, who were treated with weight adapted doses of alteplase. The rates of favorable outcome at three months were similar in the two groups, but an inverse association was observed with body weight >100 kg and probability for good outcome. Several aspects have to be considered when interpreting these findings: one hypothesis might be that the worse outcome in patients >100 kg may be related

1 to the lower corrected dose of alteplase in this group. The rather low mean body weight of
2 107.5 kg, which exceeds the weight cut-off (100 kg) by less than 10%, may have hampered
3 our ability to detect additional differences in favorable outcome. A further, rather theoretical
4 reason for the divergent outcomes (favorable vs. good outcome) could be the assumption
5 that patients >100 kg may be more handicapped by slight deficits due to overweight and
6 associated challenges as compared to lean patients. In line with our findings, Lou and Selim
7 analyzed data from NINDS trial and suggested less benefit of IVT in stroke patients >100 kg
8 as compared with their lighter counterparts [17]. Lower levels of plasma tissue plasminogen
9 activator and / or higher plasma levels of plasminogen activator inhibitor-1 have been
10 reported as potential reason for differences in outcome [8,17,18]. On the other hand,
11 however, one should be cautious not to overestimate our results in view of the observational
12 study design and the small cohort size of patients >100 kg. As consequence, our study
13 demands further large-scale studies to replicate our findings and to explore the underlying
14 mechanisms in view of potential therapeutic implications.

15 We are aware of mainly three studies targeting at higher alteplase doses for ischemic
16 stroke. In two open-label dose escalation studies preceding the National Institutes of
17 Neurological Diseases and Stroke (NINDS) trial, 32 of 94 stroke patients were treated with
18 an alteplase dose >0.9 mg/kg (31 patients received 0.95 mg/kg, one patient 1.08 mg/kg)
19 [3,4,14]. However, the maximal dose administered in the two studies was 86.6 mg. In the
20 European Cooperative Acute Stroke Study (ECASS) I trial, alteplase dose of 0.95 mg/kg was
21 used while the maximum dose was limited at 100 mg [19]. However, no data were reported
22 on the number and outcome of patients receiving alteplase doses >90 mg. Thus, we are not
23 aware of studies that proved and reported harm for alteplase exceeding the current limit of
24 90 mg in ischemic stroke. In comparison, the dose of alteplase for myocardial infarction is
25 limited at 100 mg [20]. These data indicate, that the upper dose limit of alteplase at 90 mg
26 seems to be rather arbitrary and less evidence-based.

27 Another finding of this study is the higher mortality in patients >100kg despite the
28 significantly younger age as compared with their counterparts and the correlation of body

weight >100 kg with mortality in the multivariate logistic regression analysis. Of patients > 100 kg who experienced death, the vast majority was male (94%) and death occurred early at median 6 days after stroke onset. Leading causes of death were malignant ischemic infarct and cardiopulmonary arrest, whereas no fatal SICH was observed in these patients. Obesity is associated with a higher body weight and several long-term studies reported higher mortality rates in obese patients after ischemic stroke [21-24]. It has been shown that obese stroke patients are more often prone to deep venous thrombosis [25], and other medical complications such as pneumonia or cardiovascular ischemic events are supposed to occur more frequently in obese patients [21-23]. These may not explain our findings completely, however, because body weight >100 kg does not always imply obesity, as is the case in several athletes. Lou and Selim did not report mortality in their study [17], thus no comparison with the currently existing literature is available. Nonetheless, the increased mortality observed in patients >100 kg warrants further large-scale studies to replicate our findings and to explore the mechanisms, as especially younger and male stroke patients seem to be affected by overweight and these patients probably will present a growing subgroup in future with respect to the rapidly growing incidence of obesity. An increase of alteplase dose seems to be less promising, as no randomized controlled IVT trial has proved to reduce the mortality after ischemic stroke. The incidence of SICH (by using both NINDS and ECASS II criteria) did not significantly differ between the two body weight groups.

This study has some limitations. The observational design and lack of a control group do not allow to judge the efficacy of alteplase dose in patients >100 kg. The cohort size of patients >100 kg is small, thus the possibility of a type II error must be admitted. We could not assess the causes of death in patients $\leq$ 100 kg and thus are not able to explain the increased mortality in patients >100 kg thoroughly. Measurement of plasma plasminogen activator concentration and assessment of body mass index in patients of varying weight could have been more appropriate. Other factors such as liver function, age or body surface area might have additionally influenced the pharmacokinetics of alteplase plasma concentration [26-28]. Body weight was self-reported by patients or caregivers in part.

Measurement of body weight could probably be more accurate [29], although self reported body weights have been reported to be valid in participants of the Nurses' Health Study II [30]. Finally, we did not evaluate imaging findings such as early infarct signs, vessel occlusion or early recanalization, which might have additionally influenced the outcomes.

In conclusion, our data do not suggest a reduced likelihood of favorable outcome in patients >100 kg treated with the current dose regimen. The association of body weight >100 kg with mortality and bad outcome, however, demands further large-scale studies to replicate our findings and to explore the underlying mechanisms.

1 **APPENDIX**

2 Participating centers (number of patients, study period) and contributors in alphabetic order:

3 University Hospital of Basel (359, 10 years): ST Engelter, PA Lyrer

4 University Hospital of Bern (90, 9 years): M Arnold, HP Mattle

5 University Hospital of Lausanne (298, 8 years): P Michel, C Odier

6 Kantonsspital Muensterlingen (100, 9 years): F Müller

7 Kantonsspital St. Gallen (219, 5 years): P Siebel, B Weder,

8 University Hospital of Zurich (437, 10 years): RW Baumgartner, D Georgiadis, H Sarikaya

1 Table 1. Baseline Characteristics of Alteplase Treated Stroke Patients With Body Weight >100 kg versus ≤100 kg.

	Weight >100 kg (n=95)	Weight ≤100 kg (n=1384)	P Value
Male sex (%)	79/95 (83.2)	827/1383 (59.8)	<0.001
Median age (years) [IQR]	60.1 [53.0-69.4]	70.0 [58.9-78.0]	<0.001*
Hypertension (%)	69/95 (72.6)	882/1384 (63.7)	0.080
Current smoking (%)	32/95 (33.7)	369/1383 (26.7)	0.138
Diabetes mellitus (%)	28/95 (29.5)	185/1383 (13.4)	<0.001
Hypercholesterolemia (%)	42/83 (50.6)	611/1353 (45.2)	0.334
Antiplatelet medication at stroke onset (%)	36/95 (37.9)	474/1380 (34.3)	0.482
Anticoagulation at stroke onset (%)	3/95 (3.2)	37/1380 (2.7)	0.740 [†]
Coronary heart disease (%)	18/95 (18.9)	250/1382 (18.1)	0.834
Median NIHSS score [IQR]	12.0 [6-16]	12.0 [7-17]	0.330*
Median OTT (min) [IQR]	170.0 [135.0-180.0]	157.5 [130.0-180.0]	0.575*
Median SBP (mm Hg) [IQR]	151.0 [140.0-174.0]	155.0 [139.5-173.0]	0.645*
Median DBP (mm Hg) [IQR]	86.0 [80.0-100.0]	89.0 [79.0-100.0]	0.970*
Median blood glucose (mmol/L) [IQR]	6.5 [5.7-8.3]	6.4 [5.6-7.4]	0.088*
Cause of stroke			
Large artery disease (%)	27/95 (28.4)	333/1378 (24.2)	
Cardiac embolism (%)	32/95 (33.7)	500/1378 (36.3)	
Small artery disease (%)	3/95 (3.2)	64/1378 (4.6)	0.789
Other determined etiology (%)	6/95 (6.3)	112/1378 (8.1)	
Undetermined etiology (%)	27/95 (28.4)	369/1378 (26.8)	

2

3 CI denotes confidence interval, IQR interquartile range, NIHSS National Institutes of Stroke Scale, OTT onset to

4 treatment time, SBP systolic blood pressure, DBP diastolic blood pressure.

5 P-values are calculated with chi-square test, unless otherwise indicated

6 * Mann-Whitney test, [†] Fisher exact test

Table 2. Outcomes in Patients Weighting >100 kg Compared with those Weighting ≤100 kg.

	Unadjusted analysis				Adjusted analysis [†]	
	Weight >100 kg	Weight ≤100 kg	Odds ratio [95% CI]	p value	Odds ratio [95% CI]	p value
Favorable outcome (mRS 0-1)	43/95 (45.3%)	651/1367 (47.6%)	0.909 [0.599-1.381]	0.656	0.715 [0.422-1.213]	0.213
Good outcome (mRS 0-2)	55/95 (57.9%)	874/1367 (63.9%)	0.776 [0.509-1.183]	0.270	0.462 [0.265-0.807]	0.007
Mortality	16/95 (16.8%)	168/1367 (12.3%)	1.445 [0.825-2.533]	0.196	2.640 [1.305-5.341]	0.007
SICH (NINDS definition)	1/94 (1.1%)	73/1360 (5.4%)	0.190 [0.026-1.379]	0.084*	0.303 [0.041-2.251]	0.243
SICH (ECASS II definition)	1/94 (1.1%)	62/1360 (4.6%)	0.225 [0.031-1.642]	0.182*	0.372 [0.049-2.790]	0.336

SICH denotes symptomatic intracranial hemorrhage

P-values apply to chi-square tests unless otherwise indicated

* Fisher exact test

[†] adjusted for baseline NIHSS score, age, gender, blood glucose, diastolic blood pressure (favorable outcome, good outcome, mortality);
baseline NIHSS score, age, blood glucose, antiplatelet medication and systolic blood pressure (symptomatic intracranial hemorrhage)

1
2
3
4

Figure. Proportion of patients with body weight >100 kg versus ≤100 kg according to the modified Rankin Scale (mRS) score at 3 months

5

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