Psychiatria Danubina, 2019; Vol. 31, Suppl. 1, pp S32-S38
Medicina Academica Mostariensia, 2018; Vol. 6, No. 1-2, pp 32-38 *Review*

EFFICACY AND SAFETY OF LOW-DOSE VERSUS STANDARD-DOSE ALTEPLASE REGIMENS IN PATIENTS WITH ACUTE ISCHAEMIC STROKE

Ranko Škrbić[1,3], Zoran Vujković[2], Miloš P. Stojiljković[1,3], Radoslav Gajanin[3], Dubravko Bokonjić[3] & Jasmin Komić[3]

[1]*Department of Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine, University of Banja Luka, Banja Luka, Bosnia & Herzegovina*
[2]*Clinic for Neurology, University Clinical Centre of Republic of Srpska, Faculty of Medicine, University of Banja Luka, Banja Luka, Bosnia & Herzegovina*
[3]*Centre for Biomedical Research, Faculty of Medicine, University of Banja Luka, Banja Luka, Bosnia & Herzegovina*

received: 4.9.2018; revised: 30.10.2018; accepted: 5.12.2018

SUMMARY

Background: *The use of intravenous recombinant tissue plasminogen activator, alteplase, at a dose of 0.9 mg/kg is an effective treatment for patients with acute ischaemic stroke; this dose is also associated with high intracerebral haemorrhage rates. The aim of this study was to evaluate whether the low-dose alteplase treatment is as effective and safe as the standard-dose regimen.*

Subjects and methods*: This was a retrospective, single-centre study, and data were collected from the Hospital Stroke Registry. Based on the severity of stroke and the risk of intracerebral haemorrhage, patients were divided into two groups according to the alteplase doses given; the low-dose (0.6 mg/kg) group (n=45) and the standard-dose (0.9 mg/kg) group (n=165). Ninety-day outcomes measured as modified Rankin score and National Institute for Health Stroke Scale (NIHSS) score, as well as symptomatic intracerebral haemorrhage and mortality rates were analysed.*

Results*: The standard-dose group had a slightly more favourable outcome (Rankin score 0-2) at 90 days after alteplase treatment than the low-dose group (64.24% vs. 53.33%), but the difference was not significant. The total intracerebral haemorrhage rate and mortality rate at 90 days were higher in the standard-dose group than in the low-dose group (21.2% vs. 13.3% and 6.1% vs. 0.0%, respectively), but these differences were not statistically significant.*

Conclusion*: The low-dose alteplase treatment applied to the patients with high intracerebral haemorrhage risk had comparable efficacy and safety profile to the standard-dose regimen.*

Key words: *acute ischaemic stroke - thrombolytic therapy – alteplase - low-dose - intracerebral haemorrhage*

* * * * *

INTRODUCTION

It is well-recognised that alteplase, a recombinant tissue-type plasminogen activator, serves as an effective intravenous treatment for acute ischaemic stroke (AIS). Based on two pilot studies, the alteplase dose of 0.9 mg/kg of body weight was accepted as an effective treatment for AIS (Brott et al. 1992, Haley et al. 1992). Since 1996 the US Food and Drug Administration has approved the use of alteplase for the treatment of AIS patients within 3 hours of onset, which was in 2009 expanded to up to 4.5 hours to become finally recommended by the American Heart Association and American Stroke Association (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995, Hankey 2001, Del Zoppo et al. 2009, Adams et al. 2003). The efficacy of this treatment is time-dependent, which means that the early use of alteplase provides proportionally greater benefit. However, the increased risk of intracerebral haemorrhage is the most significant complication of this therapy (Emberson et al. 2014, Wardlaw et al. 2012, van Asch et al. 2010). Stroke severity, on the other hand, has substantial effect on treatment outcomes, meaning that fatal intracerebral haemorrhage is most frequent in more severe cases of stroke and *vice versa* (Emberson et al. 2014).

There are some controversies related to the optimal dose of alteplase due to the fact that thrombolytic therapy is associated with an increased risk for intracerebral haemorrhage. Several trials conducted in Japan have shown that the low-dose alteplase (0.6 mg/kg) was as effective as the standard-dose (0.9 mg/kg), and the incidence of symptomatic intracerebral haemorrhage was comparable to the published data for the standard-dose (Ueshima & Matsuo 2002, Toyoda et al. 2009, Yamaguchi et al. 2006). The use of low-dose alteplase became very acceptable throughout Asian countries, and it is estimated to be used now in nearly half of cases of AIS thrombolysis (Sharma et al. 2010, Wang et al. 2011, Chao et al. 2010). In many countries outside Japan, the low-dose alteplase has become an alternative option, particularly for elderly patients. However, the uncertainty regarding the relative benefits and risks of low- vs. standard-dose of alteplase still remains. The results of some studies have clearly indicated that the

standard-dose was better than the low-dose (Liao et al. 2014, Dharmasaroja & Pattaraarchachai 2011). In a recent large-scale study, involving Asian population, the non-inferiority of low-dose vs. standard-dose was not confirmed in terms of efficacy, with significantly fewer symptomatic intracerebral haemorrhages found in patients with low-dose alteplase (Anderson et al. 2016).

Since 2010, the low-dose alteplase was routinely used in our stroke unit particularly as an option for elderly AIS patients with additional risk factors for intracerebral haemorrhage. The aim of this study was to compare the efficacy and safety of these two dosing regimens in patients with AIS.

SUBJECTS AND METHODS

The study was designed as a retrospective interventional study, based on the Hospital Stroke Registry database of patients treated with alteplase at the Stroke Unit of the University Clinical Centre of the Republic of Srpska, Banja Luka, Republic of Srpska, Bosnia & Herzegovina in a period from 2007 to 2017. Out of total number of patient treated with alteplase, only 210 of them with appropriate data records were included in this study. The study inclusion criteria were as follows: patients with AIS, 18 years of age or older, and fulfilment of the internationally recommended criteria for treatment with intravenous alteplase (European Stroke Organisation (ESO) Executive Committee 2008, Kaste et al. 2001). Patients with severe hypertension were assigned to early and intensive lowering of blood pressure (target systolic blood pressure <180 mmHg, and diastolic blood pressure <110 mmHg) by using the intravenous antihypertensive therapy.

All demographic and clinical data, including computerised tomography (CT) brain scans, time from onset of stroke to hospital admission ("onset to door time") and time from hospital admission to alteplase application ("door to needle time") were obtained on patients' admission. National Institutes of Health Stroke Scale (NIHSS) and modified Rankin scale were collected on admission, as well as at 72 hours and 90 days thereafter, unless the death occurred earlier.

The majority of patients in whom thrombolytic therapy was feasible received the standard-dose alteplase (0.9 mg/kg, iv) within 4.5 hours after the stroke onset. Patients with higher risk for intracerebral haemorrhage, who had at least two of the following characteristics: (1) age over 75; (2) NIHSS score of more than 18; (3) significant postischaemic defects of brain parenchyma as a consequence of earlier brain infarction; or (4) diabetes mellitus, were allocated to receive the low-dose alteplase (0.6 mg/kg). After the dosage of alteplase was determined, 10% of the dose was administered as a bolus, and the remaining 90% as an infusion over a period of 60 minutes.

Brain CT scans were done regularly for each patient before thrombolysis, 24 hours following alteplase administration, as well as for those suspected for haemorrhagic complications (haemorrhagic infarctions, or parenchymal haematomas; usually accompanied by elevation of NIHSS score by four points). Intracerebral haemorrhage was defined as any sign of haemorrhage in the follow-up CT scans. The subtypes were defined as: haemorrhagic infarctions (HI) type-1 (small petechial), HI type-2 (more confluent petechial), parenchymal haematoma (PH) type-1 (up to 30% of the infracted area with mild space-occupying effect), and PH type-2 (more than 30% of the infracted area with significant space-occupying effect) (Fiorelli et al. 1999, Hacke et al. 1998). All brain CT scans were evaluated by an independent radiologist who was not a member of the treatment team and was therefore blind to the dose of alteplase applied.

NIHSS was used to assess the stroke severity. A NIHSS-certified stroke team member at the Stroke Unit had performed the scoring and evaluation every 15 minutes during the first hour following alteplase treatment, and every 6 hours during the first 24 hours, as well as 72 hours and 90 days thereafter. The 90-days evaluations were conducted directly or by telephone. The Rankin score was used to evaluate the stroke severity and functional outcomes, where functional independence was defined as Rankin score<2, and poor recovery as Rankin score>2.

Complete statistical analysis of data was performed by means of the statistical software package, SPSS Statistics 18. In case of continuous data, variables were presented as mean value ± standard deviation (SD), minimal and maximal values. Kolmogorov-Smirnov test was used for evaluation of normality of the distribution of clinical data. Statistical significance between groups was tested by t-test or Mann-Whitney test. Most of the variables were presented as frequency of certain categories, while statistical significance of differences was tested with the Chi-square test or Fisher's Exact test (expected frequency <5). All analyses were estimated at $p<0.05$ level of statistical significance.

RESULTS

The total number of patients included in this study was 210, where 45 patients (25 female, 20 male) were in the low-dose group, and 165 patients (76 female, 89 male) were in the standard-dose group. There was no statistically significant difference between the groups regarding the gender composition. Patients enrolled in the low-dose group were significantly older, and there were significantly more patients with diabetes mellitus in the low-dose group than in the standard-dose group (62.22% vs. 8.48%). The mean age of the patients in the low-dose group was 67.47 (range 37-80) years and 61.88 (range 32-79) years in the standard-dose group.

There was no difference between the two groups regarding baseline NIHSS scores (10.84 vs. 11.93), Rankin scores (3.96 vs. 3.99) and "onset to needle time" (157.00 vs. 152.86 minutes) values. The baseline characteristics of these patients were summarised in Table 1.

Concerning the efficacy data, it was shown that the standard-dose was superior to the low-dose in terms of NIHSS score. Although baseline NIHSS score values were not significantly different between the two groups on admission (Table 1), the standard-dose treatment induced more significant improvement of NIHSS score values after 72 hours and 90 days following alteplase administration, reaching the 33.56% and 27.59% of basal values, respectively. The low-dose treatment resulted in a less pronounced improvement of NIHSS scores after 72 hours and 90 days following alteplase administration (55.51% and 51.80% of basal values, respectively; Figure 1, Table 2).

Table 1. Baseline parameters of patients according to the dose of alteplase

Variables	Low-dose alteplase, 0.6 mg/kg (N=45)		Standard-dose alteplase, 0.9 mg/kg (N=165)		P value
	mean±SD	range	mean±SD	range	
Demographic information					
Age (years)	67.47±10.10	37-80	61.88±10.83	32-79	0.002
>75	14 (31.11%)		14 (8.48%)		≤0.001
Female	25 (55.6%)		76 (46.1%)		0.334
Diabetes mellitus	28 (62.22%)		14 (8.48%)		≤0.001
Stroke information					
Onset to door time (min.)	97.02±57.32	25-210	96.89±54.99	20-240	0.864
Door to needle time (min.)	59.98±23.80	31-130	55.97±21.60	25-150	0.370
Onset to needle time (min.)	157.00±55.17	70-252	152.86±53.50	50-268	0.623
NIHSS score on admission	10.84±5.01	3-24	11.93±4.45	2-25	0.098
Rankin score on admission	3.96±1.07	2-5	3.99±1.09	0-5	0.769

Table 2. Comparison of NIHSS and Rankin scores at baseline, 72 hours and 90 days after alteplase treatment

Outcome	Alteplase		P value
	Low-Dose (N=45)	Standard-Dose (N=165)	
NIHSS score	mean±SD	mean±SD	
baseline	10.84±5.01	11.93±4.45	0.098
72 hours	5.12±4.76	4.27±4.81	0.038
90 days	4.90±4.85	3.61±4.75	0.109
Rankin score			
baseline	3.96±1.07	3.99±1.09	0.769
72 hours	2.44±1.88	2.20±2.11	0.490
90 days	2.20±1.91	1.88±2.11	0.359
Rankin score 0-2 at 90 days	24/45 (53.33%)	106/165 (64.24%)	0.245

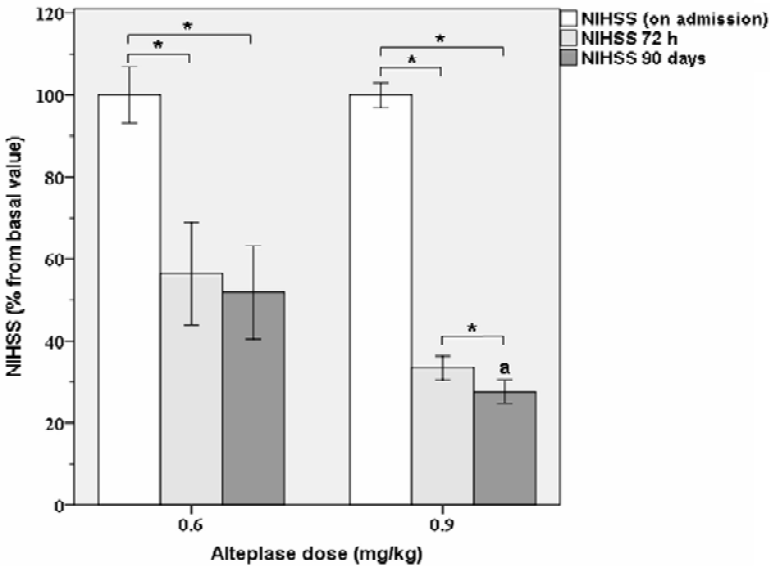

Figure 1. Relative changes of NIHSS scores at 72 hours and 90 days, after alteplase treatment, expressed as percentage of basal value on admission. Results are expressed as mean ± standard error (SE). *p<0.001

Table 3. The main safety and functional outcomes of patients received low-dose (0.6 mg/kg) or standard-dose (0.9 mg/kg) alteplase treatment

Outcome	Alteplase		P value
	Low-Dose (N=45)	Standard-Dose (N=165)	
Total intracerebral haemorrhage	6 (13.3%)	35 (21.2%)	0.231
HI type 1	1 (2.2%)	9 (5.5%)	0.693
HI type 2	2 (4.4%)	6 (3.7%)	0.682
PH type 1	2 (4.4%)	8 (4.9%)	1.000
PH type 2	1 (2.2%)	12 (7.3%)	0.309
Non cerebral haemorrhage	5 (11.1%)	17 (10.4%)	1.000
Mortality at 90 days	0 (0.0%)	10 (6.1%)	0.120

HI - haemorrhagic infarctions; PH - parenchymal haematomas

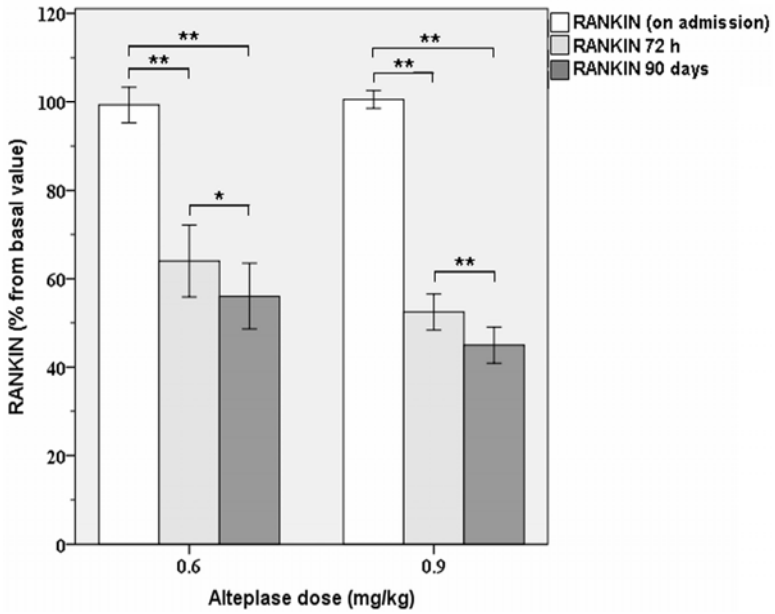

Figure 2. Relative changes of Rankin scores at 72 hours and 90 days, after alteplase treatment, expressed as percentage of basal value on admission. Results are expressed as mean ± standard error (SE). *p<0.05 and **p<0.001

The Rankin scores measured 72 hours and 90 days after alteplase administration were slightly lower in the standard-dose group (53.01% and 44.96%, respectively), than in the low-dose group (63.48% and 56.06%, respectively), but these differences were not statistically significant (p>0.05; Figure 2, Table 2). However, patients in the standard-dose group showed slightly better functional independence 90 days after alteplase administration, since mean value of their Rankin score was 1.88, compared to 2.20 n the low-dose group, although this difference was not statistically significant. A favourable outcome (Rankin score 0-2) at 90 days after alteplase treatment was achieved in 53.33% of patients in the low-dose group and in 64.24 % of patients in the standard-dose group, but the difference was not significant (Table 2).

The number of serious side effects, like parenchymal haematoma type-2, overall intracerebral haemorrhage or death, more frequently occurred in the standard-dose group than in low-dose group, but these differences were not statistically significant (Table 3).

DISCUSSION

This study was driven by the concern for intracerebral haemorrhage following thrombolytic reperfusion treatment, particularly among those considered as high risk patients who were then assigned to receive the low-dose alteplase therapy. Our Stroke Unit is the only centre in the region with recommended treatment criteria for high risk AIS patients, and thus study results could be used as a basis for additional analyses and rationality of that treatment approach.

The results of our study have shown that patients with AIS who received the low-dose (0.6 mg/kg) alteplase had comparable clinical outcomes and similar complications to those with the standard-dose (0.9 mg/kg) treatment. A favourable treatment outcome, measured as a Rankin score 0-2 at 90 days after alteplase treatment, was achieved in 64.24% of patients in the standard-dose group and in 53.33% of patients in the low-dose group, but this difference was not statistically significant. However, the slight difference between these two

groups does exist in terms of NIHSS scores, since the standard dose induced a more significant improvement of NIHSS scores at 72 hours and 90 days after treatment than did the low dose. These results are similar to the study of Korean authors who emphasised that the low-dose alteplase would be a practical alternative for patients at higher haemorrhagic risk (Kim et al. 2015), and very similar to the Taiwanese study in which early neurological improvement, symptomatic haemorrhagic transformation and early neurological deterioration were not significantly different between the low-dose and the standard-dose groups (Ong et al. 2017).

Concerning the safety outcomes, the total intracerebral haemorrhagic rate and mortality rate at 90 days were non-significantly higher in the standard-dose group compared to the low-dose group. These results are comparable to the results of some studies performed in predominantly Asian patients in whom the low-dose alteplase was similar to the standard-dose treatment with respect to the death and disability at 90 days (Anderson et al. 2016, Chen et al. 2012). The results of ENCHANTED study also showed that the haemorrhagic transformation rate was significantly lower in patients with low-dose treatment (European Stroke Organisation (ESO) Executive Committee 2008). Similarly, Ong et al. noticed that the haemorrhagic transformation rate has increased proportionally as alteplase dose increased, reaching 21.4% in the group of patient who received 0.9 mg/kg alteplase, which was similar to the haemorrhagic transformation rate observed in our study (Ong et al. 2017).

However, in a Chinese study the standard-dose treatment had more favourable functional outcomes than the low-dose alteplase with no increased risk for symptomatic intracranial haemorrhage (SICH) (Liao et al. 2014). In another, more recent, Chinese study the efficacy of low-dose alteplase thrombolytic therapy was equivalent to the standard dose regimen, but the incidence of SICH in the low-dose group was significantly lower than that of the standard-dose group (Zhao et al. 2017). In our study we noticed just one case (1/45; 2.2%) of PH type 2 (SICH) in low-dose group, and 12 cases (12/165; 7.3%) in standard-dose group, but again, this difference was not significant.

The low-dose alteplase was administered according to the institutional protocol to elderly patients with increased risk for intracerebral haemorrhage such as diabetes mellitus and/or increased stroke severity (baseline NIHSS $\geq$ 18). Patients in the low-dose group were significantly older and more of them had diabetes mellitus, but regarding all other basic parameters the groups were similar. It has been well documented that irrespective of their age or stroke severity, alteplase treatment has significantly improved the stroke outcome when applied within 4.5 hours of stroke onset (Emberson et al. 2014, Sandercock & Richi 2017). In another one Japanese study, it was confirmed that the low-dose alteplase therapy was as safe for very old AIS patients (age $\geq$80) as it was for younger people (Takayanagi et al. 2014). Therefore, there is no upper age limit for alteplase treatment, and proportional benefit increases with earlier treatment. In our study both groups of patients were treated within 4.5 hours; the onset to needle time was almost identical. However, the vast majority of patients in both groups were treated within 3 hours of stroke onset.

Concerning the stroke severity and risk of intracerebral haemorrhage, it was found that the absolute risk of fatal intracerebral haemorrhage is lowest in mild stroke and highest in more severe stroke, but having in mind the overall benefit of thrombolytic therapy, all AIS patients should be candidates for this therapeutic intervention (Sandercock & Richi 2017, Whiteley et al. 2016). In our study the NIHSS scores at admission in the low-dose group patients ranged from 3 to 24, in the standard-dose group from 2 to 25, and all patients were candidates for alteplase administration. These results are in accordance with guidelines that recommended the use of thrombolytic therapy irrespective of age and stroke severity (European Stroke Organisation (ESO) Executive Committee 2008, Mishra et al. 2010). The secondary analysis of the ENCHANTED study showed that the effects of low-dose alteplase administered to high-risk elderly patient were not clearly superior to the effects of standard-dose regime not only in Asian subgroup, but in non-Asians, as well (Wang et al. 2017). Based on this analysis it has been stated that age is not sufficient criterion for alteplase dose selection, and there are no proofs that standard-dose alteplase treatment is more hazardous for elderly, high risk patients than for younger patients.

This study has several limitations. This was a retrospective, single-centre study involving a relatively small number of patients. The study was not randomised and sample size was unequal. The selection of alteplase dose was based on clinical severity, decided by a neurologist; therefore, the patients with higher risk for intracerebral haemorrhage received the low-dose alteplase. In order to further clarify and compare the advantages and disadvantages of the low-dose vs standard-dose alteplase regimens, the prospective, randomised, double blind clinical trials is warranted.

CONCLUSION

This clinical study suggests that the low-dose alteplase treatment has comparable efficacy and safety profile to the standard-dose regimen, but there is no proof that low-dose alteplase treatment is associated with significantly lower risk of SICH in elderly patients, and/or patients with diabetes mellitus.

Acknowledgements: None.

Conflict of interest : None to declare.

Contribution of individual authors:

Ranko Škrbić, Zoran Vujković, Miloš P. Stojiljković & Radoslav Gajanin: design of the study, literature searches and analyses, interpretation of data, manuscript writing.

Dubravko Bokonjić & Jasmin Komić: statistical analyses, interpretation of dana.

References

1. *Adams HP Jr, Adams RJ, Brott T, del Zoppo GJ, Furlan A, Goldstein LB, et al.: Guidelines for the early management of patients with ischemic stroke: A scientific statement from the stroke council of the American Stroke Association. Stroke 2003; 34:1056-83*
2. *Anderson CS, Robinson T, Lindley RI, Arima H, Lavados PM, Lee TH, et al.: Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke. N Engl J Med 2016; 374:2313–23*
3. *Brott TG, Haley EC Jr, Levy DE, Barsan W, Broderick J, Sheppard GL, et al.: Urgent therapy for stroke. Part I. Pilot study of tissue plasminogen activator administered within 90 minutes. Stroke 1992; 23:632–40*
4. *Chao AC, Liu CK, Chen CH, Lin HJ, Liu CH, Jeng JS, et al.: Low-dose versus standard-dose tissue plasminogen activator for intravenous thrombolysis in Asian acute ischemic stroke patients. Stroke 2010; 41:e545– e546*
5. *Chen CH, Hsieh CY, Lai TB, Chuang MT, Chen WL, Sun MC.: Optimal dose for stroke thrombolysis in Asians: low dose may have similar safety and efficacy as standard dose. J Thromb Haemost 2012;10:1270-5*
6. *Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr. American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: A science advisory from the American Heart Association/American Stroke Association: Stroke 2009; 40:2945-8*
7. *Dharmasaroja PA, Pattaraarchachai J.: Low versus standard dose of recombinant tissue plasminogen activator in treating East Asian patients with acute ischemic stroke. Neurol India 2011; 59:180–4*
8. *Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al.: Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014; 384:1929-35*
9. *European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008.: Cerebrovasc Dis 2008; 25:457-507*
10. *Fiorelli M, Bastianello S, von Kummer R, del Zoppo GJ, Larrue V, Lesaffre E, et al.: Hemorrhagic transformation within 36 hours of cerebral infarct Relationship with early clinical deterioration and 3-month outcome in the European cooperative acute stroke study I (ECASS I) cohort. Stroke 1999; 30:2280–4*
11. *Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al.: Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 1998; 352:1245–51*
12. *Haley EC Jr, Levy DE, Brott TG, Sheppard GL, Wong MC, Kongable GL, et al.: Urgent therapy for stroke. Part II. Pilot study of tissue plasminogen activator administered 91-180 minutes from onset. Stroke 1992; 23:641–45*
13. *Hankey GJ.: Thrombolysis for acute ischemic stroke. J Clin Neurosci 2001; 8:103-5*
14. *Kaste M, Thomassen L, Grond M, Hacke W, Holtas S, Lindley RI, et al.: Thrombolysis for acute ischemic stroke: a consensus statement of the 3rd KarolinskaStroke Update, October 30-31, 2000. Stroke 2001; 32:2717-8*
15. *Kim BJ, Han MK, Park TH, Park SS, Lee KB, Lee BC, et al.: Low-versus standard-dose alteplasefor ischemic strokes within 4.5 hours: a comparative effectiveness and safety study. Stroke 2015; 46:2541-8*
16. *Liao X, Wang Y, Pan Y, WangC, Zhao X, Wang DZ, et al.: Standard-dose intravenous tissue-type plasminogen activator for stroke is better than low doses. Stroke 2014; 45:2354–8*
17. *Mishra NK, Ahmed N, Andersen G, Egido JA, Lindsberg PJ, Ringleb PA, et al.: Thrombolysis in very elderly people: controlled comparison of SITS International Stroke Thrombolysis Registry and Virtual International Stroke Trials Archive. BMJ 2010; 341:c6046*
18. *Ong CT,Wong YS, Wu CS, Su YH: Outcome of stroke patients receiving different doses of recombinant tissue plasminogen activator. Drug Des Devel Ther 2017; 11:1559-66*
19. *Sandercock PAG, Richi S. Contraversies in thrombolysis. Curr Neurol Neurosci Rep 2017; 17:60*
20. *Sharma VK, Tsivgoulis G, Tan JH, Wong LY, Ong BK, Chan BP, et al.: Feasibility and safety of intravenous thrombolysis in multiethnic Asian stroke patients in Singapore. J Stroke Cerebrovasc Dis 2010; 19:424–30*
21. *Takayanagi S, Ochi T, Hanakita S, Suzuki Y, Maeda K: The safety and effectiveness of low-dose recombinant tissue plasminogen activator (0.6 mg/kg) therapy for elderly acute ischemic stroke patients (≥80 years old) in the pre-endovascular era. Neurol Med Chir (Tokyo) 2014; 54:435-40*
22. *The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke: N Engl J Med 1995; 333:1581-7*
23. *Toyoda K, Koga M, Naganuma M, Shiokawa Y, Nakagawara J, Furui E, et al.: Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients; General outcomes and prognostic factors from the SAMURAI register. Stroke 2009; 40:3591-5*
24. *Ueshima S, Matsuo O: The differences in thrombolytic effects of administrated recombinant t-PA between Japanese and Caucasians. ThrombHaemost 2002; 87:544–546*
25. *van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ: Incidence, case fatality, and functional*

outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol 2010; 9:167–76

26. *Wang X, Robinson TG, Lee TH, Li Q, Arima H, Bath PM, et al.: Low-dose vs standard-dose alteplase for patients with acute ischemic stroke: Secondary analysis of the ENCHANTED randomized clinical trial. JAMA Neurol 2017; 74:1328-1335*
27. *Wang Y, Liao X, Zhao X, Wang DZ, Wang C, Nguyen-Huynh MN, et al: China National Stroke Registry Investigators. Using recombinant tissue plasminogen activator to treat acute ischemic stroke in China: analysis of the results from the Chinese National Stroke Registry (CNSR). Stroke 2011; 42:1658–64*
28. *Wardlaw JM, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley RL, et al.: Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet 2012; 379:2364-72*
29. *Whiteley WN, Emberson J, Lees KR, Blackwell L, Albers G, Bluhmki E, et al.: Risk of intracerebral haemorrhage with alteplase after acute ischaemic stroke: a secondary analysis of an individual patient data meta-analysis. Lancet Neurol 2016; 15:925–33*
30. *Yamaguchi T, Mori E, Minematsu K, Nakagawara J, Hashi K, Saito I, et al.: Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). Stroke 2006; 37:1810-5*
31. *Zhao G, Huang T, Zheng M, Cui Y, Liu Y, Cheng Z, et al.: Comparative analysis on low- and standard-dose regimes of alteplase thrombolytic therapy for acute ischemic stroke: efficacy and safety. Eur Neurol 2017; 79:68-73*

Correspondence:

Professor Ranko Škrbić, MD, PhD
Faculty of Medicine, University of Banja Luka
Save Mrkalja 16, 78000 Banjaluka, Bosnia & Herzegovina
E-mail: ranko.skrbic@med.unibl.org