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The comparison of tenecteplase and alteplase in acute stroke treatment: meta-analysis of 5 randomized clinical trials

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ABSTRACT

Thrombolysis with the use of intravenously administrated alteplase is the only approved thrombolytic treatment of acute ischemic stroke. Tenecteplase is a fibrinolytic protein bioengineered from human tissue plasminogen activator with higher fibrin specificity, enhanced affinity to fibrin-rich clots, faster clot lysis and prolonged plasma half-life. The aim of this study was to determine which thrombolytic therapy (tenecteplase versus alteplase) provides better efficacy and safety outcomes. Eligible studies for meta-analysis published from their inception to May 2018 were identified through a search of PubMed database and two clinical trial registries websites: ClinicalTrials.gov and EU Clinical Trials Register. A meta-analysis was conducted with the use of Statistica software version 13.1. Five studies comprising 1529 patients were included. Tenecteplase 0,25mg/kg administration resulted in significantly higher number of patients with excellent score (0-1) in modified Rankin Scale at 90 days compared to alteplase group (RR 1,30, p=0,0215, 95% CI 1,04–1,62). Additionally, more patients treated with tenecteplase 0,25 mg/kg tended to develop favorable score changes in NIHSS at 24 hours after stroke onset ($\geq$8 point improvement, scale quantifying stroke severity) compared to alteplase treatment (RR 1,60, p=0,0545, 95% CI 0,99–2,58). No above correlation were observed in higher dose of tenecteplase group (0,4 mg/kg). There were no significant differences in the frequency of symptomatic intracerebral hemorrhage (ICH) and the mortality rates within 90 days after stroke onset in comparison of tenecteplase and alteplase groups. Tenecteplase 0,25 mg/kg administration in acute ischemic stroke resulted in better functional outcome at 90 days after ischemic stroke onset and

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tended to restrict the severity of stroke at 24 hours in NIHSS compared to alteplase 0,9 mg/kg. The frequency of symptomatic ICH occurrence and mortality within 3 months between tenecteplase and alteplase were comparable.

***Keywords*:** tenecteplase, alteplase, rt-PA, thrombolysis, ischemic stroke, cerebral infarction

1. INTRODUCTION

Ischemic stroke is the most common type of stroke (85% of all cases) and ranges from mild transient ischemic attack (TIA) to severe, proximal (large) vessel occlusion [1]. The primary therapeutic goal for patients with ischemic stroke is the rapidly restoration of blood flow to not already infarcted brain tissue using thrombolysis and mechanical thrombectomy [2]. Intravenously administered alteplase (a recombinant tissue plasminogen activator, rt-PA) is the only approved thrombolytic treatment of patients within 4.5 hours of ischemic stroke onset [3].

The clinical use of alteplase was approved by The European Medicines Agency (EMEA) in 2002 followed by the confirmation of safety and effectiveness in large, observational study published in 2017, which recommended wider use of thrombolytic therapy in stroke centers [4,5]. Despite many advantages, thrombolysis with alteplase is characterized by some adverse features and effects, include short half-life requiring continuous infusion, relatively low recanalization rate and the risk of intracranial hemorrhage [3]. Tenecteplase is a fibrinolytic protein bioengineered from human tissue plasminogen activator (alteplase) with 15-fold higher fibrin specificity and 6-fold prolonged plasma half-life which results in a possibility of a single intravenous bolus administration instead of significantly longer alteplase infusion [6].

The pharmacodynamic and pharmacokinetic properties of tenecteplase (like high fibrin specificity and high resistance to plasminogen activator inhibitor-1) are responsible for enhancement of the affinity to fibrin-rich clots and faster clot lysis than alteplase. Moreover, less consumption of fibrinogen, plasminogen, and a2-antiplasmin, results in bleeding risk reduction [7].

The aim of this meta-analysis is to compare the efficacy and safety of intravenous administration of tenecteplase and alteplase in acute ischemic stroke treatment.

2. MATERIALS AND METHODS

2. 1. Search strategy

Systematic literature searches of NCBI/NLM PubMed database published from their inception to May 2018 were performed. The following combinations of search terms were used: "(tenecteplase) AND ((tissue plasminogen activator) OR (alteplase)) AND ((stroke) OR (cerebral infarction) OR (brain infarction) OR (brain ischemia))". Two clinical trial registries websites were also analyzed: ClinicalTrials.gov and EU Clinical Trials Register.

2. 2. Inclusion and exclusion criteria

For this review, we included only randomized controlled trials comparing intravenous tenecteplase with intravenous alteplase in acute stroke treatment. Participants of the studies were adults (aged 18 years and over) who were diagnosed with acute ischemic stroke and assessed with the use of National Institutes of Health Stroke Scale (NIHSS). Tenecteplase and alteplase used in the included studies was administered intravenously.

The following exclusion criteria were applied: intraarterial route of tenecteplase or alteplase administration, no group of patients treated with alteplase as a control group, and insufficient dose of tenecteplase less than 0,25 mg/kg (lower effectiveness of dose 0,1 mg/kg had been confirmed previously [8]).

2. 3. Main outcomes

This meta-analysis measured four outcomes:

1. Early major neurological improvement defined as a reduction of ≥ 8 points in NIHSS (scale used for objectively quantify the impairment caused by a stroke) at 24 hours.
2. Excellent score in modified Rankin scale (0 or 1) in the assessment at 90 days after stroke onset. Modified Rankin scale (mRS) runs from 0 to 6 and is used for measuring the degree of disability or dependence in the daily activities. The score of 0 point means no symptoms and the score of 1 point means no significant disability with the almost full ability to carry out all usual activities.
3. Symptomatic intracerebral hemorrhage (ICH).
4. Mortality within 90 days after stroke onset.

2. 4. Search strategy and data extraction

The searching criteria described above resulted in 162 studies extracted. Studies were excluded with following reasons: not clinical trial (110), condition different from stroke (22), duplicate publications (11), ongoing trials (8), withdrawn before enrolling first participant (1), no comparison with alteplase (1), intraarterial administration (1), insufficient dose of tenecteplase (1), use of sonothrombolysis (1). After rejection of above findings, five published randomized trials enrolled 1 529 patients were included in the meta-analysis (Figure 1) [9].

Data from the five included studies were extracted using a Microsoft Excel spreadsheet. Details obtained from the articles were: author's name, publication year, number of participants, study design, average time from onset to treatment, baseline score in NIHSS and outcome measures. Studies were divided into two groups depending on tenecteplase doses. The main results of the included studies were presented in Table 1 [10-14].

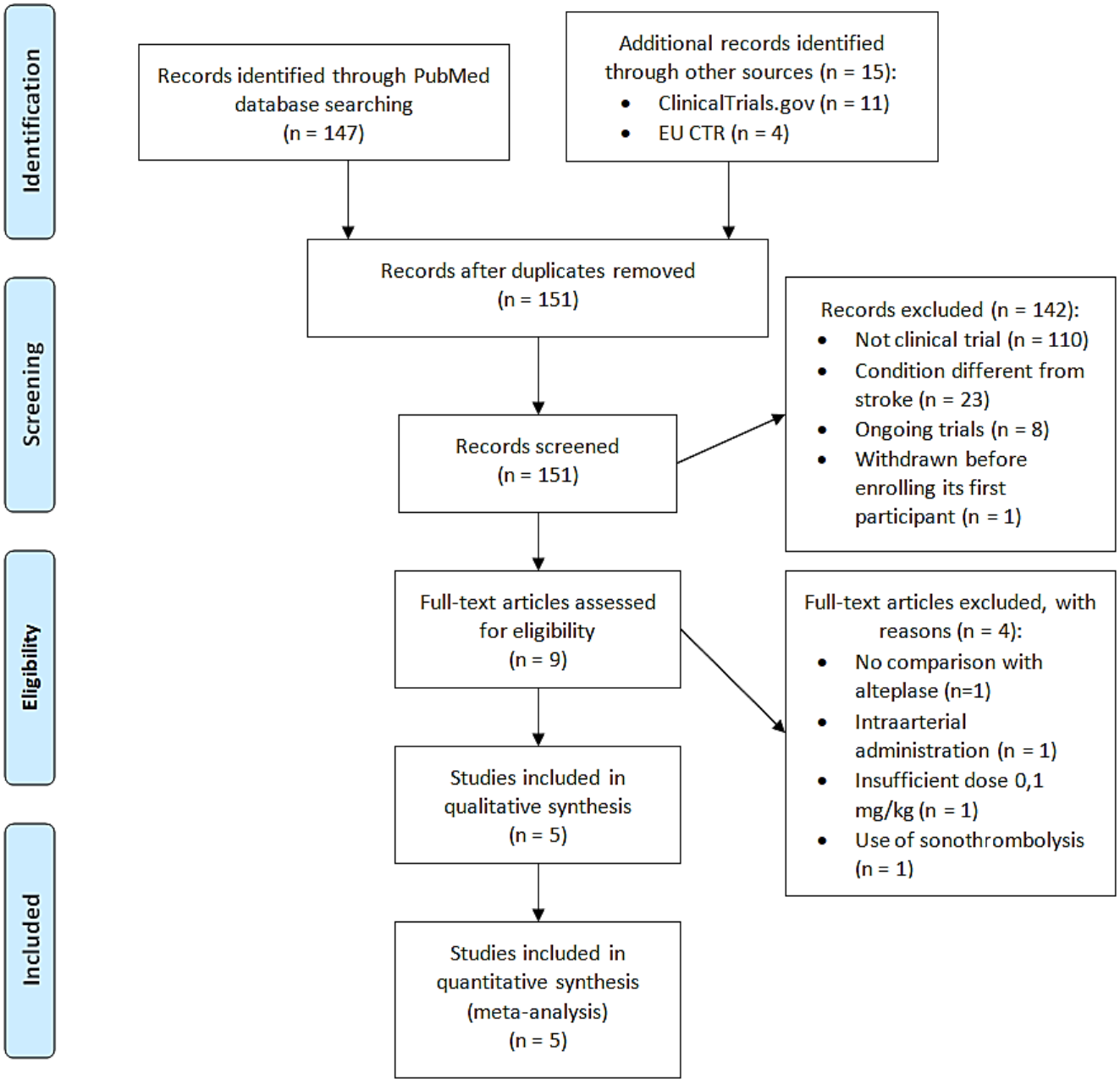

Figure 1. The consecutive phases of a systematic review shown in PRISMA flow diagram [9].

Table 1. Studies on comparison between intravenous tenecteplase and alteplase.

Sample size			TT	NIHSS	Study design	TNK group versus rt-PA group	Y Ref
All	TNK	rt-PA					
Tenecteplase **0,25 mg/kg**							
62	31	31	U	T: 10 A: 13	randomized double-blind controlled	Most statistically insignificant (p>0,05): MNI: 35,5% v. 16,1%, mRS 0-1 at 90 days: 48,4% v. 36,8%, Symptomatic ICH: 6,5% v. 3,2%, death at 3 months: 22,6% v. 25,8%.	2010 [10]
50	25	25	TNK: 180 rt-PA: 162	T: 14,6 A:14,0	randomized open-label blinded	mRS 0-1 at 90 days: 72% v. 40%, death at 3 months: 4% v. 12%, greater reperfusion, more patients with MNI reduced infarct growth at 24h and 90 days, lower risk for symptomatic ICH.	2012 [11]
96	47	49	TNK: 184 rt-PA: 191	T: 12 A: 11	randomized open-label blinded endpoint	No significant differences noted for neurological and radiological outcomes: percentage of penumbral salvaged (68% v. 68%, p=0,81), symptomatic ICH (8% v. 12%, p=0,50-0,59), death at 90 days (17% v. 12%, p=0,51). Tend to favour TNK: MNI (40% v. 24%, p=0,1), mRS 0-1 at 90 days (28% v. 20%, p=0,28).	2015 [12]
202	101	101	TNK: 125 rt-PA: 134	T: 17 A: 17	randomized open-label blinded endpoint	TNK before thrombectomy: higher incidence of reperfusion and better functional outcome substantial reperfusion: 22% v. 10% (p=0,03), death at 3 months: 10% v. 18% (p=0,049), mRS at 90 days: median: 2 v. 3 (p=0,04), excellent (0-1): 52% v. 43% (p=0,2), functionally independent: (0-2) 65% v. 52% (p=0,06). Statistically insignificant: MNI: 72% v. 69% (p=0,7), symptomatic ICH: 1% v. 1% (p=0,99).	2018 [14]
Tenecteplase **0,4 mg/kg**							
50	19	31	U	T: 9 A: 13	randomized double-blind controlled	Most statistically insignificant (p>0,05): MNI: 21,1% v. 16,1%, mRS 0-1 at 90 days: 36,8% v. 41,9%, symptomatic ICH: 15,8% v. 3,2%, death at 3 months: 15,8% v. 25,8%,	2010 [10]
1 100	549	551	TNK: 118 rt-PA: 111	T: 4 A: 4	randomised open-label blinded endpoint	No superiority of TNK, similar safety profile. MNI: 42% v. 39% (p=0,97), mRS 0-1 at 90 days: 64% v. 63% (p=0,52), symptomatic ICH: 3% v. 2% (p=0,49), death at 3 months: 5% v. 4% (p=0,49).	2017 [13]

TNK – tenecteplase administration**, rt-PA** – alteplase administration, **TT –** time from the onset of symptoms to treatment (min), **NIHSS** – baseline score of National Institutes of Health Stroke Scale (median), **Y** – year of publication, **Ref** – references, **U** – undefined, **mRS** – modified Rankin scale, **v.** – versus, **MNI** – major neurological improvement (≥ 8 points reduction in NIHSS at 24 hours), **ICH –** intracranial hemorrhage.

2. 5. Statistical analysis

Statistical treatment of results was performed with the use of Statistica software version 13.1. Data from published studies were used to generate risk ratio (RR) with 95% confidence intervals (CIs). A summary RR with 95% CIs was calculated having regard to the weights of included studies. Statistical significance was identified as $p \leq 0.05$. Four main outcomes were assessed as the comparisons of tenecteplase 0,25 mg/kg with alteplase 0,9 mg/kg and tenecteplase 0,4 mg/kg with alteplase 0,9 mg/kg.

3. RESULTS

3. 1. Efficacy outcomes

Statistical significance was found in the assessment of excellent score in mRS at 90 days when the comparison referred to tenecteplase 0,25 mg/kg and alteplase administration (RR 1,30, p = 0,0215, 95% CI 1,04 – 1,62). Tenecteplase 0,25 mg/kg treatment in acute phase of ischemic stroke increased the number of patients with no post-stroke symptoms or no relevant disability. Above correlation was absent in the group treated with hither dose of tenecteplase 0,4 mg/kg (RR 0,98, p = 0,7134, 95% CI 0,86 – 1,11).

The administration of tenecteplase 0,25 mg/kg tended to result in more favourable score changes in NIHSS assessed at 24 hours after thrombolytic treatment, however it was statistically insignificant (RR 1,60, p = 0,0545, 95% CI 0,99 – 2,58). No significant correlation was found between administration of higher dose of tenecteplase and alteplase (RR 1,08, p = 0,309, 95% CI 0,93 – 1,24). Above outcomes were presented on Table 2 and Figure 2.

Table 2. Statistical analysis of the efficacy outcomes.

				Haley et al. 2010 [10]	Parsons et al. 2012 [11]	Huang et al. 2015 [12]	Logallo et al. 2017 [13]	Campbell et al. 2018 [14]
			Dose mg/kg	**81**	**50**	**96**	**1 100**	**202**
Early major neurological improvement[1]	TNK	Effect /Total	0,25	11/31	21/25	19/47		72/101
			0,4	4/19			229/549	
		No effect	0,25	20	4	28		29
			0,4	15			320	
	rt-PA	Effect /Total	0,9	5/31	9/25	12/49	214/551	69/101
		No effect		26	16	37	337	32
	TOTAL		T: 0,25 A: 0,9	**RR 1,60 p = 0,0545, 95% CI (0,99 – 2,58)**				
			T: 0,4 A: 0,9	RR 1,08 p = 0,309, 95% CI (0,93 – 1,24)				
Excellent score in mRS at 90 days[2]	TNK	Effect /Total	0,25	15/31	18/25	13/47		52/101
			0,4	7/19			244/549	
		No effect	0,25	16	7	34		49
			0,4	12			305	
	rt-PA	Effect /Total	0,9	13/31	10/25	10/49	250/551	43/101
		No effect		18	15	39	301	58
	TOTAL		T: 0,25 A: 0,9	**RR 1,30 p = 0,0215, 95%CI (1,04 – 1,62)**				
			T: 0,4 A: 0,9	RR 0,98 p = 0,7134, 95%CI (0,86 – 1,11)				

TNK – tenecteplase, **rt-PA** – alteplase, **RR** – relative risk, **CI** – confidence interval
[1] Early major neurological improvement defined as a reduction of ≥ 8 points in NIHSS at 24 hours [2] Excellent score in modified Rankin scale defined as a score of 0 or 1 as a result of assessment at 90 days.

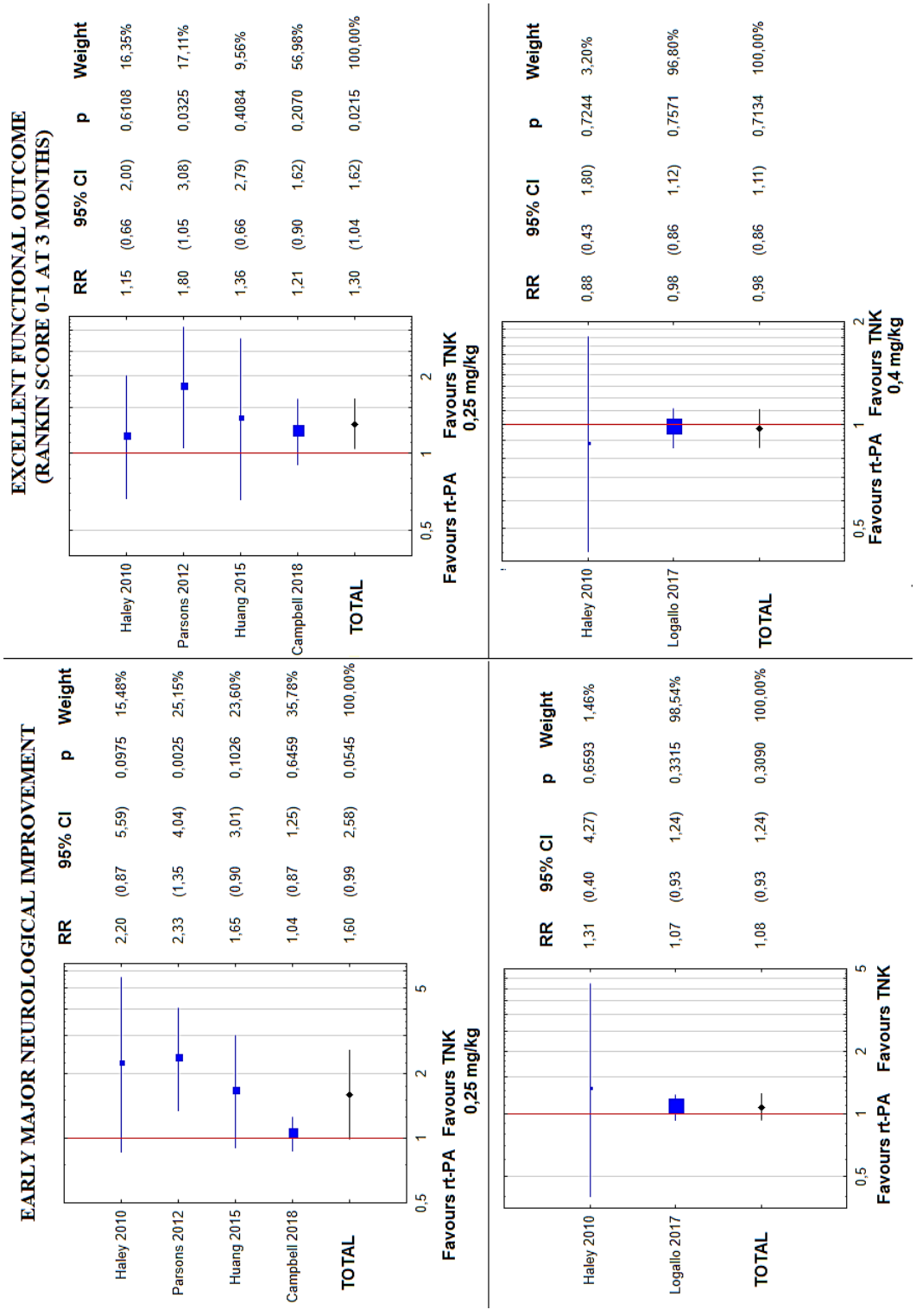

Figure 2. Major neurological improvement at 24 hours and excellent functional outcome at 90 days in modified Rankin scale (mRS 0 or 1). **TNK** – tenecteplase, **rt-PA** – alteplase, **RR** – relative risk, **CI** – confidence interval.

3. 2. Safety outcomes

There was no significant difference in the frequency of symptomatic cerebral hemorrhage between tenecteplase 0,25 mg/kg and alteplase (RR 0,75, p = 0,5278, 95% CI (0,30 – 1,85) or tenecteplase 0,4 mg/kg and alteplase (RR 1,73, p = 0,2316, 95% CI 0,70 – 4,26). Similarly, no significant difference was found in the mortality rates at 90 days between tenecteplase 0,25 mg/kg (RR 0,77, p = 0,2714, 95% CI 0,48 – 1,23) and alteplase or tenecteplase 0,4 mg/kg and alteplase (RR 1,06, p = 0,8571, 95% CI 0,56 – 1,99). Above outcomes were presented on Table 3 and Figure 3.

Table 3. Statistical analysis of the safety outcomes

				Haley et al. 2010 [10]	**Parsons et al. 2012 [11]**	**Huang et al. 2015 [12]**	**Logallo et al. 2017 [13]**	**Campbell et al. 2018 [14]**
			Dose mg/kg	**81**	**50**	**96**	**1 100**	**202**
Symptomatic cerebral hemorrhage	TNK	Effect /Total	0,25	2/31	1/25	4/47		1/101
			0,4	3/19			11/389	
		No effect	0,25	29	24	43		100
			0,4	16			378	
	rt-PA	Effect /Total	0,9	1/31	3/25	6/49	8/400	1/101
		No effect		30	22	43	392	100
	TOTAL		T: 0,25 A: 0,9	RR 0,75 p = 0,5278, 95% CI (0,30 – 1,85)				
			T: 0,4 A: 0,9	RR 1,73 p = 0,2316, 95% CI (0,70 – 4,26)				
Mortality at 3 months	TNK	Effect /Total	0,25	7/31	1/25	8/47		10/101
			0,4	3/19			20/382	
		No effect	0,25	24	24	39		91
			0,4	16			362	
	rt-PA	Effect /Total	0,9	8/31	3/25	6/49	16/391	18/101
		No effect		23	22	43	375	83
	TOTAL		T: 0,25 A: 0,9	RR 0,77 p = 0,2714, 95% CI (0,48 – 1,23)				
			T: 0,4 A: 0,9	RR 1,06 p = 0,8571, 95% CI (0,56 – 1,99)				

TNK – tenecteplase, **rt-PA** – alteplase, **RR** – relative risk, **CI** – confidence interval.

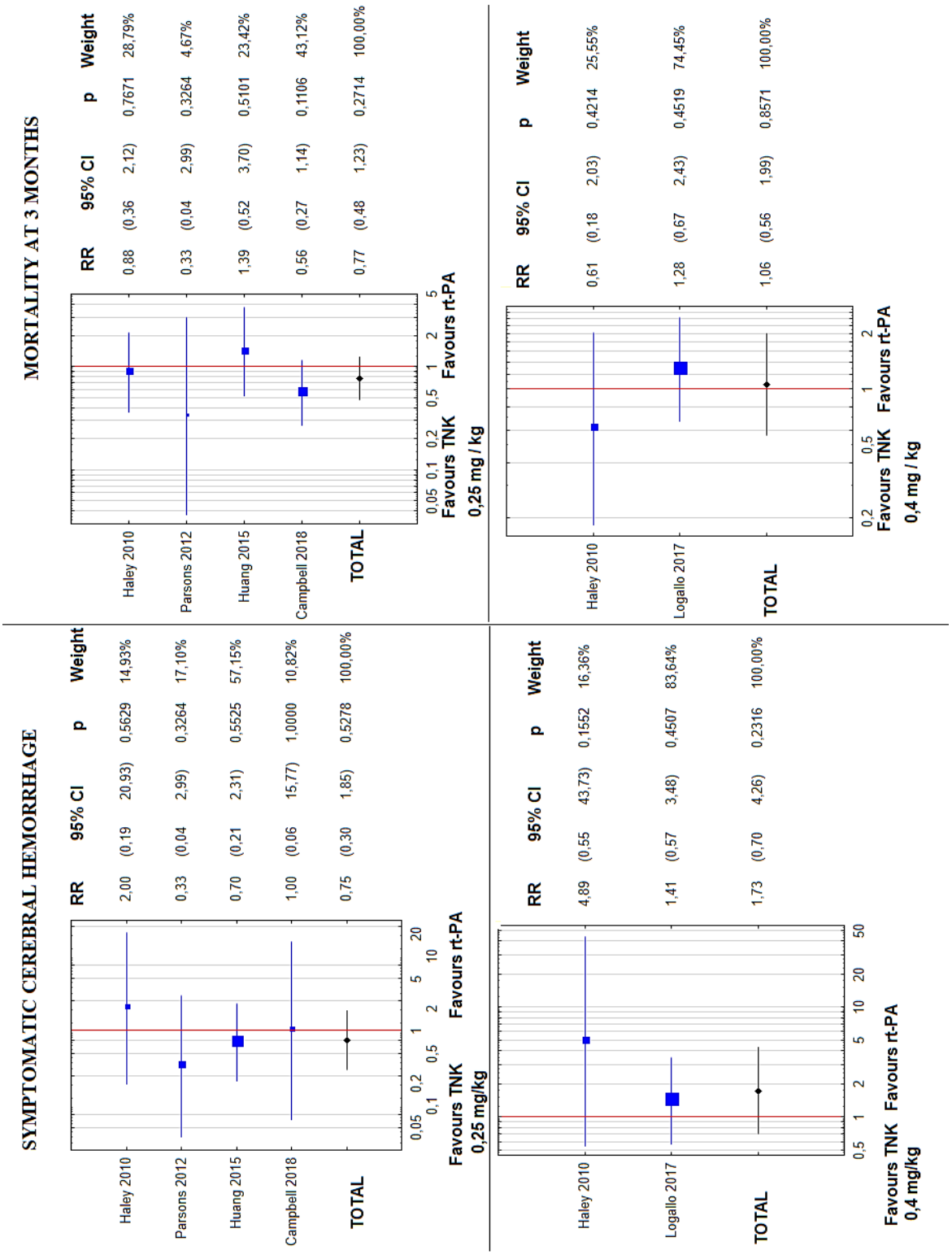

Figure 3. The statistical analysis of the frequencies of the symptomatic cerebral hemorrhage and mortality at 90 days after stroke. **TNK** – tenecteplase, **rt-PA** – alteplase, **RR** – relative risk, **CI** – confidence interval.

4. DISCUSSION

Our meta-analysis showed one statistically significant correlation (more patients in tenecteplase 0,25 mg/kg group developed excellent functional outcome at 90 days in mRS scale compared to alteplase, p=0,0215) and one tendency close to the threshold value of statistical significance (more patients in tenecteplase 0,25 mg/kg group developed $\geq$ 8 points reduction in NIHSS at 24 hours after stroke onset compared to alteplase, p=0,545). Above correlation vary from the outcome of the most recent meta-analysis published in 2018 by Thelengana et al, in which no significant difference was found between tenecteplase and alteplase in excellent functional outcome at 90 days, but significantly better early major neurological improvement was observed in tenecteplase group [15]. These differences may emerge from three major causes. Firstly, one randomized, open-label, blinded endpoint study (Campbell et al, 2018) was not included in meta-analysis published by Thelengana et al. as the performing of mechanical thrombectomy in both groups (alteplase and tenecteplase) was one of the exclusion criteria. Secondly, the statistical tools used in meta-analyses were similar but not identical. Thirdly, Thelegana et al. combined both doses of tenecteplase (0,25 mg/kg and 0,4 mg/kg) in one group, which might affect major outcomes.

This meta-analysis did not include the comparison of reperfusion rates. Campbell et al. described higher incidence of reperfusion and better functional outcome of substantial reperfusion (22% v. 10%, p=0,03) in group of tenecteplase 0,25 mg/kg administration before thrombectomy compared to alteplase [14]. Greater reperfusion was also described by Parsons et al., however several differences in "reperfusion" definition and no comparable outcomes measured in other included studies precluded an appropriate assessment in this meta-analysis [11].

Most significant correlations might be probably found if the definition of efficacy assessed in mRS score will be expanded on "score reduction" rather than "score of 0-1" (excellent functional outcome). Unfortunately, data reported in included studies were not enough detailed to obtain precise point change in all cases. For example, in one study statistical significance was found in comparison of reduction in mRS median score (2 v. 3, p=0,04), but not in comparison of the number of excellent scores (0-1) and other scores (52% v. 43%, p=0,2) [14].

Thrombolytic treatment is characterized by some restrictions. The modest rate of early reperfusion is observed among patients with large-vessel occlusion. Even early alteplase administration in these cases result in nutritive reperfusion only one third of the time and 60 to 80% of patients die within 90 days after stroke onset or do not regain functional independence despite alteplase treatment [1,17]. Second the most significant problem of insufficient efficacy of thrombolytic treatment of acute stroke is the relatively short "time window" for thrombolysis. Following the most recent recommendations from the guidelines for the early management of patients with acute ischemic stroke, alteplase should be administered to the patients who may be treated within 3 hours of ischemic stroke symptom onset or within 4,5 hours when treatment can fulfill additional criteria [16]. Only half of stroke victims get to the hospital in time for standard intravenous thrombolysis with alteplase [1]. To improve the effectiveness of thrombolytic therapy in both alteplase and tenecteplase cases, the time from stroke onset to treatment initiation have to be as short as possible.

Summarizing, results of this meta-analysis indicate that tenecteplase administration in acute phase of ischemic stroke do not differ from alteplase in safety characteristics and may

result in better efficacy outcomes. The ongoing studies should add strength to above correlations.

5. CONCLUSION

Tenecteplase 0,25 mg/kg administration in acute ischemic stroke resulted in better functional outcome at 90 days after stroke onset and tended to restrict the severity of stroke at 24 hours in NIHSS compared to alteplase 0,9 mg/kg. No significant differences were found in the frequency of intracerebral hemorrhage occurrence and mortality within 3 months after stroke onset between tenecteplase and alteplase.

References

[1] M. Goyal, M.D. Hill, J.L. Saver, M. Fisher, Challenges and Opportunities of Endovascular Stroke Therapy. *Annals of Neurology* 79 (2016) 11–17.

[2] S. Bhaskar, P. Stanwell, D. Cordato, J. Attia, C. Levi. Reperfusion therapy in acute ischemic stroke: dawn of a new era? *BMC Neurology* 18 (2018) doi:10.1186/s12883-017-1007-y.

[3] G. Nepal, G. Kharel, S.T. Ahamad, B. Basnet. Tenecteplase versus Alteplase for the Management of Acute Ischemic Stroke in a Low-income Country-Nepal: Cost, Efficacy, and Safety. *Cureus* 10 (2018) e2178. doi: 10.7759/cureus.2178.

[4] B.A. Keyt, N.F. Paoni, C.J. Refino, L. Berleau, H. Nguyen, A. Chow, J. Lai, L. Peña, C. Pater, J. Ogez, A faster-acting and more potent form of tissue plasminogen activator. *Proceedings of the National Academy of Sciences of the United States of America* 91 (1994) 3670-3674.

[5] N. Wahlgren, N. Ahmed, A. Dávalos, G.A. Ford, M. Grond, W. Hacke, M.G. Hennerici, M. Kaste, S. Kuelkens, V. Larrue, K.R. Lees, R.O. Roine, L. Soinne, D. Toni, G. Vanhooren, SITS-MOST investigators, Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet* 369 (2007) 275-282.

[6] P. Tanswell, N. Modi, D. Combs, T. Danays, Pharmacokinetics and pharmacodynamics of tenecteplase in fibrinolytic therapy of acute myocardial infarction. *Clinical Pharmacokinetics* 41 (2002) 1229-1245.

[7] N. Logallo, C.E. Kvistad, L. Thomassen, Therapeutic Potential of Tenecteplase in the Management of Acute Ischemic Stroke. *CNS Drugs* 29 (2015) 811-818.

[8] Y. Zang, J. Hou, L.Y. Wang, Therapeutic effect of tenecteplase on treatment of cerebral arterial thrombosis: a meta-analysis. *European Review for Medical and Pharmacological Sciences* 20 (2016) 4369-4379.

[9] D. Moher, A. Liberati, J.Tetzlaff, D.G. Altman, The PRISMA Group (2009), Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine* (2009) e1000097. doi:10.1371/journal.pmed1000097.

[10] E.C. Haley, J.L.P. Thompson, J.C. Grotta, P.D. Lyden, T.G. Hemmen, D.L. Brown, C. Fanale, R. Libman, T.G. Kwiatkowski, R.H. Llinas, S.R. Levine, K.C. Johnston, R. Buchsbaum, G. Levy, B. Levin, Phase IIB/III Trial of Tenecteplase in Acute Ischemic Stroke: Results of a Prematurely Terminated Randomized Clinical Trial. *Stroke* 41 (2010) 707–711.

[11] M. Parsons, N. Spratt, A. Bivard, B. Campbell, K. Chung, F. Miteff, B. O'Brien, C. Bladin, P. McElduff, C. Allen, G. Bateman, G. Donnan, S. Davis, C. Levi, A Randomized Trial of Tenecteplase versus Alteplase for Acute Ischemic Stroke. *The New England Journal of Medicine* 366 (2012) 1099-1107.

[12] X. Huang, B.K. Cheripelli, S. M Lloyd, D. Kalladka, F.C. Moreton, A. Siddiqui, I. Ford, K.W. Muir, Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. *The Lancet Neurology 14* (2015) 14: 368–376.

[13] N. Logallo, V. Novotny, J. Assmus, C.E. Kvistad, L. Alteheld, O.M. Rønning, B. Thommessen, K.Fr. Amthor, H. Ihle-Hansen, M. Kurz, H. Tobro, K. Kaur, M. Stankiewicz, M. Carlsson, Å. Morsund, T. Idicula, A. Hege Aamodt, C. Lund, H. Næss, U. Waje-Andreassen, L. Thomassen, Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. *The Lancet Neurology* 16 (2017) 781–788.

[14] B.C.V. Campbell, P.J. Mitchell, L. Churilov, N. Yassi, T.J. Kleinig, R.J. Dowling, B. Yan, S.J. Bush, H.M. Dewey, V. Thijs, R. Scroop, M. Simpson, M. Brooks, H. Asadi, T.Y. Wu, D.G. Shah, T. Wijeratne, T. Ang, F. Miteff, C.R. Levi, E. Rodrigues, H. Zhao, P. Salvaris, C. Garcia‐Esperon, P. Bailey, H. Rice, L. de Villiers, H. Brown, K. Redmond, D. Leggett, J.N. Fink, W. Collecutt, A.A. Wong, C. Muller, A. Coulthard, K. Mitchell, J. Clouston, K. Mahady, D. Field, H. Ma, T.G. Phan, W. Chong, R.V. Chandra, L.-A. Slater, M. Krause, T.J. Harrington, K.C. Faulder, B.S. Steinfort, C.F. Bladin, G. Sharma, P.M. Desmond, M.W. Parsons, G.A. Donnan, and S.M. Davis, Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. *The New England Journal of Medicine* 378 (2018) 1573-1582.

[15] A. Thelengana, D.M. Radhakrishnan, M. Prasad, A. Kumar, K. Prasad, Tenecteplase versus alteplase in acute ischemic stroke: systematic review and meta-analysis. *Acta Neurologica Belgica* (2018) doi: 10.1007/s13760-018-0933-9

[16] W.J. Powers, A.A. Rabinstein, T. Ackerson, O.M. Adeoye, N.C. Bambakidis, K. Becker, J. Biller, M. Brown, B.M. Demaerschalk, B. Hoh, E.C. Jauch, C.S. Kidwell, T.M. Leslie-Mazwi, B. Ovbiagele, P.A. Scott, K.N. Sheth, A.M. Southerland, D.V. Summers, D.L. Tirschwell; American Heart Association Stroke Council, 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 49 (2018) e46-e110. doi: 10.1161/STR.0000000000000158.

[17] M. Goyal, A.M. Demchuk, B.K. Menon, M. Eesa, J.L. Rempel, J. Thornton, D. Roy, T.G. Jovin, R.A. Willinsky, B.L. Sapkota, D. Dowlatshahi, D.F. Frei, Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke. *The New England Journal of Medicine* 372 (2015) 1019-1030.