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THE IMPACT OF THROMBOLYTIC THERAPY ON ANXIETY, DEPRESSION AND QUALITY OF LIFE OF PATIENTS WITH ACUTE ISCHEMIC STROKE

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SUMMARY

Background: *It is well established that thrombolytic therapy improves the functional recovery by reducing disability measured as National Institutes of Health Stroke Scale (NIHSS) and Rankin score in patients with ischemic stroke. However, the role of alteplase treatment on anxiety and depression in those patients is less clear. Therefore, the aim of this study was to determine whether patients treated with thrombolytic therapy had a better quality of life, less anxiety and depression compared to patients who were not treated with thrombolysis.*

Subjects and methods: *In this "single canter study" 60 patients with acute ischemic stroke were divided into two groups: alteplase treated (AT) group, and not treated (NT) group. The sociodemographic data including gender, age, marital status, education, employment, financial status, place of residence, refugee status were collected at the beginning of study. The NIHSS score and modified Rankin score (mRS) were performed on admission and at discharge from hospital. Six months following discard from hospital the Beck's Anxiety Inventory (BAI), Beck's Depression Inventory (BDI) and the Short Form 36 quality of life (SF-36 QoL) were performed.*

Results: *There were no differences in mean NIHSS and mRS at admission to hospital between the groups. At discharge from hospital patients in AT group had significantly lower NIHSS and mRS than patients in NT group. In post-stroke period the patients from AT group had significantly less anxiety and depression than patients from NT group (BAI in AT 6.4+4.17 vs BAI in NT 14.27+7.01 and BDI in AT 9.20+6.61 vs BDI in NT 18.0+7.49). Patients in AT group had significantly better SF-36 QoL score in all components than NT group.*

Conclusion: *The results of this study showed that thrombolytic therapy reduced the intensity of anxiety and depression and improves the quality of life of patients six months after ischemic stroke.*

Key words: *ischemic stroke, intravenous thrombolytic therapy, post-stroke anxiety, post-stroke depression, quality of life*

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INTRODUCTION

Stroke remains a leading cause of death and long-term disability worldwide despite more accurate and earlier diagnosis and aggressive treatments (Caprio 2019). As such, stroke is a common and debilitating neurological disorder having a negative impact on quality of life and is the largest contributor to neurological disability responsible for 42.2% of disability-adjusted life-years (GBD Neurology Collaborators 2019). Thrombolytic therapy with recombinant tissue plasminogen activator is pharmacological causal therapy and method of choice in the treatment of brain infarction. The neurological benefit of intravenous thrombolysis is well documented for adult patients with disabling stroke symptoms regardless of age and stroke severity (Lees et al. 2016, Minnerup et al. 2016, Muruet et al. 2018, Campbell 2017).

The standard alteplase dose of 0.9 mg/kg of body weight was well established and clinically approved (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995), but there are also clinical evidences that administration of lower dose (0.6 mg/kg) for patient with increased risk of bleeding is also effective (Liao et al. 2014, Anderson et al. 2016, Škrbić et al. 2019). The vast majority of thrombolytic therapy efficacy studies have been primarily focused on the clinical outcomes related to neurological improvement and less on the patient's psychological condition. The links between stroke and depression and/or anxiety developed afterwards have already been well documented. It has been found that the post stroke depression occurs in 18%-60% cases (Carota et al. 2002, Carod-Artal & Egido 2009, Carod-Artal 2006), and anxiety occurs in 25-50% of cases (Carota et al. 2002, Schöttke & Giabbiconi 2015). It was noticed that even a decade after the stroke occurred, depressive symptoms and anxiety were present and associated with poor functional recovery (Maaijwee et al. 2016). Several other studies showed that post-stroke depression significantly reduces the quality of life and has contributed to the increased risk of mortality in the first couple of years after a stroke (Bartoli et al. 2103: Robinson & Jorge 2016). Beside the fact that there are abundant number of published data related to post-stroke depression and anxiety (Kotila et al. 1998, Wolfe et al. 2011, Naess et al. 2005) there are only a few studies that have investigated the effect of thrombolytic therapy on the post-stroke development of depression and anxiety. It has been shown that the frequency of depression at 12 months after stroke does not differ significantly between those treated or not treated with thrombolytic therapy (deWeerd at al. 2012), while it was concluded in another study that thrombolyzed patients may develop depression despite good functional outcome (Schwab-Malek et al. 2010). The major reason for these discrepancies in treatment outcomes could be ascribed to different study designs, treatment protocols, patients' inclusion criteria and selection of test applied. In order to elucidate the effect of thrombolytic therapy on the occurrences of anxiety, depression and quality of life of patients having cerebrovascular insult, the study was designed in which the late treatment outcomes of the two patient's groups were compared with very similar demographic and clinical characteristics. Therefore, the aim of this study was to determine whether patients treated with thrombolytic therapy had better post-stroke quality of life, less anxiety and depression compared to patients who were not treated with thrombolysis.

SUBJECTS AND METHODS

Study design

The "single-center study" was performed from April, 2018 to January, 2020 at the Department of Neurology of the University Clinical Centre of the Republic of Srpska, Banja Luka, Bosnia & Herzegovina and all data related to patient's characteristics were collected from clinical information system. Two study groups of patients with 30 participants in each were included in the study: the first group of patients who's "onset to door time" was within the 4.5 hours, and all fulfilled the inclusion criteria for thrombolytic therapy (alteplase treated, AT group), and the second group of patients who were not thrombolyzed (not treated, NT group), mainly due to late hospital arrival, or had other exclusion criteria. These patients constituted a gender/age-matched group for comparison with the AT group. In the second, prospective part of the study, all selected patients from both groups were invited for psychological and quality of life testing. These tests were performed six months following discharge from hospital. The study was approved by the local ethics committee, and all patients gave their informed consent for the follow-up interviews.

Patients and procedures

Stroke evaluation

At the time of hospitalization, all patients were clinically evaluated at the Stroke Unit of the Department of Neurology. Brain infarction was confirmed at admission by computerized tomography (CT) scanner, or by nuclear magnetic resonance (NMR), when needed. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) score and modified Rankin score (mRS), both on admission and at discharge from hospital, by trained and certified stroke physicians. All patients in the AT group had to meet internationally recommended criteria for intravenous alteplase treatment (European Stroke Organisation Executive Committee 2008).

Study interviews

Only the patients who fulfilled the inclusion criteria were invited to participate in study interviews. The non-inclusion criteria in the study were: any kind of disability present before brain infarction occurred due to other neurological, orthopedic, or rheumatic conditions, patients with intracranial bleeding, consciousness disorders, sensory motor dysphasia or suicidal ideation, as well as patients with severe somatic illnesses that do not allow further patient follow-up.

Post-stroke anxiety (PSA) and post-stroke depression (PSD) were examined by Beck's Anxiety Inventory (BAI) and Beck's Depression Inventory (BDI), respectively, and the quality of life (QOL) test was estimated by the Short Form 36 quality of life (SF-36 QoL) survey.

The BAI is a brief measure of anxiety, composed of 21 items, and mainly focused on somatic symptoms of

anxiety. Respondents indicate how much they have been bothered by each symptom over the past week and they are rated on a 4-point scale, ranging from 0 (not at all) to 3 (severely). By summing scores for items, the total score could range from 0 to 63. Based on guidelines the scores can be considered as follows: normal or no anxiety (0–9), mild to moderate anxiety (10–18), moderate to severe anxiety (19–29) and severe anxiety (30–63).

The BDI is a measure of depression and consists of 21 items with a total score ranging from 0 to 63, where a higher score indicates more severe depressive symptoms. A cut-off point at 18 was used to distinguish between the absence and presence of a clinically relevant depression.

The SF-36 QoL is quality of life self-report survey that assesses eight domains of functional health and wellbeing such as: general health perceptions (GH), physical functioning (PF), social functioning (SF), role limitations due to physical problems (RLP), role limitations due to emotional problems (RLE), body pain (BP), mental health (MH) and vitality (VT). Scores were calculated for each of the eight domains of the SF-36 QoL.

Statistical methods

The statistical analysis was done using the software package Statistical Product and Service Solutions (SPSS), version 20.0. Statistical significance between groups was tested by t-test, Mann-Whitney test, Fisher's test and $\chi 2$ test.

RESULTS

Socio-demographic data showed that there were no significant baseline differences between AT and NT groups in all parameters except in patients age and employment status. The AT group included 16 women and 14 men, with a mean age of 63.1 years and better employment status with less pensioners. The NT group consisted of 13 women and 17 men, with a mean age of 70.3 years, and as such was significantly older than the AT group (Table 1).

There were no differences in mean NIHSS and Rankin scores at admission to hospital between the groups. However, at discharge from hospital patients in AT group had significantly lower NIHSS and Rankin score than patients in NT group (Table 2).

Completed questionnaires were obtained from all patients enrolled in the study giving a response rate of 100%. In the post-stroke period patients from AT group had significantly less anxiety and depression than patients from NT group, as measured with BAI and BDI (Table 3).

In post-stroke period the alteplase-treated patients had significantly better SF-36 QoL score in all components than the non-treated patients (Table 4).

Table 1. Socio-demographic data of patients with ischemic stroke treated (AT) or non-treated (NT) with alteplase

Variables	AT group N=30 (%)	NT group N=30 (%)	P value
Gender			0.605
Female	16(55.2)	13 (44.8)	
Male	14 (45.2)	17(54.8)	
Mean age, years (SD)	63.1 (SD±12.45)	70.3 (SD±7.47)	<0.05
Marital status			0.398
Married	23 (54.8)	19(45.2)	
Not married	4(50)	4(50)	
Divorced	3(30)	7(70)	
Education			0.764
Illiterate or elementary school	• 9(50)	9(50)	
High School	18(47.4)	20 (52.6)	
Faculty	3(75)	1(25)	
Employment			<0.005
Employed	11 (91.7)	1 (8.3)	
Unemployed	3(30)	7(70)	
Pensioner	16(42.1)	22 (57.9)	
Financial status			0.796
Poor	13(46.4)	15(53.6)	
Appropriate	17(53.1)	15(42.9)	
Place of residence			0.159
Urban	24(57.1)	18 (42.9)	
Rural	6 (33.3)	12 (66.7)	
Refugee status			1.000
Domestic	29 (49.2)	30 (50.8)	
Refugee	1 (100)	0(0)	

AT- alteplase treated group; NT- non-treated group; N- number of patients

Table 2. The NIHSS and mRS at hospital admission and discharge in both, alteplase treated and non-treated patients with ischemic stroke

Scores	AT group mean ±SD	NT group mean ±SD	P value
NIHSS at admission	9.96±3.71	10.78±3.84	0.350
NIHSS at discharge	2.23±3.29*	7.39±3.90	<0.001
mRS at admission	4.00±0.95	4.14±0.97	0.493
mRS at discharge	1.00±1.51*	3.11±1.28	<0.001

AT- alteplsase treated group; NT- non-treated group; mRS- modified Rankin score; SD- standard deviation; *significant difference at discharge

Table 3. Six months post-stroke anxiety and post-stroke depression in both, alteplase treated and non-treated group of patients

Scales	AT group mean ±SD	NT group mean ±SD	P value
BAI	6.40±4.17	14.27±7.01	<0.001
BDI	9.20±6.61	18.00±7.49	<0.001

BAI -Beck's anxiety inventory; BDI- Beck's depression inventory; AT- alteplsase treated group; NT- non-treated group

Table 4. SF-36 QoL score in both, alteplase treated and non-treated groups of patients six months after acute ischemic stroke

SF-36 QoL domains	AT group Mean ± SD (min-max)	NT group Mean ± SD (min-max)	p-value
General health perceptions (GH)	52.17± 9.44 (35- 70)	44.17±7,66 (25- 60)	0.001
Physical functioning (PF)	72.00±30.69 (10-100)	26.83±29.61 (0-100)	0.001
Social functioning (SF)	65.00±31.72 (0-100)	47.92±30.28 (0-100)	0.032
Role limitations: Physical (RLP)	68.95±29.70 (25-100)	24.79±25.56 (0-100)	0.001
Role limitations: Emotional (RLE)	77.22±29.68 (0-100)	26.11±28.00 (0-100)	0.001
Bodily pain (BP)	89.17±18.78 (25-100)	60.00±17.80 (25-100)	0.001
Mental health (MH)	71.67±17.97 (25-90)	49.67±19.20 (0-90)	0.001
Vitality (VT)	60.42±28.30 (0-100)	35.42± 30.63(0-100)	0.004

AT- alteplase treated group; NT- non-treated group; SD- standard deviation

DISCUSSIONS

The results of this study showed that thrombolytic therapy not only improved the patients' functional recovery by reducing disability measured as NIHSS and Rankin score, but also reduced the presence of anxiety and depression, and improved the quality of life six months after stroke. It is well known that many stroke patients suffer from post-stroke depression and have poor quality of life (Carson et al. 2000, Hackett et al. 2005). The role of thrombolysis on the development of post-stroke anxiety and depression, as well as on the quality of life is still unclear, although several studies have focused on this topic (de Weerd et al. 2012, Stefanović Budimkić et al. 2017, Grabowska-Fudala et al. 2018). The results of TEMPIS study clearly showed that depressive symptoms and impaired quality of life were present at substantial proportion in stroke patients after thrombolysis (Schwab-Malek et al. 2010). After analyzing the current literature, it was found that different authors used very diverse study designs, patients' selection and tests applied to estimate the role of thrombolysis on post-stroke mood disorders and quality of life. The authors of a Polish study found that thrombolyzed and non thrombolyzeed stroke survivors

had similar frequency of depressive symptoms measured three and twelve months after acute ischemic stroke. However, in their study the treatment group had more severe stroke symptoms and had a higher percentage of subjects with moderate/severe stroke compared to the group with non-thrombolyzed patients. The authors assumed that the thrombolytic therapy seemed to have a positive, but indirect, effect on patients' mood, especially in the first months after stroke. No anxiety was monitored in this study (Grabowska-Fudala et al. 2018). The Netherlands observational study showed that the elderly stroke patients who received thrombolytic therapy had significantly better health-related quality of life only for the 'mental health' and 'vitality' scales than the non-treated patients measured by RAND-36. They found no statistical difference between the treated and non-treated groups in terms of anxiety and depression. However, the study groups were not homogenous, since the thrombolysis group had more severe stroke score and patients in that group were younger than those in non-treated group (de Weerd et al. 2012). Our study was structured on the way that studied groups of ischemic stroke patients were homogenous in terms of stroke severity, since the NIHSS and Rankin scores at the hospital admission were not different between AT and NT groups. Stroke severity is crucial for the development of depression and anxiety after a stroke. Therefore, it is very important for the study design that patients had a stroke of the same severity. Moreover, no major differences between two groups regarding the socio-demographic data were observed except in two variables; patients in AT group were significantly younger than those in NT group and had better employment status with less pensioners. Therefore, in that sense it was easier to study the impact of thrombolytic therapy on post stroke anxiety, depression and quality of life. The previous two studies were similar in terms of age and gender proportion and in that respect they are comparable to our study, but very much different in terms of the stroke severity. Differently from our study, the NIHSS scores at admission in the studies performed in the Nederlands and Poland were significantly higher in trombolyzed than in non-thrombolyzed group of patients (9.97 vs. 2.6 and 8.0 vs. 4.0, respectively) (de Weerd et al. 2012, Grabowska-Fudala et al. 2018). In our study the NIHSS scores at admission in both, the AT and NT groups were similar and much higher than in previous studies (9.96 vs. 10.78). Moreover, the efficacy of thrombolytic therapy on reducing patient's disability were more pronounced in the present study, since the NIHSS and Rankin scores at discharges significantly decreased for 77.6% and 75%, respectively, while in Polish study the NIHSS score decreased just by 50% (Grabowska-Fudala et al. 2018). These are important facts that could explain the better functional outcomes and lower incidence of anxiety and depression in thrombolyzed patients in the present study. The recently published WAKE UP study showed that thrombolytic therapy had a positive effect on the development of depression after stroke. Depression was present in 42.9% patients in the alteplase group and 53.7% in the placebo group 90 days following CVI and authors concluded that intravenous thrombolysis causes less depression due to less anatomical damage (Königsberg et al. 2021). In the most recent Chinese study, Zhang and collaborators monitored the effects of thrombectomy in stoke patients compared with the group of patients treated with combination of intravenous thrombolysis plus thrombectomy. They found that anxiety and depression were significantly higher in the thrombectomy group than in the combination therapy group and proposed that this effect of alteplase could be ascribed to its additional biological effects (Zhang et al. 2022). The results of Han et al. 2019 emphasized that aside of its cleavage effect, the tissue type plasminogen activator (tPA) possesses an important neurotrophic action, which is important for the development of depression. It is well known that the fibrinolytic system plays a role in the pathogenesis of depression. Some recent studies indicated that the increased inflammation in brain is associated with the elevated plasminogen activator inhibitor type 1 (PAI-1) level and the decreased tissue tPA activity (Idell RD et al. 2017). Moreover, the tPA/plasminogen system is involved in regulation level of brain derived neurotrophic factor (BDNF), which has a role in the synapsis plasticity, neurogenesis and neuron survival and the activity of which is associated with the development of depression. Studies in rats have shown that BDNF levels are lowered in the brain of stressed rats (Jiang et al. 2017). Stress can stimulate PAI-1 expression, suppressing tPA cleavage activity and resulting in compromised BDNF maturation (Han et al. 2019). Therefore, these findings give a scientific explanation that alteplase administration can reduce the incidence of depression after stroke. This study has some limitations. First, the study groups had relatively small number of patients. It is, however, the case with all studies cited in this paper. Second, the groups of examined patients were not identical. There were differences in sociodemographic data; the non-treated group of patients were significantly older than alteplase treated group, while the employment rate was significantly higher in alteplase treated group which might have influenced the outcomes of the study. Third, there were no data related to the existence of depression or the possible use of antidepressants before the stroke.

The study strengths could be attributed to the method of data acquisition. The study questionnaires related to BDI, BAI, and SF-36 QoL were performed by a single researcher, psychiatrist, during a clinical examination of the patient. We believe that data obtained through direct conversation are more valuable compared to the telephone interview that is present in some other studies. Additional strength is related to the very

harmonized and uniformed study groups of patients with similar intensity of acute ischemic stroke, and therefore the effects of alteplase treatment could be easily compared.

CONCLUSIONS

These results of this study confirmed that thrombolytic therapy improves the functional recovery in patients suffering acute ischemic stroke by reducing their disability measured by NIHSS and Rankin scores. The patients treated with alteplase had significantly less anxiety and depression and they had better quality of life score compared to patients who did not receive thrombolytic therapy.

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Contribution of individual authors:
Prof. Zoran Vujković Design of the study, literature searches and analyses, interpretation of data, manuscript writing.
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References

1. *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.*
2. *Bartoli F, Lillia N, Lax A, Crocamo C, Mantero V, Carrà G et al.: Depression after stroke and risk of mortality: a systematic review and meta-analysis. Stroke Res Treat 2013:862978. doi:10.1155/2013/862978.*
3. *Campbell B: Thrombolysis and Thrombectomy for Acute Ischemic Stroke: Strengths and Synergies. Semin Thromb Hemost 2017; 43:185-190.*
4. *Caprio FZ & Sorond FA: Cerebrovascular Disease: Primary and Secondary Stroke Prevention. Med Clin North Am 2019; 103:295-308.*
5. *Carod-Artal FJ: Post-stroke depression (II): its differential diagnosis, complications and treatment. Rev Neurol 2006; 42:238-44.*
6. *Carota A, Staub F, Bogousslavsky J.: Emotions, behaviours and mood changes in stroke. Curr Opin Neurol 2002; 15:57-69.*
7. *Carod-Artal FJ & Egido JA: Quality of life after stroke: the importance of a good recovery. Cerebrovasc Dis. 2009; 27 Suppl 1:204-14.*
8. *Carson AJ, MAcHale S, Allen K, Lawrie SM, Dennis M, House A et al.: Depression after stroke and lesion location: a systematic review. Lancet 2000; 356:122-6.*
9. *de Weerd L, Luijckx GJR, Groenier KH, van der Meer K: Quality of life of elderly ischaemic stroke patients one year after thrombolytic therapy. A comparison between patients with and without thrombolytic therapy. BMC Neurol 2012; 12:61. doi:10.1186/1471-2377-12-61.*
10. *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.*
11. *Grabowska-Fudala B, Jaracz K, Górna K, Miechowicz I, Wojtasz I, Jaracz J et al. : Depressive symptoms in stroke patients treated and non-treated with intravenous thrombolytic therapy: a 1-year follow-up study. J Neurol 2018; 265:1891-1899.*
12. *GBD 2016 Neurology Collaborators: Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019; 18:459-480.*
13. *Hackett ML, Yapa C, Parag V, Anderson CS: Frequency of depression after stroke: a systematic review of observational studies. Stroke 2005; 36:1330-40.*
14. *Han W, Dang R, Xu P, Li G, Zhou X, Chen L et al. : Altered fibrinolytic system in rat models of depression and patients with first-episode depression. Neurobiol Stress 2019; 11:100188. doi: 10.1016/j.ynstr.2019.100188.*
15. *Idell RD, Florova G, Komissarov AA, Shetty S, Girard RB, Idell S: The fibrinolytic system: A new target for treatment of depression with psychedelics.Med Hypotheses. 2017; 100:46-53.*
16. *Jiang H, Chen S, Li C, Lu N, Yue Y, Yin Y et al.: The serum protein levels of the tPA-BDNF pathway are implicated in depression and antidepressant treatment. Transl Psychiatry 2017; 7:e1079. doi: 10.1038/tp.2017.43.*
17. *Kotila M, Numminen H, Waltimo O, Kaste M: Depression after stroke: results of the FINNSTROKE Study. Stroke 1998; 29: 368–372.*
18. *Königsberg A, Sehner S, Arlt S, Cheng B, Simonsen CZ, Boutitie F et al.; WAKE-UP investigators: Effect of intravenous alteplase on post-stroke depression in the WAKE UP trial. Eur J Neurol 2021; 28:2017-2025.*
19. *Lees KR, Emberson J, Blackwell L, Bluhmki E, Davis SM, Donnan GA et al.: Stroke thrombolysis trialists collaborators group. Effects of alteplase for acute stroke on the distribution of functional outcomes: A pooled analysis of 9 trials. Stroke 2016; 47:2373-9.*
20. *de Weerd L, Luijckx G, Groenier K, van der Meer K: Quality of life of elderly ischaemic stroke patients one year after thrombolytic therapy. A comparison between patients with and without thrombolytic therapy. BMC Neurol. 2012 ;12:61. doi:10.1186/1471-2377-12-61.*
21. *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.*

22. *Maaijwee NA, Tendolkar I, Rutten-Jacobs LC, Arntz RM, Schaapsmeerders P, Dorresteijn LD et al.: Long-term depressive symptoms and anxiety after transient ischaemic attack or ischaemic stroke in young adults. Eur J Neurol 2016; 23:1262-8.*
23. *Minnerup J, Wersching H, Teuber A, Wellmann J, Eyding J, Weber R et al.: Outcome After Thrombectomy and Intravenous Thrombolysis in Patients With Acute Ischemic Stroke: A Prospective Observational Study. Stroke 2016; 47:1584-92.*
24. *Muruet W , Rudd A , Wolfe C, Douiri A: Long-Term Survival After Intravenous Thrombolysis for Ischemic Stroke: A Propensity Score-Matched Cohort With up to 10-Year Follow-Up. Stroke. 2018; 49:607-613.*
25. *Naess H, Nyland HI, Thomassen L, Aarseth J, Myhr KM: Mild depression in young adults with cerebral infarction at long-term follow-up: a population-based study. Eur J Neurol 2005; 12:194–198.*
26. *Robinson RG & Jorge RE: Post-stroke depression: a review. Am J Psychiatry 2016; 173:221–231.*
27. *Schwab Malek S, Vatankhah B, Bogdahn U, Horn M, Audebert HJ: Depressive symptoms and quality of life after thrombolysis in stroke: the TEMPiS study. J Neurol 2010; 257:1848-54.*
28. *Skrbic R, Vujković Z, Stojiljković MP, Gajanin R, Bokonjić D, Komic J.: Efficacy and Safety of Low-Dose Versus Standard-Dose Alteplase Regimens in Patients with Acute Ischaemic Stroke. Psychiatr Danub 2019; 31(Suppl 1):32-38.*
29. *Stefanovic Budimkic M, Pekmezovic T, Beslac-Bumbasirevic L, Ercegovac M, Berisavac I, Stanarcevic P et al: Long-Term Prognosis in Ischemic Stroke Patients Treated with Intravenous Thrombolytic Therapy. J Stroke Cerebrovasc Dis 2017; 26:196-203.*
30. *Schöttke H & Giabbiconi C.: Post-stroke depression and post-stroke anxiety: prevalence and predictors. Int Psychogeriatr 2015; 27:1805-12.*
31. *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.*
32. *Zhang P, Shen HJ, Chen L, Zhu X, Zhang MM., Jiang Y et al.: Patient-Reported Anxiety/Depression After Endovascular Thrombectomy: A post-hoc Analysis of Direct-MT Trial. Front Neurol 2022; 13:811629. doi:10.3389/fneur.2022.811629.*
33. *Wolfe CD, Crichton SL, Heuschmann PU, McKevitt CJ, Toschke AM, Grieve AP et al.: Estimates of outcomes up to ten years after stroke: analysis from the prospective South London Stroke Register. PLoS Med 2011; 8: e1001033. doi:10.1371/journal.pmed.1001033.*

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