World Scientific News

An International Scientific Journal

Prevention of seizures after ischemic stroke: association between statin use and the risk of seizures

Michał Marciniec[1], Sylwia Popek-Marciniec[2], Marcin Kulczyński[1], Katarzyna Pasterczyk[1,*], Anna Szczepańska-Szerej[1], Konrad Rejdak[1]

[1] Chair and Department of Neurology, Medical University of Lublin, Poland

[2] Department of Cancer Genetics with Cytogenetics Laboratory, Medical University of Lublin, Poland

*E-mail address: lekpasterk@gmail.com

ABSTRACT

More than 50 million people worldwide suffer from epilepsy. In approximately 50% cases of newly diagnosed patients over 60 years of age seizures are related to stroke. Post-stroke lesions in brain tissue may result in 7 fold increase risk of seizures compared to the general population. The most significant risk factors for post-stroke seizures (PSS) and post-stroke epilepsy (PSE) include stroke severity, intracerebral or subarachnoid hemorrhage and cortical involvement. Increased incidence of PSS was also observed in younger patients especially with previous early PSS occurrence. Statins (HMG-CoA reductase inhibitors) are a class of lipid-lowering medications characterized by neuroprotective and antiepileptic effects. The main result of the performed studies was significantly reduced risk of developing PSS associated with a post-stroke, but not pre-stroke statin use. Moderate to high doses of statin and early administration in acute phase of stroke potentiated the beneficial effects of the treatment. The evidences for the association between PSS prevention and statin treatment become more significant, however the most recent AHA/ASA recommendations do not include any medications in the PSS prophylaxis. This article summarizes the current knowledge about the prediction and prevention of PSS and PSE.

Keywords: Post-stroke seizure, ischemic stroke, epilepsy, HMG-CoA reductase inhibitor, statin, rt-PA

1. INTRODUCTION

Epilepsy is one of the most common neurological disorders. The recurrent seizures, multiple comorbidities and the side effects of anti-seizure medications aggravate the social stigma and discrimination of patients who develop epilepsy [1]. In meta-analysis of 222 studies published in 2017 the lifetime prevalence of epilepsy was 7.60 per 1,000 persons [2]. According to above statistics more than 50 million people worldwide suffer from epilepsy.

The post-stroke lesions in brain tissue play a crucial role in epileptogenesis and are responsible for approximately 50% of newly diagnosed epilepsy among patients over 60 years of age [3]. The overall incidence of seizures within a decade after an ischemic stroke was estimated at almost 10% which implies approximately 7-fold higher risk of seizures than in the general population [4].

2. POST-STROKE EPILEPSY

2. 1. Definition

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. Following the most recent recommendations of The International League Against Epilepsy (ILAE) epilepsy is defined by one of the conditions below [5]:

1. at least two unprovoked (or reflex) seizures occurring >24 h apart,
2. one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures occurring over the next 10 years,
3. diagnosis of an epilepsy syndrome.

Consequently, in accordance with the second point of the above definition even a single seizure occurring in late post-stroke period has to be qualified as epilepsy as a result of the high probability (up to 65–90%) of further seizures development [5].

Post-stroke seizures (PSS) occurrence is characterized by two peaks – within the 24 hours after a stroke and between six to twelve months [6]. It should be noticed that the nomenclature of seizures having regard to the time of occurrence used in publications is unclear. Early seizures are defined as occurring within 24 hours up to 30 days, and late seizures are usually defined as occurring after the early seizure period [7]. Following the recommendations of ILAE for a definition of symptomatic seizure, acute symptomatic seizures occur within 1 week of stroke [8].

The most recent classification of seizure types are presented on figure 1. A focal aware seizure corresponds to the prior term simple partial seizure in previous classification. A focal impaired awareness seizure corresponds to the prior term complex partial seizure [9]. Unfortunately, there is a lack of evidence which type of seizure occurs the most common after stroke.
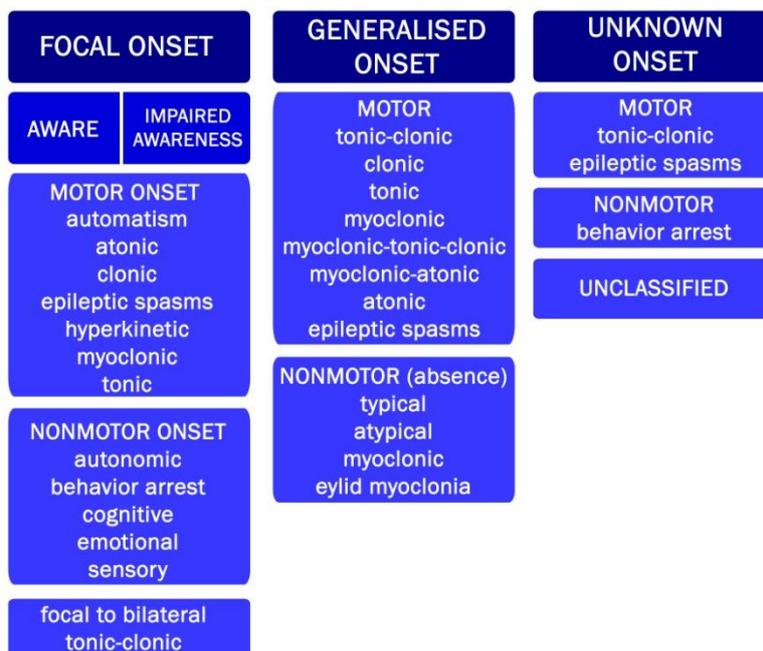
Figure 1. The expanded ILAE 2017 operational classification of seizure types [9].

2. 2. Pathogenesis

Electrophysiological instability and neurotransmitter imbalance are major alterations participating in early seizures occurrence. Acute phase of stroke results in cellular metabolic and biochemical dysfunction [3]. Loss of neurovascular unit integrity, blood–brain barrier disruption, ion channel dysfunction and increased release of neurotransmitters (glutamate and others) are major factors contributing to early presence of PSS [10].

Pathogenesis of late PSS or PSE (post-stroke epilepsy) includes genetic factors, neurovascular units disintegration, post-stroke gliocyte proliferation and neurodegenerative processes [3]. The localization of stroke is also important as the presence of cortical lesion is associated with higher risk of PSE [10].

3. PREDICTION OF SEIZURES AFTER STROKE

3. 1. Risk factors for post-stroke seizures

In accordance with the findings of various reports, the most significant risk factors for PSS are neurological and include stroke severity, intracerebral or subarachnoid hemorrhage and cortical involvement [4,11-13].

PSS occur more frequently in younger patients, however there is no one adopted age threshold and the age of 65 or higher is usually considered [4,7,12,14]. Conversely, elderly patients with PSE have a double mortality rate compared to younger patients. There is also a synergistic effect between acute ischemic stroke and status epilepticus (SE) in increasing fatality among elderly patients. It has to be noticed that SE alone does not modify long-term mortality as opposed to SE of cerebrovascular etiology [15,16].

The correlations between other risk factors and PSS occurrence have been studied, however results remain unclear. Hypertension is usually described as a risk factor for PSE, although in many reports the correlation was statistically insignificant [7,13,17-19]. In one trial including 1073 patients describing lower risk of early seizures after stroke in patients with hypertension on admission [14]. Similarly, most reports investigated statistically insignificant or no correlations between post-stroke seizures and other stroke or cardiovascular risk factors (serum total cholesterol, history of myocardial infarction, peripheral vascular disease, atrial fibrillation, smoking, diabetes mellitus, nonwhite race) [4,7,17-19]. PSS occurrence did not differ significantly even between the groups in TOAST classification (Trial of ORG 10172 in Acute Stroke Treatment), which divide ischemic strokes into etiological groups: large artery, cardio-embolism, lacunar, other determined, multiple or undetermined [7,18].

3. 2. The SeLECT score

The most recent seizures prediction tool was published in 2018. The SeLECT scale (acronym includes first letters of evaluated parameters – Severity of stroke, Large-artery atherosclerosis, Early seizure, Cortical involvement, Territory of Middle cerebral artery) summarize the impact of post-stroke epilepsy predictors in 5-section scale. To calculate the probability of late seizures after ischemic stroke (defined as occurring > 7 days), the sum of points assigned to predictors from table 1. has to be referred to the total risk score from table 2 [20].

Table 1. The SeLECT score. Point's valuation of each predictor of late (>7 days) seizures after ischemic stroke [20].

Severity of stroke		Large-artery atherosclerosis		Early seizure (≤7 days)		Cortical involvement		Territory of MCA	
NIHSS ≤3	**0**	No	**0**	No	**0**	No	**0**	No	**0**
NIHSS 4–10	**1**	Yes	**1**	Yes	**3**	Yes	**2**	Yes	**1**
NIHSS ≥11	**2**								

NIHSS – National Institutes of Health Stroke Scale, a scale used to quantify the post-stroke impairment, **MCA** – Middle cerebral artery.

Table 2. The risk of late seizures according to SeLECT score [20].

Risk of seizures after 1 year	0,7%	1%	2%	4%	6%	11%	18%	28%	44%	63%
SeLECT total score	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Risk of seizures after 5 years	1,3%	2%	4%	6%	11%	18%	29%	45%	65%	83%

3. 3. The impact of thrombolytic treatment on PSS

Thrombolysis is the lysis of blood clots with the use of recombinant tissue plasminogen activators (rtPA) and is a treatment of choice in many cases of acute ischemic stroke. In thrombolysis-treated patients seizures are uncommon and in most cases predict poor recovery [21]. It should be noticed that thrombolysis has a potential neurotoxic effect. The correlation between rtPA administration and early PSS occurrence was found in a study of 2,327 patients with acute ischemic strokes (OR 4.6, p = 0.01) and cannot be explained by recanalization and symptomatic or radiological hemorrhagic transformation of stroke in authors opinion. PSS was associated with worse outcome at 3 months without any difference in NIHSS scale (a tool used to quantify the post-stroke impairment) on patients hospital admission. Despite lack of seizure reported as a possible rtPA side-effect in the randomized studies, authors concluded that use of others non-epileptogenic thrombolytic agents different from rtPA should be profitable [22]. In another study, early seizures in thrombolytic patient independently predict mortality and unfavorable outcome (2.2-fold risk for death, 1.6-fold risk for unfavorable outcome). Authors noticed that there is a need for trials for prophylactic anticonvulsive treatment in patients receiving endovascular therapy for acute stroke [23].

Conversely, the early-onset PSS may be related to the severity of the stroke rather than the rtPA or other applied treatment. This statement was supported by the comparison of anticoagulants or antithrombotics with the rtPA treatment of acute cardiac- or thrombo-embolic stroke. The rtPA administration, through a better reperfusion of the ischemic brain regions may result in partial prevention of the late-onset PSS occurrence [24].

The frequency of acute PSS as a complication of the thrombolytic therapy evaluated in two minor studies was not significantly different between rtPA treated and non-treated patients and was comparable with rates from pre-thrombolysis decades. In some cases of patients very early seizures may even reflect the success of thrombolytic treatment and favorable outcome [25,26].

The relationship between rt-PA and PSS occurrence remains unclear, although the impact of post-trombolysis seizure on poor recovery is well documented. Major disability, unfavorable ordinal shift of scales used for measuring the degree of disability or dependence in the daily activities and even death are independently predicted by early PSS occurrence following thrombolysis therapy [21-23,25,26].

4. PREVENTION OF POST-STROKE EPILEPSY

4. 1. The Code Stroke System

Rapid access to diagnostic and treatment tools plays crucial role in the restriction of post-stroke complications. In the most recent study published in 2018, the American Academy of Neurology underscored the importance of the Code Stroke System (CSS) in the prevention of PSE development. CSS provide a set of procedures used in the management of acute stroke cases: rapid assessment, revascularization, and harmonization of hemodynamic and metabolic disturbances. The authors of the most recent report published in 2018 indicated that the implementation of CSS recommendations in clinical practice was associated with decreased incidence of PSE (OR, odds ratio = 0.36, 95% CI, confidence interval 0.14–0.87, p = 0.024). Similarly, the hazard rates for post-stroke epilepsy within

5 years after stroke were lower in patients managed under the code stroke system (HR, hazard ratio = 0.60, 95% CI 0.47–0.79, p<0.001). For the above benefits CSS has been adopted by major stroke centers worldwide [27].

4. 2. Statin treatment and the risk of post-stroke seizure

Statins (HMG-CoA reductase inhibitors) are a class of lipid-lowering medications widely used in patients after stroke. The relationship between statin therapy and improved general outcome or reduced fatality after ischemic stroke was confirmed in one of the largest meta-analysis of mostly observational studies [28].

The results of studies with animal models of seizures provided evidence that statins are characterized by neuroprotective and antiepileptic effects besides cholesterol-lowering properties. The molecular activity of statins is responsible for increased gabaergic activity, decreased glutamatergic activity and other effects mediated by nitric oxide (NO) release which result in increased seizure threshold and significant anticonvulsant effect [29-32]. The reduction of brain inflammation, infarction volume and the permeability of the blood–brain barrier may participate in observed beneficial effect of statin therapy after ischemic stroke [33].

The clinical studies confirm above correlations. The largest study was published recently in 2018. 20 858 ischemic stroke patients were divided into 3 groups: pre-stroke users of statins, post-stroke users of statins and non-users. Medications used in the study were either lipophilic (atorvastatin, fluvastatin, lovastatin, pitavastatin, simvastatin) and hydrophilic (pravastatin, rosuvastatin). The main result of the study was significantly reduced risk of developing PSE associated with a post-stroke, but not pre-stroke statin use (aHR, adjusted HR 0.55; p<0.001). Authors described also a dose-response correlation between higher post-stroke statin cumulative defined daily doses (cDDD) and lower PSE hazards. CDDD were measured as the sum of average daily doses used in the monthly treatment. The aHRs for increasing 4 quartiles of cDDD (the lowest, second, third, and highest) equal to 0.84, 0.67, 0.53, and 0.50. The lipophilicity characteristics was without significance – either lipophilic or hydrophilic statins reduced the risk of PSE [34]. The most effective doses of statins in PSS prevention were from moderate to high and this association was confirmed by the other studies on various types of seizures [34-36].

The results of minor studies are comparable. Statin use in the acute phase of ischemic stroke was found to reduce the risk of early-onset PSS (OR 0.35, p<0.001) in the study involving 1,832 patients. Above correlation was even more relevant in patients who used statins only in the acute phase of stroke (OR 0.36, p<0.001). The impact on PSE diagnosis varied significantly depending on early-onset seizures occurrence: if patient had experienced early PSS, statin use prevented further seizures defined as PSE (OR 0.34, p = 0.026), however if seizure had not occurred, PSE incidence was independent on statin treatment during a mean follow-up period of 2.5 years [37].

Moreover, similar correlation was observed between statins treatment and the presence of status epilepticus (SE). The significant association of SE with general lower patients mortality might be a result of a possible anti-epileptogenic role of statins [38]. The limited evidences of statin effectiveness were also obtained in the studies on the preventing of special types of epilepsy: the geriatric epilepsy and the epilepsy after radiation [39,40]. Interestingly, other lipid-lowering medications do not significantly modify the risk of seizures [35,36,40].

Table 3. Clinical studies on the association between statin treatment and the risk seizures after ischemic stroke.

No	Time	Intervention	Result	Ref
20 858	1 year before and 3 years after first index date	Pre- and post-stroke statin use in patients with new-onset stroke. Statins divided into two categories: lipophilic (atorvastatin, fluvastatin, lovastatin, pitavastatin simvastatin) and hydrophilic (pravastatin, rosuvastatin).	Only post-stroke statin use significantly reduced risk of developing PSE (aHR 0.55; p<0.001). No positive effect observed in cases of pre-stroke statin use. A dose-response correlation between PSE risk reduction and quartiles of the statin cDDD was observed (HR 0.84, 0.67, 0.53, and 0.50 for the lowest, second, third, and highest quartiles of cDDD, respectively). The lipophilicity characteristics was without significance.	[34]
1 832	2,5 years	Atorvastatin, simvastatin or rosuvastatin administered in the acute phase or/and before stroke or no use of statin. Patients with a first-ever ischemic stroke and no history of epilepsy.	Statin use reduced the risk of early PSS (OR 0.35, p<0.001), mainly in patients received statin only in the acute phase of stroke (OR 0.36, p<0.001). No significant association was found between statin use and PSE without previous early PSS (OR 0.81, p=0.349). Statin use in patients with early PSS reduced risk of PSE (OR 0.34, p=0.026).	[37]

No – number of patients, **Time** – the mean duration of the study, **PSS** – post-stroke seizures, **PSE** – post-stroke epilepsy**, OR** – odds ratio, **aHR** – adjusted hazard ratio, **cDDD** – cumulative defined daily dose.

Table 4. The examples of clinical studies on association between statin treatment and the risk of seizures in the course of certain conditions different from ischemic stroke.

No	Time	Intervention	Result	Ref
1 025 222	U	Statin and other lipid-lowering drugs administration to geriatric veterans with and without epilepsy.	Statin prescription reduced the risk of geriatric epilepsy. No significant effect off other lipid-lowering drugs.	[40]
43 438	6,2 years	Statin use and epilepsy risk in a general population and in a healthy population.	No significant beneficial or deleterious effect of statin use on risk of being diagnosed with epilepsy. Clinicians should not withhold statins, whenever indicated, in patients with epilepsy.	[41]
7 435	17,6 months	Statin use before and after intracranial hemorrhage.	Reduced risk of PSE if statins administered post-stroke, but not pre-stroke (aHR 0.62, p = 0.01). A significant	[36]

No	Time			Ref
			PSE risk reduction was correlated with a higher cumulative statin dose.	
2 387	2,7 years	Statin therapy of patients suffered from cardiovascular diseases after revascularization procedure.	Lower risk for epilepsy was found among current statin users (aHR 0.65) and past users of statins (aHR 0.72). No benefit among non-statin cholesterol-lowering drugs users.	[35]
532	28,1 months	Statin administration to patients with nasopharyngeal carcinoma and a history of radiotherapy.	Early statin use significantly reduced the risk of epilepsy after radiation (HR = 0.36, p = 0.015).	[39]
413	U	Statin use in patients with the incident of status epilepticus*.	Statin therapy correlated significantly with lower mortality after the episodes of status epilepticus (RR 0.38, p = 0.046).	[38]

No – number of patients, **Time** – the mean duration of the study, **U** – undefined, **PSS** – post-stroke seizures, **HR** – hazard ratio, **aHR** – adjusted hazard ratio, **OR** – odds ratio, **RR** – relative risk ratio. *Status epilepticus was defined as continuous epileptic seizures or recurrent seizures without recovery of consciousness for >30 min (until 2008) and >5 min (since 2008).

Not all studies confirmed the significant effect of statins on epilepsy development. The authors of study in which statins were administrate to healthy persons emphasized that these medications should not be prescribed when there are no lipid-lowering indications in patients with epilepsy [41]. Hovewer, as confirmed in animal model of generalized tonic-clonic seizures, co-administration of statins and some antiepileptic drugs (most notably carbamazepine, diazepam, felbamate, lamotrigine, topiramate and valproate) has an additive anticonvulsant effect as a result of positive pharmacological interactions [42]. The use of statins in other than post-stroke groups of seizures are presented in Table 4.

5. ANTIEPILEPTIC THERAPY OF PSS

Despite the fact early PSS are a risk factor for PSE, the antiepileptic therapy of early PSS may not modulate post-stroke epileptogenesis [43]. In 2018, the American Heart Association/American Stroke Association (AHA/ASA) has published the updated guidelines for the early management of patients with acute ischemic stroke. Following the recommendations prophylactic use of anticonvulsants should not be applied routinely. The treatment of recurrent seizures after stroke should not vary considerably from the therapy of seizures occurring in the course of other neurological conditions and the antiepileptic medication should be selected by specific patient characteristics [44].

6. CONCLUSIONS

Based on the results of numerous studies, the identification of patients vulnerable to PSS occurrence is easier. Unfortunately, there are no medications approved to use in seizure prophylaxis in patients with no history of any seizure despite being at high risk of PSS

development. In conclusion, there is growing evidence that post-stroke administration of moderate to high doses of statin may reduce the risk of PSE incidence through neuroprotective and antiepileptic effects. The co-administration of statins and antiepileptic medications results in a potential additive anticonvulsant effect. To date, evidence for the association between PSS prevention and statin treatment become more significant but is still lacking. Further research is needed to issue an unambiguous recommendation.

References

[1]   S. Saxena, S. Li, Defeating epilepsy: A global public health commitment. *Epilepsia Open* 2 (2017) 153-155.

[2]   K.M. Fiest, K.M. Sauro, S.Wiebe, S.B. Patten, C. Kwon, J. Dykeman, T. Pringsheim, D.L. Lorenzetti, N. Jetté, Prevalence and incidence of epilepsy A systematic review and meta-analysis of international studies. *Neurology* 88 (2017) 296-303.

[3]   H. Yang, G. Rajah, A. Guo, Y. Wang, Q. Wang, Pathogenesis of epileptic seizures and epilepsy after stroke. *Neurological Research* (2018) 1-7 doi: 10.1080/01616412.2018.1455014

[4]   A.E. Merkle, G. Gialdini, M.P. Lerario, N.S. Parikh, N.A. Morris, B. Kummer, L. Dunn, M.E. Reznik, S.B. Murthy, B.B. Navi, Z.M. Grinspan, C. Iadecola, H. Kamel, Population-Based Assessment of the Long-Term Risk of Seizures in Survivors of Stroke. *Stroke* 49 (2018) DOI: 10.1161/STROKEAHA.117.020178.

[5]   R.S. Fisher, C. Acevedo, A. Arzimanoglou, A. Bogacz, J.H. Cross, C.E. Elger, J. Engel Jr, L. Forsgren, J.A. French, M. Glynn, D.C. Hesdorffer, B.I. Lee, G.W. Mathern, S.L. Moshé, E. Perucca, I.E. Scheffer, T. Tomson, M. Watanabe, S. Wiebe, ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 55 (2014) 475-82.

[6]   T.S. Olsen, Post-stroke epilepsy. *Current Atherosclerosis Reports* 3 (2001) 340-344.

[7]   T. Bryndziar, P. Sedova, N.M. Kramer, J. Mandrekar, R. Mikulik, R.D. Brown, J.P. Klaas, Seizures Following Ischemic Stroke: Frequency of Occurrence and Impact on Outcome in a Long-Term Population-Based Study, *Journal of Stroke and Cerebrovascular Diseases* 25 (2016) 150–156.

[8]   E. Beghi, A. Carpio, L. Forsgren, D.C. Hesdorffer, K. Malmgren, J.W. Sander, T. Tomson, W.A. Hauser, Recommendation for a definition of acute symptomatic seizure. *Epilepsia* 51 (2010) 671-675.

[9]   R.S. Fisher, J.H. Cross, J.A. French, N. Higurashi, E. Hirsch, F.E Jansen, L. Lagae, S.L. Moshé, J. Peltola, E. Roulet Perez, I.E. Scheffer, S.M. Zuberi, Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 58 (2017) 522-530.

[10] T. Tanaka, M. Ihara, Post-stroke epilepsy. *Neurochemistry International* 107 (2017) 219-228.

[11] C. Zhang, X. Wang, Y. Wang, J.G. Zhang, W. Hu, M. Ge, K. Zhang, X. Shao, Risk factors for post-stroke seizures: a systematic review and meta-analysis. *Epilepsy Research* 108 (2014) 1806-1816.

[12] N.S. Graham, S. Crichton, M. Koutroumanidis, C.D. Wolfe, A.G Rudd, Incidence and associations of poststroke epilepsy: the prospective South London Stroke Register. *Stroke* 44 (2013) 605-611.

[13] G.J. Jungehulsing, P.U. Heuschmann, M. Holtkamp, S. Schwab, P.L. Kolominsky-Rabas, Incidence and predictors of post-stroke epilepsy. *Acta Neurologica Scandinavica* 127 (2013) 427–430.

[14] Z. Hundozi, A. Shala, D. Boshnjaku, S. Bytyqi, J. Rrustemi, M. Rama, F. Jashari, Hypertension on admission is associated with a lower risk of early seizures after stroke. *Seizure* 36 (2016) 40-43.

[15] H. Stefan. Epilepsy in the elderly: facts and challenges. *Acta Neurologica Scandinavica* 124 (2011) 223–237.

[16] F. Rosenow, H. M. Hamer, S. Knake, The epidemiology of convulsive and nonconvulsive status epilepticus. *Epilepsia* 48 (2007) 82–84.

[17] F. Brigo, F. Tezzon, R. Nardone, Late-onset seizures and risk of subsequent stroke: a systematic review. *Epilepsy & Behavior* 31 (2014) 9-12.

[18] R. Arntz, L. Rutten-Jacobs, N. Maaijwee, H. Schoonderwaldt, L. Dorresteijn, E. van Dijk, F.E. de Leeuw, Post-Stroke Epilepsy in Young Adults: A Long-Term Follow-Up Study. *PLoS One* 8 (2013) e55498.

[19] T. Tanaka, H. Yamagami, M. Ihara, R. Motoyama, K. Fukuma, T. Miyagi, K. Nishimura, K.Toyoda, K. Nagatsuka, Seizure Outcomes and Predictors of Recurrent Post-Stroke Seizure: A Retrospective Observational Cohort Study. *PLoS One* 10 (2015) e0136200.

[20] M. Galovic, N. Döhler, B. Erdélyi-Canavese, A. Felbecker, P. Siebel, J. Conrad, S. Evers, M. Winklehner, T.J. von Oertzen, H.P. Haring, A. Serafini, G. Gregoraci, M. Valente, F. Janes, G.L. Gigli, M.R. Keezer, J.S. Duncan, J.W. Sander, M.J. Koepp, B. Tettenborn, Prediction of late seizures after ischaemic stroke with a novel prognostic model (the SeLECT score): a multivariable prediction model development and validation study. *The Lancet Neurology* 17 (2018) 143–152.

[21] Y. Xu, M.L. Hackett, J. Chalmers, R.I. Lindley, X. Wang, Q. Li, T. Robinson, H. Arima, P.M. Lavados, C.S. Anderson; ENCHANTED Study Group. Frequency, determinants, and effects of early seizures after thrombolysis for acute ischemic stroke: The ENCHANTED trial. *Neurology Clinical Practice* 7 (2017) 324-332.

[22] VAlvarez, A.O. Rossetti, V. Papavasileiou, P. Michel, Acute seizures in acute ischemic stroke: does thrombolysis have a role to play? *Journal of Neurology* 260 (2013) 55-61.

[23] S. Jung, K. Schindler, O. Findling, M.L. Mono, U. Fischer, J. Gralla, M. El-Koussy, A. Weck, A. Galimanis, C. Brekenfeld, G. Schroth, H.P. Mattle, M. Arnold, Adverse effect of early epileptic seizures in patients receiving endovascular therapy for acute stroke. *Stroke* 43 (2012) 1584-1590.

[24] J. De Reuck, G. Van Maele, Acute ischemic stroke treatment and the occurrence of seizures. *Clinical Neurology and Neurosurgery* 112 (2010) 328-331.

[25] C. Bentes, H. Martins, A.R. Peralta, C. Morgado, C. Casimiro, A.C Franco, A.C. Fonseca, R. Geraldes, P. Canhão, E.M.T Pinho, T. Paiva, J.M. Ferro. Epileptic manifestations in stroke patients treated with intravenous alteplase. *European Journal of Neurology* 24 (2017) 755-761.

[26] Bianchin, M., Brondani, R., de Almeida, A., Cherubini, P., de Oliveira, M., Mota, S., & Krammer, B. (2017). Seizures and epilepsy after thrombolysis for acute ischemic stroke: a cohort study. *Journal of the Neurological Sciences* 381, 86-87.

[27] Z. Chen, L. Churilov, Z. Chen, J. Naylor, M. Koome, B. Yan, P. Kwan, Association between implementation of a code stroke system and poststroke epilepsy. *Neurology* 90 (2018) e1126-e1133.

[28] D. Ní Chróinín, K. Asplund, S. Åsberg, E. Callaly, E. Cuadrado-Godia, E. Díez-Tejedor, M. Di Napoli, S.T. Engelter, K.L. Furie, S. Giannopoulos, A.M. Gotto Jr, N. Hannon, F. Jonsson, M.K. Kapral, J. Martí-Fàbregas, P. Martínez-Sánchez, H.J. Milionis, J. Montaner, A. Muscari, S. Pikija, J. Probstfield, N.S. Rost, A.G. Thrift, K. Vemmos, P.J. Kelly, Statin therapy and outcome after ischemic stroke: systematic review and meta-analysis of observational studies and randomized trials. *Stroke* 44 (2013) 448-456.

[29] M. Kesim, E. Yulug, M. Kadioglu, I. Erkoseoglu, D.A. Aykan, N.I. Kalyoncu, E. Yaris, The effect of simvastatin on picrotoxin-induced seizure in mice. *Journal of Pakistan Medical Association* 62 (2012) 1187-1191.

[30] H. Shafaroodi, L. Moezi, A. Fakhrzad, M. Hassanipour, M. Rezayat, A.R. Dehpour, The involvement of nitric oxide in the anti-seizure effect of acute atorvastatin treatment in mice. *Neurological Research* 34 (2012) 847-853.

[31] K. Moazzami, S. Emamzadeh-Fard, M. Shabani, Anticonvulsive effect of atorvastatin on pentylenetetrazole-induced seizures in mice: the role of nitric oxide pathway. *Fundamental & Clinical Pharmacology* 27 (2013) 387-392.

[32] L. Moezi, H. Shafaroodi, M. Hassanipour, A. Fakhrzad, S. Hassanpour, A.R. Dehpour, Chronic administration of atorvastatin induced anti-convulsant effects in mice: the role of nitric oxide. *Epilepsy & Behavior* 23 (2012) 399-404.

[33] A. Siniscalchi, S. Mintzer, Statins for poststroke seizures. The first antiepileptogenic agent? *Neurology* 85 (2015) 1–2.

[34] F.J. Lin, H.W. Lin, Y.F. Ho, Effect of Statin Intensity on the Risk of Epilepsy After Ischaemic Stroke: Real-World Evidence from Population-Based Health Claims. *CNS Drugs* 32 (2018) 367-376.

[35] M. Etminan, A. Samii, J.M. Brophy, Statin use and risk of epilepsy: a nested case-control study. *Neurology* 75 (2010) 1496-1500.

[36] H.W. Lin, Y.F. Ho, F.J. Lin, Statin Use Associated with Lower Risk of Epilepsy after Intracranial Hemorrhage: A Population-Based Cohort Study. *Br J Clin Pharmacol* (2018) doi: 10.1111/bcp.13626.

[37] J. Guo, J. Guo, J. Li, M. Zhou, F. Qin, S. Zhang, B. Wu, L. He, D. Zhou, Statin treatment reduces the risk of poststroke seizures. *Neurology* 85 (2015) 701-707.

[38] A. Sierra-Marcos, V. Alvarez, M. Faouzi, B. Burnand, A.O. Rossetti, Statins are associated with decreased mortality risk after status epilepticus. *European Journal of Neurology* 22 (2015) 402-405.

[39] X. Rong, J. Yin, H. Wang, X. Zhang, Y. Peng, Statin treatment may lower the risk of postradiation epilepsy in patients with nasopharyngeal carcinoma. *Epilepsia* 58 (2017) 2172-2177.

[40] M.J. Pugh, J.E. Knoefel, E.M. Mortensen, M.E. Amuan, D.R. Berlowitz, A.C. Van Cott, New-onset epilepsy risk factors in older veterans. *Journal of the American Geriatrics Society Soc* 57 (2009) 237-242.

[41] L.U. Trivedi, C.A. Alvarez, I.A. Mansi, Association of Statin Therapy With Risk of Epilepsy in 2 Propensity Score-Matched Cohorts. *Annals of Pharmacotherapy* 52 (2018) 546-553.

[42] E. Russo, E. Donato di Paola, P. Gareri, A. Siniscalchi, A. Labate, L. Gallelli, R. Citraro, G. De Sarro. Pharmacodynamic potentiation of antiepileptic drugs' effects by some HMG-CoA reductase inhibitors against audiogenic seizures in DBA/2 mice. *Pharmacological Research* 70 (2013) 1-12.

[43] A. Pitkänen, R. Roivainen, K. Lukasiuk, Development of epilepsy after ischaemic stroke. *The Lancet Neurology* 15 (2016) 185-197.

[44] 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.