Effects of Statin Therapy in Patients with Stroke and Atheromatosis

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Recent studies have shown that as the average life expectancy increases, more people will suffer a stroke in their lives, diminishing their quality of life. Secondary stroke prevention involves reducing the cardiovascular risk factors and administering medication for preventive purposes, where statins play an important role. The purpose of this study is to highlight the correlations of statins dosage with cardiovascular risk factors (atheromatosis, uric acid value, obesity, etc), in stroke patients receiving hypolipidemic treatment with statins.

Keywords: statins, stroke, uric acid, liver enzymes

Stroke is the third cause of morbidity and mortality worldwide, both in Europe and the US, after ischemic heart disease and oncologic pathology [1-3]. Like many other pathologies, stroke results from the interaction between genetic predisposition and environmental factors. Genetic risk factors cannot be changed, while lifestyle consists of behavioural components that can be improved. Unchangeable risk factors for stroke are: age, familial antecedents, race, sex, previous vascular events. The modifying risk factors include: arterial hypertension, diabetes mellitus, atrial fibrillation, asymptomatic carotid atheromatosis, cardiac disease, hypercholesterolemia, obesity, smoking, sedentarism, poor socio-economic condition, drug use or alcohol abuse [4]. Secondary prevention already involves administration of preventive medication (anti-aggregation, hypolipidemic, antihypertensive), depending on aetiology and associated diseases [5-7]. Two very important risk factor in the etiology of stroke (both constituted and transient) are atherosclerosis and dyslipidemia [8-10]. Consequently, following the international guidelines in force recommend the use of statins in patients with a history of stroke as a prognostic element with a double action: to lower the use of statins in patients with a history of stroke as a following the international guidelines in force recommend

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Experimental part

The purpose of this study is to highlight the correlations between the value of statins and other cardiovascular risk factors (diabetes, atheromatosis, uric acid value) in patients with stroke receiving hypolipidemic therapy with statins as secondary prevention. Also, we monitored the side effects of statins by analyzing the liver enzymes.

In our retrospective study, we included 58 patients with a history of ischemic stroke, hospitalized between 01.01-30.09.2018 in the Neurology Department inside the Clinical Rehabilitation Hospital in Iasi, Romania. All patients were assessed for anthropometric measurements (age, weight, height, BMI), biochemical analysis: hepatic enzymes, uric acid, glycemia, glycylated hemoglobin and lipid profile. Doppler cervical ultrasound was also performed at the level of the bilateral common carotid artery for the identification of atheromatosis and its degree, with a Siemens Accuson X300 system using a 7.5 MHz linear probe through a standardized method [23]. Patients with arterial occlusion or embolic stroke were excluded. All subjects before being examined and included were informed of the research method and signed an informed consent. Statistical analysis was performed with SPSS v.18. In interpreting statistical results we considered p=0.005 as the reference value for significance, which corresponds to a confidence interval of 95%. Continuous type variables were presented as mean ± standard deviation.

In our study we had 23 females and 35 males, with mean age 65.9±13.1 years. Most patients had a history of ischemic stroke, hospitalized between 01.01-30.09.2018 in the Neurology Department inside the Clinical Rehabilitation Hospital in Iasi, Romania. All patients were assessed for anthropometric measurements (age, weight, height, BMI), biochemical analysis: hepatic enzymes, uric acid, glycemia, glycylated hemoglobin and lipid profile. Doppler cervical ultrasound was also performed at the level of the bilateral common carotid artery for the identification of atheromatosis and its degree, with a Siemens Accuson X300 system using a 7.5 MHz linear probe through a standardized method [23]. Patients with arterial occlusion or embolic stroke were excluded. All subjects before being examined and included were informed of the research method and signed an informed consent. Statistical analysis was performed with SPSS v.18. In interpreting statistical results we considered p=0.005 as the reference value for significance, which corresponds to a confidence interval of 95%. Continuous type variables were presented as mean ± standard deviation.

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patients were overweight and 25.8% were obese. 53 of the patients included associated type 2 diabetes mellitus insulin dependent.

The mean value for AST was 25.5±17.7 mg/dL, with a maximum of 106 mg/dL, for ALT it was 36.7±36.7 mg/dL, with a maximum of 191.6 mg/dL, for uric acid the mean value was 4.5±1.7 mg/dL, with a maximum of 8.16 mg/dL. As for the lipid profile, mean cholesterol was 145.7±40.4 mg/dL and for tryglicerides was 116.7±56.2 mg/dL (table 1).

Most of the study subjects had statins (87.9%) in the treatment regimen, but there were also patients who did not receive statin therapy at home, even after the cerebrovascular event. Among the statin type, atorvastatin was the most used (69%), then rosuvastatin (17.2%) and simvastatin (1.7%) last (table 2).

Regarding the statin doses used, the most frequent dose was 10 mg (37.9%), followed by 20 mg (31.0%), then 40 mg (17.2%) and only 1.7% of patients were treated with the 80 mg dose (table 3).

Results and discussions

The international guidelines in place for ischemic stroke mention the need for statins to be used as secondary prevention [13]. In our study, 12% of patients did not have chronic statin treatment, 37.9% had statin at the 10 mg dose, 31% had a statin dose of 20 mg, 17.2% had 40 mg of statin and 1.7% had the statin dose of 80 mg. The recommended doses in the European Cardiology Guide are 40 mg, respecting 80 mg in patients with a history of stroke [13]. The same guidelines mention the possibility of decreasing the statin dose when the hepatic enzymes increase by 3-5 times the normal value, 3 weeks after initiation of the statin-lipid lowering regimen. In our study, the altered aspartate aminotransferase (AST) value was found in a similar percentage of 1.7% in patients taking statin of 10 mg, 20 mg, 40 mg or 80 mg. The recommended doses in the European Cardiology Guide are 40 mg, respecting 80 mg in patients with a history of stroke [13]. The same guidelines mention the possibility of decreasing the statin dose when the hepatic enzymes increase by 3-5 times the normal value, 3 weeks after initiation of the statin-lipid lowering regimen. In our study, the altered aspartate aminotransferase (AST) value was found in a similar percentage of 1.7% in patients taking statin of 10 mg, 20 mg, 40 mg or 80 mg. Note that the statistically significant percentage of patients with increased liver enzymes by 3.4% in the absence of hypolipidemic therapy (fig. 1). Among hepatic enzymes, we found a statistically significant correlation between the AST value and the statin dose used (p = 0.039).

Another risk factor for vascular disease is the uric acid. In our study, we noticed a statistically significant difference between the uric acid value and the statin concentration used. Thus, elevated uric acid was found in 2% of patients receiving 10 mg statin treatment, the same proportion as patients receiving the 20 mg or 40 mg dose. It should be noted that the uric acid value is not altered when the dyslipidemic treatment is administered at the maximum dose of 80 mg. Increased uric acid was quantified in 6% of patients, decreased in 65.3% of them and normal in 28.7%. The value of uric acid was taken into account in all patients regardless of whether or not they are taking urate-lowering therapy, so it seems that statins, besides their hypolipidemic role, also have a role in lowering the uric acid, a demonstrated cardiovascular risk factor. The statistically significant difference was observed between the statin dose used versus the normal uric acid value (p = 0.046) and the elevated uric acid value (fig. 2).

Statin therapy is absolutely mandatory in patients with a history of stroke, especially if they present with diabetes also. Unfortunately, only 8.5% of diabetic patients undergoing insulin treatment were also treated with statin and there was a statistically significant difference between statin dose in diabetic patients, respectively, without diabetes (p = 0.003). Patients with oral diabetes mellitus did not show any statistically significant correlation between doses of statins used. Although the percentage

| Mean | AST         | ALT         | Uric acid  | Cholesterol | Triglycerides |
|------|-------------|-------------|------------|-------------|--------------|
|      | 25.5±17.7  | 36.7±36.7   | 4.5±1.7    | 145.7±40.4  | 116.7±56.2   |
| Std Deviation | 17.7±47.6  | 56.7±194    | 1.7±4.5    | 40.4±5919   | 56.29±924    |
| Minimum | 11.3±10.6  | 1.26±15.6   | 1.2±1.2    | 85.8±43     | 43±40        |
| Maximum | 106±60     | 191±60     | 8.16±1.6   | 25±6.0      | 30±2.0       |

**Table 1**

**Table 2**

**Table 3**
of diabetic patients receiving dyslipidemic therapy is low, we noticed that most (3.4%) took the 40 mg dose, statistically significant from the other doses used in our patients. The percentage is similar for the 10 mg and 20 mg dose. Note that the 80 mg dose is found only in patients with stroke and diabetes, unfortunately in a low percentage of 1.7% (fig. 3).

According to the recommendations of the international protocols for the secondary prevention management of ischemic stroke patients it is recommended to quantify carotid atheromatosis by cervical Doppler ultrasound. In our study, atheromatosis was found in 53.4% of patients with ischemic stroke. 8.6% did not have statin treatment. There was a statistically significant difference between the percentage of patients with atheromatosis and the percentage of patients without atheromatosis. For the statin dose of 10 mg and 20 mg respectively, the percentage of patients treated with statin but without atheromatosis was statistically significant compared to atherosclerotic patients (22.4% vs. 15.5% at the 10 mg dose, respectively 17.2% vs. 13.8% at the 20 mg dose). The percentages are reversed with a statistically significant difference in patients with stroke, atheromatosis and 40 mg statin and patients without atheromatosis. The statin dose of 80 mg, as recommended by the guidelines, was identified in 1.7% of stroke patients with established atheromatosis (fig. 4). So, patients with atheromatosis and stroke are treated optimally at a rate of 15.5%. We did not find any statistically significant difference between cholesterol and triglycerides and the statin dose.

Conclusions
In our study, we found a significant link between atheromatosis and statin treatment, more obvious in patients taking a higher dose. We also found a connection between the statin dose and the decrease of uric acid value, another cardiovascular risk factor. So, it is imperative to use statins to lower cholesterol value and to stabilize the atheroma plaque in patients with stroke.

References
1. LOPEZ AD, MATHERS CD, EZZATI M, JAMISON DT, MURRAY CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 367, 2006, p. 1747-1757.
2. ROTHWELL PM, COULL AJ, SILVER LE, FAIRHEAD JF, GILES MF, LOVELOCK CE et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). Lancet 366, 2005, p. 1773-1783.
3. WAFA HA, WOLFE CDA, RUDD A, WANG Y. Long-term trends in incidence and risk factors for ischemic stroke subtypes: Prospective population study of the South London Stroke Register. PLoS Med 15, no. 10, 2018, e1002669.
4. SUN Q, CHANG S, LU S, ZHANG Y, CHANG Y. The Efficacy and Safety of 3 Types of Interventions for Stroke Prevention in Patients With Cardiovascular and Cerebrovascular Diseases: A Network Meta-analysis. Clin Ther. 39, no. 7, 2017, p. 1291-1312.
5. MORTENSEN MB, NORDESTGAARD BG, AFZAL S, FALK E, ACC/AHA guidelines superior to ESC/EAS guidelines for primary prevention with statins in non-diabetic Europeans: the Copenhagen General Population Study. Eur Heart J. 38, 2017, p. 586-594.
6. KERNAN WN. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 45, 2014, p. 2115-236.
7. AMARENCO P, GOLSTEIN LB, MESSING M, et al.; SPARCL Investigators, 2009 Relative and cumulative effects of lipid and blood pressure control in the stroke prevention by aggressive reduction in cholesterol levels trial. Stroke. 40, 2009, p. 2486-2492.
8. POLAK JF, SZKLO M, KRONMAL RA, et al. The value of carotid artery plaque and intima-media thickness for incident cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis. J Am Heart Assoc. 2, 2013, p. e000857.
9. OSAWA K, PEREZ TREJO ME, NAKANISHI R, MCCLELLAND RL, BLAHA MJ, BLANKSTEIN R et al. Coronary artery calcium and carotid artery intima-media thickness for the prediction of stroke and benefit from statins. Eur J Prev Cardiol. 0, no. 0, 2018, p. 1-8.

10. KIM JS, BANG OY. Medical treatment of intracranial atherosclerosis: an update. Stroke. 19, 2017, p. 261-270.

11. ZHONG P, WU D, YE X, WU Y, LI T, TONG S, LIU X. Secondary prevention of major cerebrovascular events with seven different statins: a multi-treatment meta-analysis. Drug Des Devel Ther. 11, 2017, p. 2517-2526.

12. SIRTORI CR. The pharmacology of statins. Pharmacol Res 88, 2014, p. 3-11.

13. PIEPOLI MF, HOES AW, AGEWALL S, ALBUS C, BROTONS C, CATAPANO AL et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J. 37, no. 29, 2016, p. 2315-2381.

14. MILLER PE, MARTIN SS. Approach to Statin Use in 2016: an Update, Curr Atheroscler Rep, 18, no. 5, 2016, p.20.

15. AMARENCO P, GOLDSTEIN LB, SZAREK M, SILLESEN H, RUDOLPH AE, et al. Effects of intense low-density lipoprotein cholesterol reduction in patients with stroke or transient ischemic attack: The stroke prevention by aggressive reduction in cholesterol levels (SPARCL) trial. Stroke. 38, 2007, p. 3198-204.

16. MANCINI GB, BAKER S, BERGERON J, FITCHETT D, FROHLICH J, GENEST J et al. Diagnosis, prevention, and management of statin adverse effects and intolerance: Canadian Consensus Working Group Update. Can J Cardiol. 32, 2016, p. 535-565.

17. PREISS D. et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 305, 2011, p. 2556-2564.

18. ABDO TT, JACOBSON TA. Statin-induced myopathy: a review and update. Expert Opin. Drug Saf. 10, 2011, p. 373-387.

19. KARAHALIL B et al. Hepatotoxicity is associated with statins. Arh Hig Rada Toksikol. 68, 2017, p. 254-260.

20. MACH F, RAY KK, WIKLUND O, CORSINI A, CATAPANO AL, BRUCKER E et al. Adverse effects of statin therapy: perception vs. the evidence – focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract Eur Heart J. 0, 2018, p. 1-18.

21. BETTERIDGE DJ, CARMENA R. The diabetogenic action of statins—mechanisms and clinical implications. Nat Rev Endocrinol. 12, 2016,12:90-110.

22. BELLAOSTA S, CORSINI A. Statin drug interactions and related adverse reactions. Expert Opin. Drug Saf. 11, 2012, p. 933-946.

23. STEIN JH, KORCARZ CE, HURST RT, LONN E, KENDALL CB, MOHLER ER et al. ASE Consensus Statement. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography. J Am Soc Echocardiogr. 21, 2008, p. 93-111.

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