

# INFLUENCE OF TREATMENT WITH STATINS VERSUS OMEGA-3 FATTY ACIDS ON INFLAMMATORY AND OXIDATIVE STATUS IN PATIENTS WITH ISCHEMIC STROKE

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**Abstract.** Many studies point an important anti-inflammatory and antioxidant effect for statins and more recently are several similar studies for omega 3 fatty acids. **Objective.** To show how these two therapeutic classes influence oxidative and inflammatory status in patients with ischemic stroke. **Patients and Methods.** Prospective study, including 55 patients with acute ischemic stroke. We administered all the patients' one of the two drugs: 40 mg Sortis or 1g Omacor and appreciate how each of this therapy influence the dynamic evolution of oxidative and inflammatory status, by evaluating the specific markers in the two lots. **Results.** There were no significant differences between the individual and total oxidative stress and nor between the inflammatory markers, in the lot treated with Omacor; 2 months after initiation of treatment, in the group treated with Sortis, TAS (Total Antioxidant Status) values were higher ( $p=0,06$ ) and CRP levels were statistically significant lower ( $p=0,01$ ) than initially. **Conclusions.** It is suggested an anti-oxidant and anti-inflammatory effect stronger for statins than for omega-3 fatty acids in patients with ischemic stroke.

**Key words:** statins, omega-3 fatty acids, oxidative stress, inflammation, stroke.

## 1. Introduction

At the present time characterization of cardiovascular diseases is realized in correlation with the two important biological processes, inflammation and oxidative stress, which detain a determinant etiopathogenic role.

In the last two decades, many studies revealed the role of inflammation, both in pathogenesis of atherosclerosis and in

generation of brain tissue lesions, that appear during the ischemic stroke.

More recently, there are experimental evidences that oxidative stress plays a major role, too, by production of free radicals, in the ischemic brain injury and in atherogenesis. Despite numerous defenses, the brain is vulnerable to oxidative stress resulting from ischemia and reperfusion.

There is also some recent evidence of an association between oxidative damage and

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tissue inflammation as measured by C-reactive proteins (CRPs) in subjects with stroke disease.

Thus, many studies point an important anti-inflammatory and antioxidant effect for statins and more recently are several similar studies for omega 3 fatty acids.

## 2. Objectives

The aim of the present study is to show how these two therapeutic classes influence oxidative and inflammatory status quantified by oxidative stress and inflammatory markers in patients with ischemic stroke.

## 3. Patients and methods

In a prospective study, we included 55 patients with acute ischemic stroke. All stroke patients were clinical assessed by NIHSS score and imagistic by cerebral computerized tomography, done in the first 24 hours after the onset of the ischemic stroke.

We administered to all the patients included in the study one of the two different therapeutic classes: 40 mg Sortis or 1 g Omacor [460 mg eicosapentaenoic acid ethyl ester (EPA) plus 380 mg docosahexaenoic acid ethyl ester (DHA)]. Sortis was administered to 35 patients. Of them, 20 patients came at the second visit (T1), 2 months after the onset of stroke. Omacor was administered to the rest of 20 patients; of them 17 came at T1. We

considered both of drugs as representative for the class effect of statins, respectively of omega-3 fatty acids.

We appreciate how each of these of therapies influences the dynamic evolution of oxidative and inflammatory status, by evaluating the specific markers in the two lots: lot S – treated with statin versus lot O – treated with omega-3 fatty acids. Oxidative status was assessed by values of albumin, uric acid, copper and total antioxidant status (TAS) and inflammatory status by levels of C reactive protein (CRP) and fibrinogen, measured twice: first time (T0), in the first 72 hours after the onset of stroke and second, 2 months after (T1).

### 3.1. Laboratory

Total Antioxidant Status (TAS) was measured spectrophotometrically, Randox Laboratories Ltd. U.K. Uric acid, copper, total cholesterol, HDL, LDL, triglycerides, albumin, C-reactive protein, were analyzed with Hitachi 717 Boehringer Mannheim automatic analyzer, using Futura System (Italy) reagents.

*Statistical analyses* were performed using the program STATISTICA Six Sigma version 8.0.

## 4. Results

Levels of albumin, uric acid and copper were not significant influenced by the two drugs.

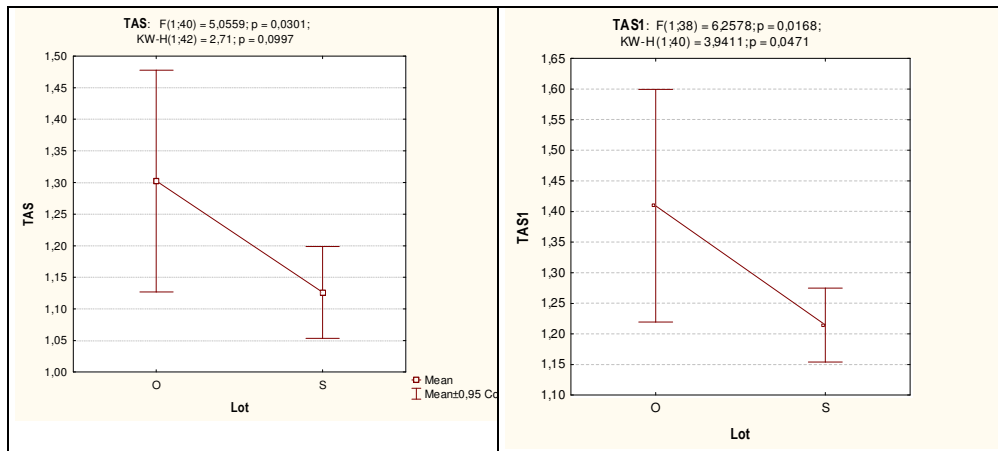


Fig. 1. TAS values comparative in lot Stain versus lot Omega-3 at T0 and T1

Total antioxidant status (TAS) presented from the onset, by selection of the patients, significant higher values in Omega-3 than in Statin lot. The difference between these

values is lower, but still statistic significant, two months after initiation of the different type of treatment in the 2 groups.

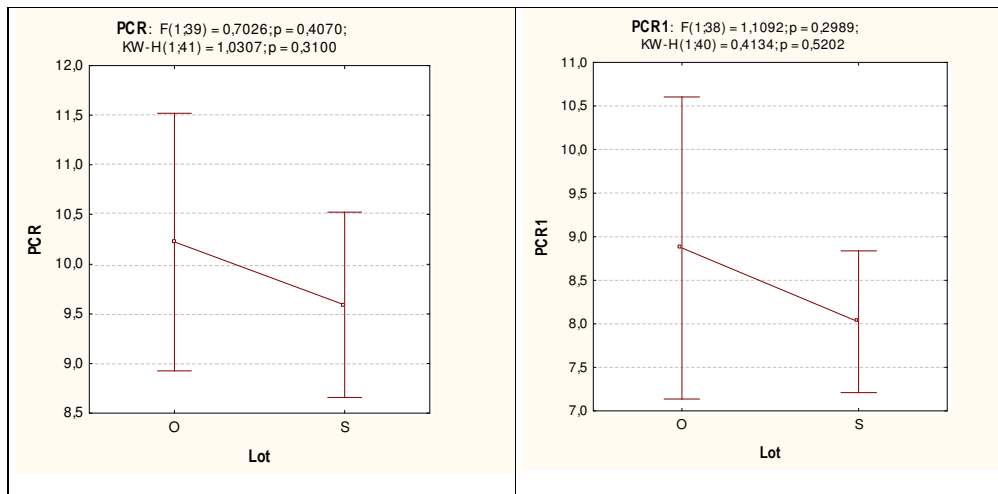


Fig.2. CRP values comparative in lot Statin versus lot Omega-3 at T0 and T1

Related to the inflammatory status, we notice a similar variation of CRP in the two lots (Fig.2); there are insignificant

lower levels of fibrinogen after 2 months, in the lot treated with statin. (Fig.3)

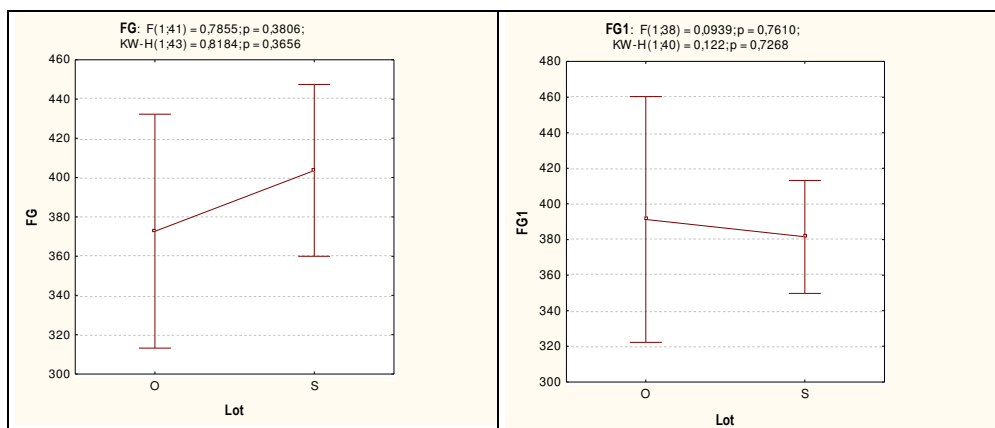


Fig. 3. Fibrinogen values comparative in lot Statin versus lot Omega-3 at T0 and T1

There were no differences between the individual oxidative stress markers at both determinations in the group treated with Sortis.

Nevertheless, TAS values were higher 2 months after initiation of treatment than initial; the difference was slightly over the statistical significance limit ( $p=0,06$ ). CRP levels were statistically significant lower at the second evaluation ( $p=0,01$ ). (Table 1)

Statistic analyze in lot treated with Sortis - comparative T0 with T1

Table 1

		T0	T1	t-value	df	p	Std. Dev T0	Std. Dev T1	F ratio variances	p variances
<b>Alb</b>	vs.	3,178	3,4124	-1,4269	49	0,15995	0,6358	0,527	1,5	0,36375
<b>Alb1</b>										
<b>Ac. uric</b>	vs.	307,39	305,53	0,0806	50	0,93608	96,3638	65,57	2,2	0,06194
<b>Ac uric1</b>										
<b>Cu</b>	vs.	107,60	104,44	0,6662	49	0,50842	10,8907	21,51	3,9	0,00121
<b>Cu1</b>										
<b>TAS</b>	vs.	1,126	1,2145	-1,9194	49	0,06076	0,1800	0,146	1,5	0,31502
<b>TAS1</b>										
<b>PCR</b>	vs.	9,591	8,0240	2,5978	49	0,01235	2,3139	1,974	1,4	0,43977
<b>PCR1</b>										

On the other hand, there were no significant differences between the individual and total oxidative stress markers, nor between the inflammatory markers, in the lot treated with Omacor, after two months of treatment. (Table 2)

Statistic analyze in lot treated with Omacor - comparative T0 with T1

Table 2

	Mean – T0	Mean – T1	t-value	df	p	Std. Dev T=0	Std. Dev T=1	F-ratio Var.	p Var.
<b>Alb vs. Alb1</b>	3,17	3,386	-0,85	24	0,403	0,69	0,537	1,7	0,376
<b>Uric ac. vs. Uric ac.1</b>	342,7	330,8	0,31	28	0,758	97,17	111,9	1,3	0,603
<b>Cu vs. Cu 1</b>	107,98	106,11	0,38	27	0,706	13,57	12,83	1,1	0,845
<b>TAS vs. TAS1</b>	1,32	1,40	-0,65	28	0,515	0,32	0,342	1,1	0,819
<b>CRP vs. CRP1</b>	10,08	8,87	1,17	27	0,250	2,37	3,128	1,7	0,325
<b>FG vs. FG1</b>	368,6	391,2	-0,51	28	0,609	114,4	124,5	1,2	0,756

## Discussion

### *Oxidative status*

There are many studies in the last years demonstrating an important antioxidant effect for statins and more recently, also for omega-3 fatty acids.

We remarked in both lots, treated with Sortis and respective with Omacor, an improving in levels of the individual oxidative stress markers by increasing the values of albumin in the same time with decreasing those of uric acid, but with important rising of TAS. Atorvastatin determined a higher growing of TAS - almost to the limit of the statistical significance – different from the treatment with Omacor, which didn't influence the level of TAS. This fact suggests a stronger antioxidant effect of statins versus omega-3 fatty acids. From the "pleiotropic" effect of statins, inhibition of oxidative stress seems to play an essential role; it is demonstrated that oxidative stress is involved not only in initiation but also in progression of the atherosclerotic disease.

Statins could have neuroprotective effect by many antioxidant mechanisms. It is not yet demonstrated if one of the statins detains a stronger antioxidant effect or intervenes faster than the others in reducing oxidative stress. There are

ongoing clinical trials, which compare inhibition effect of oxidative stress for simvastatin and atorvastatin.[1]

Buyukhatipoglu, in a recent study, found higher values for TAC (Total Antioxidant Capacity) in patients with coronary disease treated 3 months with atorvastatin comparing to those with no treatment. [2] <http://clinicaltrials.gov/show/NCT00404599>

Referring to omega-3 fatty acids, this therapeutic class demonstrated neuroprotective and neurotrophic effects in severe chronic degenerative diseases. [3] Administration of EPA in patients with diabetes mellitus determined significant increasing of TAC (Total Antioxidant Capacity), SOD (Superoxidismutase) and GPX (Glutation Peroxidase) levels, concomitant with decrease in MDA (Malondialdehyde) values. [4]

Kesavulu remarked diminishing of GPX, without changing in the seric levels of catalase and SOD, after 2 months of treatment with omega-3 fatty acids associated with oral antidiabetic drugs. [5, 6]

In our study, we observed rising of TAS values more evident in patients with ischemic stroke treated with statin than in those treated with Omacor.

Studies referring to stroke appreciate the effect of omega-3 fatty acids in primary and secondary prevention of ischemic stroke.

Relatively few studies evaluate the influence of treatment with PUFA-Omega-3 on oxidative stress markers in patients with cerebral attack. Poppit, after administration for 12 months of moderate doses of supplements with fish oil in patients with ischemic stroke didn't show significant changes of triglycerides, cholesterol, associated lipoproteins or of the inflammatory or haemostatic markers; the cause was, may be, the insufficient dose and/or the short period of treatment. [7]

#### *Inflammatory status*

Referring to the inflammatory status, we remarked that statin was, also, significant more efficient than omega-3 fatty acids in decreasing of CRP levels after 2 months of treatment.

Due to the 'pleiotropic' effects of statins we, also, should mention the effect of stabilization of atheroma plaque, improving of endothelial function, decreasing of platelet aggregability and reducing of vascular inflammation. [8,9]

It was demonstrated the role of statins in lowering levels of CRP – inflammatory marker, proved as independent risk factor for ischemic stroke. Di Napoli showed a greater decrease of risk in patients with higher levels of CRP, independent from the lipid profile. In patients with intensive inflammatory activity, with persistent CRP values, higher than 4,5 mg/l, statins exerted a limited anti-inflammatory effect. These patients have to be followed in time, to decide the moment for initiation of an efficient anti-inflammatory treatment. [10]

In MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) trial, administration of 80 mg/d of atorvastatin in subjects with acute coronary syndromes cause decrease with 50% of ischemic stroke incidence; decline in the levels of CRP was greater in patients treated with statin. [11]

The rate of cardiovascular events was reduced, also, in patients with low values of LDL- cholesterol <70 mg/dl and CRP <1.0 mg/l, in subjects included in PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction-22) study. (Ridker cited by Robinson). [12]

Relatively recent, in JUPITER clinical trial, treatment with rosuvastatin 20 mg/d versus placebo, determined decline with 50% in the level of LDL and with 37% in CRP values. Plasmatic levels of CRP presented a significant decreasing from 4,2 mg/l, initially to 2,2 mg/l, after 12 months. Those with initial values of CRP>5 mg/dl, presented higher risk for stroke and benefited from the therapy. CRP may serve as a non-lipid marker in identification of patients who benefit from the treatment with statin. [13,14]

The studies regarding to omega-3 fatty acids are not so many; they highlight a lot of benefic actions of this therapeutic class as: anti-inflammatory and immunomodulatory effects which become more relevant due to their action to atherosclerosis and its clinical manifestations: myocardial infarct, ischemic stroke and sudden death. [15]

In this respect, there are some reports, demonstrating after administration of PUFA-Omega-3, decline in the plasmatic level of CRP and IL6 in healthy people and respectively decrease in CRP with 15% and in IL6 with 23%, in patients with hypertriglyceridemia after 91 days of treatment. [16, 17]

Some authors recommend utilization of omega-3 fatty acids for lowering of CRP levels, starting from the observation of a reduction of this marker with 30% under treatment with krill oil – supplement of omega-3 fatty acids that presents important effects in modulation of other inflammatory biomarkers and less side effects.

In **conclusion**, in our study we found in both groups, treated with statin and respectively with omega-3 fatty acids, an improving of oxidative stress and inflammatory markers after 2 months of therapy. Treatment with Sortis determined increasing of TAS (Total Antioxidant Status) level – at the mathematical statistical limit and significant decreasing of CRP comparing with the lot treated with Omacor, suggesting an anti-oxidant and anti-inflammatory effect stronger for statins.

Modulation of oxidative and inflammatory markers was more evident in patients with acute ischemic stroke treated with statin, but for a better appreciation of the effect of omega-3 fatty acids on oxidative and inflammatory status it should be necessary a third placebo lot – ethically unacceptable.

PUFA-Omega-3 remains, for the moment as an alternative therapy for statins, but they could be recommended as first choice in patients who present contraindications or side effects for statins.

We consider that the present study could bring some elucidation in this not very known field – of oxidative stress and inflammation in cerebrovascular disease pathogenesis – and in the mechanism of action of the two therapeutic classes, statins and omega-3 fatty acids.

Further studies including a larger number of patients are needed to confirm and complete these data, to appreciate the optimal moment and type of interventional strategy to minimize the oxidative and inflammatory lesions that appear after onset of ischemic stroke.

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