# EFFECTIVENESS OF THE COMBINATION OF ATORVASTATIN AND ASPIRIN ON THE INFLAMMATION AND PROGRESSION OF CAROTID ATHEROSCLEROSIS IN PATIENTS WITH ACUTE CEREBRAL INFARCTION

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#### Abstract

Background: This study is aimed at investigating the relationship between effectiveness of 3 month -combination therapy Atorvastatin plus Aspirin in patients with acute cerebral infarction on inflammatory factors (hs-CRP, fibrinogen) and the progression of carotid atherosclerosis. Patients and Method: Clinical research trials and longitudinal follow-up, 66 patients with acute cerebral infarction treated at Hue University Hospital. Data were processing by conventional statistics methods and SPSS 15.0. Results: 1. The concentration of hs-CRP, serum fibrinogen, Intimal-Medial Thickness (IMT) and carotid atherosclerosis in patients with acute cerebral infarction highly increased: hs-CRP was  $6.46 \pm 4.49$  mg/l; fibrinogen was  $4.59 \pm 1.52$  g/l; carotid IMT was  $1.67 \pm 0.72$  mm and carotid atherosclerosis was  $2.88 \pm$ 1.24 mm. 2. The effective coordination of Atorvastatin therapy plus aspirin versus aspirin therapy alone: (i) Effect of serum hs-CRP levels between the two groups after 1 month of treatment was  $(1.60 \pm 0.65 \text{ vs.})$  $4.11 \pm 2.54$  mg l) with paired t -3.06 and p <0.05; effect after 3 months was ( $1.26 \pm 0.53$  compared with  $3.24 \pm 3.03$  mg/l) with paired t -3.85 and p <0.01; (ii) Effect of fibrinogen concentration between the two groups after 1 month of treatment was  $(2.80 \pm 0.93 \text{ vs}, 3.30 \pm 0.73 \text{ g/l})$  with paired t -2.41 and p <0.05; effect after 3 months ( $2.67 \pm 0.79$  vs.  $3.09 \pm 0.59$  mg/l) with paired t -2.58 and p <0.01; (iii) Treatment effectiveness on IMT and carotid atherosclerosis between the combination therapy group compared with the monotherapy: improvement effect of IMT (t paired -2.06 and p < 0.05) and carotid atherosclerosis (t paired -3.04 and p < 0.01). Conclusion: Patients with acute cerebral infarction treated by combination therapy of Atorvastatin plus Aspirin significantly reduced the concentration of inflammatory factors hs-CRP, fibrinogen and carotid atherosclerosis progression.

Key words: carotid atherosclerosis, acute cerebral infarction, inflammation.

#### **1. BACKGROUND**

Stroke was quite popular and became an urgent medical problem for all countries in the world. In particular, cerebral infarction (CI) accounting for more cases, often in severe condition, high mortality and non-fatal cases may leave sequelae, decreased quality of life, increased the burden on families and society. However, some scientific research showed that the prevention of risk factors of stroke (hypertension, atherosclerosis, diabetes, dyslipidemia, transient brain stroke, etc.) have contributed to reduce significantly the incidence of stroke. Many projects have been carried out to understand the pathogenesis, especially risk factors with the aim of controlling the development of this serious disease, and atherosclerosis lesions: such as cerebrovascular atherosclerosis, carotid atherosclerosis is a common cause of CI. Recently, a number of the world's research study on the effect of statin therapy in patients with CI and coronary artery disease showed that it is not only help to stabilize the plaque, improvement of clinical symptoms, but also help to reduce risk factors such as inflammatory marker hs-CRP, fibrinogen, VSS, etc., but our country still do not have any research on statin therapy in patients with CI. Derived from these issues, we made this

- Corresponding author: Le Chuyen, email: lechuyen@doctor.com - Received: 31/3/2013 \* Revised: 2/5/2013 \* Accepted: 15/6/2013 research with two objectives:

1. Survey levels of hs-CRP, serum fibrinogen, IMT lesion and carotid atherosclerosis in patients with acute cerebral infarction.

2. Evaluate the effect of Atorvastatin+Aspirin therapy on the changing of hs-CRP levels, serum fibrinogen and carotid atherosclerosis progression in patients with acute cerebral infarction.

## 2. PATIENTS AND METHOD 2.1. Research Materials

- We selected 66 patients treated at the General Internal Medicine - Endocrinology Hue University Hospital with the diagnosis of acute CI includes clinical symptoms combined computerized tomography brain scan. Subjects were divided into two groups that was similar in age, gender, risk factors (hs-CRP, fibrinogen, IMT, carotid atherosclerosis) to facilitate the research, evaluation and comparison view, including:

Group A: 33 patients with acute CI treated with standard therapy and Atorvastatin+Aspirin.

Group B: 33 patients with acute CI treated with standard therapy and aspirin.

- We did not choose the following cases:

+ Patients with CI not in acute phase, there was evidence of acute and chronic infection detected on clinical and paraclinical, fever, immunodeficiency, cancer,...

+ Brain injury, local paralysis following focal epilepsy, a history of seizures.

+ The intracranial pathology other than CI as: transient stroke, intracranial abscess, brain hemorrhage, brain tumors, etc.

## 2.2. Research Methodology

Clinical research trials and longitudinal followup, each patient surveyed by questionnaire, all data were written research questionnaire.

**2.2.1.** *Clinical method*: Ask the medical history, history, thorough clinical examination to select research subjects, evaluation of risk factors (hypertension, smoking, history of cardiovascular disease...), scale of Glasgow.

Definitive diagnosis of acute CI: based on clinical and computerized tomography brain scan.

2.2.2. Functional exploration methods: including computerized tomography brain scan, ECG, Chest X-ray, abdominal ultrasound, carotid Doppler ultrasound, echocardiogram.

*2.2.3. Laboratory test methods:* quantified hs-CRP, blood count, VSS, Fibrinogen, glycemia, lipid panel, SGOT, SGPT, CK.

# 2.2.4. Research process including:

- Patients in hospital: clinical follow-up examination, paraclinical test (carotid Doppler ultrasound, hs-CRP, fibrinogen, lipid balance, SGOT, SGPT, CK, computerized tomography brain scan, etc.).

+ Group A: 33 patients with acute CI treated with standard therapy and Atorvastatin 20mg/day + Aspirin 100mg/day.

+ Group B: 33 patients with acute CI treated with standard therapy and aspirin 100mg/day.

- When patients leave the hospital, evaluation of the clinical situation, functional disability, scale of Glasgow,...

+ After 1 month of treatment: clinical examination and paraclinical tests (hs-CRP, fibrinogen, lipid balance, SGOT, SGPT, CK, glycemia, etc.).

+ After 3 months of treatment: clinical followup examination, paraclinical test (carotid Doppler ultrasound, hs-CRP, fibrinogen, lipid balance, SGOT, SGPT, CK, glycemia, etc).

- All data were recorded in the research questionnaire.

- Management of data on SPSS 15.0 program.

## 3. RESULTS

# 3.1. Distribution by age and sex

 Table 3.1. Distribution of cerebral infarction

 patients by age and sex

		Group A (n=33)	Group B (n=33)	р
Sex	Male	19	19	
	Tỷ lệ %	57.58	57.58	
	Female	14	14	>0.05
	%	42.42	42.42	
Age	Х	69.36	69.30	
	SD	12.22	12.17	

Table 3.1 shows the average age of group A was  $69.36 \pm 12.22$ ; Group B was  $69.30 \pm 12.17$ , with the similarities, as well as sex, p > 0.05.

**3.2.** Concentration of hs-CRP, serum fibrinogen, IMT lesion and carotid atherosclerosis in the two groups at the hospital Table 3.2. Concentration of hs-CRP.

serum fibrinogen, the secondary lining and atherosclerosis in the carotid atherosclerosis of two groups at the hospitalization

	Group	Χ	SD	р	
	Total (n=66)	6.46	4.49		
hs-CRP (mg/l)	A (n=33)	6.27	4.67	>0.05	
	B (n=33)	6.64	4.28		
Fibrinogen (g/l)	Total (n=66)	4.59	1.52		
	A (n=33)	4.56	1.48	>0.05	
	B (n=33)	4.63	1.60		
C CINT	Total (n=66)	1.67	0.72		
(mm)	A (n=33)	1.76	0.68	>0.05	
()	B (n=33)	1.55	0.76		
Carotid	Total (n=66)	2.88	1.24		
atherosclerosis	A (n=33)	2.91	1.09	>0.05	
(mm)	B (n=33)	2.76	1.46		

Table 3.2 shows the general levels of hs-CRP group 2 was  $6.46 \pm 4.49 \text{ mg} / \text{l}$ , fibrinogen concentration was  $4.59 \pm 1.52 \text{ g} / \text{l}$ ; well as IMT lesion was 1.67 mm and carotid atherosclerosis was 2.88 mm; no difference between the two groups with p > 0.05.

**3.3.** Treatment effects of coordination Atorvastatin + aspirin group after 3 months

**Table 3.3.** Effects on inflammation of the coordination group after 3 months of treatment

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	n	Χ	SD	р		
hs-CRP A1(mg/l)	33	6.27	4.67			
hs-CRP A2	33	1.60	0.65	< 0.001		
hs-CRP A3	33	1.26	0.53			
Fibrinogen A1(g/l)	33	4.56	1.48			
Fibrinogen A2	33	2.80	0.93	< 0.01		
Fibrinogen A3	33	2.67	0.79			

Carotid IMT A1(mm)	33	1.76	0.68	< 0.001
Carotid IMT A3	33	1.44	0.55	
Carotid atherosclerosis A1(mm)	33	2.91	1.09	< 0.001
Carotid atherosclerosis A3	33	2.32	0.82	

The results shows that the concentration of serum hs-CRP and fibrinogen decreased significantly after 3 months of combination therapy Atorvastatin+Aspirin with p < 0.001 and p < 0.01; well as on IMT and carotid atherosclerosis with p < 0.001.

**3.4. Treatment effects of aspirin-alone group after 3 months** 

 Table 3.4. Treatment effects

 of aspirin-alone group after 3 months

	n	X	SD	р		
hs-CRP B1(mg/l)	33	6.64	4.28			
hs-CRP B2	33	4.11	2.54	< 0.01		
hs-CRP B3	33	3.24	3.03			
Fibrinogen B1(g/l)	33	4.63	1.60			
Fibrinogen B2	33	3.30	0.73	< 0.05		
Fibrinogen B3	33	3.09	0.59			
IMT <b>ĐMC B1(mm)</b>	33	1.55	0.76	< 0.01		
IMTÐMC B3	33	1.80	0.83	< 0.01		
Carotid atherosclerosis B1(mm)	33	2.76	1.46	< 0.01		
Carotid atherosclerosis B3	33	3.16	1.33			

The results also shows that the concentration of serum hs-CRP and fibrinogen decreased after 3 months of therapy alone with p < 0.01 and p < 0.05; yet effective treatment on IMT and carotid atherosclerosis not improve with p < 0.01.

**3.5.** Compare the treatment effectiveness of two groups after 3 months

3.5.1. Effect of concentration of hs-CRP, fibrinogen between the two groups after 1 month of treatment

normogen between the two groups after 1 month of treatment						
$\smallsetminus$		Fibrinogen(g/l)				
	hs-CRP(A2)	hs-CRP(B2)	$\Delta X$ (hs-CRP:A2-B2)	Fib(A2)	Fib(B2)	$\Delta X$ (Fib:A2-B2)
n	33	33	33	33	33	33
X	1.60	4.11	-2.51	2.80	3.30	-0.50
SD	0.65	2.54	-1.89	0.93	0.73	0.20
t paired	-3.06			-2.41		
р	< 0.05				<	0.05

**Table 3.5.** Effect of the concentration of hs-CRP, fibrinogen between the two groups after 1 month of treatment

The above table shows effect of serum hs-CRP levels after 1 month of treatment groups combined (A) than alone group (B) was (t paired -3.06 and p <0.05); effect of concentration of fibrinogen level of group A compared to group B was (t paired -2.41 and p < 0.05).

# 3.5.2. Effect of hs-CRP concentration, fibrinogen between the two groups after 3 months of treatment

normogen between the two groups after 5 months of treatment						
$\searrow$		g/l)	Fibrinogen(g/l)			
	hs-CRP(A3)	hs-CRP(B3)	∆X(hs-CRP:A3-B3)	Fib(A3)	Fib(B3)	ΔX (Fib:A3-B3)
n	33	33	33	33	33	33
X	1.26	3.24	-1.98	2.67	3.09	-0,42
SD	0.53	3.03	-2.50	0.79	0.59	0,20
t paired	-3.85				-2.5	8
р		< 0.01			< 0.0	01

Table 3.6.	Effect of hs-CRP concentration,
fibringgen between	the two groups after 3 months of treatment

The above table shows effect of serum hs-CRP levels after 3 months of treatment of group A compared to group B is (t paired -3.85 and p <0.01); effect of serum fibrinogen levels of group A compared group B is (t paired -2.58 and p <0.01).

3.5.3. Treatment effects on the IMT lesion and Carotid atherosclerosis of the two groups after 3 months

Table 3.7. Treatment effects on the IMT lesion and Carotid atherosclerosis

$\smallsetminus$		(mm)	Carotid atherosclerosis (mm)			
	IMT(A3)	IMT(B3)	ΔX (IMT:A3-B3)	XV(A3)	XV(B3)	ΔX (XV:A3-B3)
n	33	33	33	33	33	33
X	1.44	1.80	-0.36	2.32	3.16	-0.84
SD	0.55	0.83	-0.28	0.82	1.33	-0.51
t paired	-2.06				-3.0	4
р	< 0.05				< 0.0	)1

In Table 3.7 showed significant treatment effect on the IMT lesion and carotid atherosclerosis of the group coordinate Atorvastatin plus aspirin versus aspirin alone group with the order was (t paired -2.06 and p < 0.05) and (t paired -3.04 and p < 0.01).

## 4. DISCUSSION

Our study on 66 patients with acute CI divided into two groups, with group A receiving combination treatment (Atorvastatin+Aspirin) and group B receiving alone treatment (Aspirin), the average age of group A was  $69.36 \text{ B} \pm 12.22$ and  $69.30 \pm 12.17$ ; gender ratio of male / female was 57.58% / 42.42% homology with p> 0.05. Our subjectives were only patients with acute CI; in addition, we eliminated cases not suitable to the research (cerebral hemorrhage, CI having combined disease, similar factors risk, etc.). This is also consistent with a number of studies in the country and in the world such as: Elkind researched on the 3103 patients with CI in the community with an average age of infection was  $69.20 \pm 10.30$  and male was more dominant than female, rate of 61.9%; Koutousis studied on 114

patients with CI disease hospitalized with an average age of  $67 \pm 8$ ; research of Roudbary et al, the average age of the study patients was  $70.9 \pm 9.4$  years; study of Di Napoli on 128 CI patients with an average age of  $73.01 \pm 9.17$ , the age group with high percentage above 65 years; Le Van Thanh found that age group was 65-74.

Table 3.2 shows that hs-CRP level of patients with acute CI of 2 groups is  $6.46 \pm 4.49$  mg/l; fibrinogen concentration is  $4.59 \pm 1.52$  g/l. The results demonstrated that the concentration of serum hs-CRP and fibrinogen in patients with acute CI was significant higher than the normal value. The study also shows that the study of the concentration of hs-CRP and fibrinogen are important in the treatment and prognosis of CI in high-risk patients and may identify patients after acute CI at risk of disability, the concentration of serum hs-CRP and fibrinogen are increased in patients with acute CI and thereby reflect their concentration increases, the more CI lesions and spreadwide, the occurrence of CI. Extensive CI itself is a cause of increased levels of serum hs-CRP and fibrinogen, necrosis of infarction will stimulate liver to produce inflammatory substances such as hs-CRP and fibrinogen, fibrinogen increased impact on the clotting process and can make more widespread infarction. Our study is also consistent with studies in the country and the world:

Indeed, the study by Emre U. about the role of acute phase reactant in 43 patients with acute CI and 37 cases of control group also showed the result: average CRP levels in patients with CI was 10.5 mg/L, higher than the control group, 3.13 mg/L (p <0.01) and the association between fibrinogen levels and the severity of CI (p <0.05) and the association between fibrinogen with CRP (p <0.05), so fibrinogen and CRP are closely related, as a marker of inflammation in the acute phase of CI.

Camerlingo M. et al studied serum CRP concentrations of patients within 3 hours of onset of 387 patients with acute CI and in 387 cases of the control group. The results showed that CRP was significantly higher in patients with CI (5.0 mg/L, p < 0.0001).

Research of Di Napoli on the association between elevated CRP and fibrinogen levels in patients with acute CI showed that average fibrinogen levels at admission was 4.76 g/L, average CRP levels at the hospital was 13mg/L and on discharge was 6 mg/L, statistically significant difference compared to the control group with p <0.001. The authors also found close correlation between CRP and fibrinogen levels with r = 0.45; p <0.0001, elevated CRP levels and elevated fibrinogen levels are related to prognosis of acute CI.

Research of Le Thi Hoai Thu, Hoang Khanh also noted the results of the average hs-CRP levels of acute CI group was  $6.25 \pm 4.35$  mg/L, higher than the control group,  $0.88 \pm 0.70$  mg/L and there was a statistically significant difference with p <0.001, serum hs-CRP values predict coronary heart disease and cerebrovascular disease in the future.

Research of Paul R., Sinha P. shows the concentration of hs-CRP and fibrinogen on acute CI patients are higher than the control group ( $3.29 \pm 2.28$  vs.  $1.55 \pm 0.86$  mg/L), the concentration of fibrinogen in the patient group was  $4.48 \pm 0.51$  g/l compared with the control group was  $3.89 \pm 0.63$  g/l and have significant differences with p <0.001, considering the correlation between hs-CRP and fibrinogen, there are moderate correlation with the correlation coefficient r = 0.307; p = 0.005.

Research of Soliman RH, AA Helmy and colleagues said there is a significant difference between the levels of hs-CRP in patients with acute CI and control groups, p <0.01. CI patients with large size have higher CRP levels (4.5 mg/l) compared to patients with small and medium size (0.5 mg/l), p <0.001.

Varoglu AO, Kuyucu M et al assess the relationship between the volume of brain damage and serum fibrinogen concentration on 33 CI cases and 28 cases of cerebral haemorrage. Results showed that the concentration of fibrinogen in the first day correlated with amount of acute CI lesions (r = 0.5, p = 0.02; r = 0.4, p = 0.02; r = 0, 5, p = 0.005). Whereas, patients with cerebral hemorrhage have fibrinogen levels correlated with volume of hemorrhage lesion on the third day (r = 0.6, p = 0.04).

Thus, the inflammatory response in the acute phase activated in acute CI related to the severity of the acute CI. The results of this study demonstrated an increase in the concentration of fibrinogen, hs-CRP after acute CI and have a close relationship with each other. Reducing inflammatory factors will be beneficial for patients with acute CI and vascular diseases in future.

In Table 3.3, the concentration of serum hs-CRP and fibrinogen decreased significantly after 3 months of combination therapy Atorvastatin+Aspirin with p <0.001 and p <0.01; as well as the results in Table 3.4 also shows that the concentration of hs-serum CRP and fibrinogen decreased after 3 months of therapy alone Aspirin with p <0.01 and p <0.05. Especially our study compared the effects of two anti-inflammatory treatment group results in Table 3.5 and 3.6: effect of concentration of hs-CRP between the two groups after 1 month of treatment of group A was  $1.60 \pm 0.65$  mg/L

compared with group B was  $4.11 \pm 2.54$  mg/L; effect of serum fibrinogen concentrations after 1 month of treatment of group A was  $2.80 \pm 0.93$ g/L compared with group B was  $3.30 \pm 0.73$  g/L and have differences with p < 0.05; following 3 months of treatment, results significantly improved with effect of serum hs-CRP levels after 3 months of treatment of group A compared to group B is (t paired -3.85, p<0.01); effect of serum fibrinogen levels of group A compared to group B is (t paired -2.58, p<0.01). Research results have shown that the combination therapy Atorvastatin+Aspirin in patients with acute CI has anti-inflammatory effects by significant reduction in the concentration of inflammatory risk factors for hs-CRP, fibrinogen, and prognostic factors and the prevention of recurrence in the future.

Our study also aims to compare the treatment effect of Atorvastatin on carotid damage of patients with acute CI. Through research results in table 3.3 on the effectiveness of combination therapy Atorvastatin + Aspirin showed a markedly improved IMT damage and carotid atherosclerosis after 3 months in the order of  $1.76 \pm 0.68$  versus  $1.44 \pm 0.55$  mm;  $2.91 \pm 1.09$  versus  $2.32 \pm 0.82$  mm, which was statistically significant with p < 0.001. While in the group merely Aspirin therapy in Table 3.4 shows treatment effects on IMT and carotid atherosclerosis not improve with p < 0.01. When comparing the effects of treatment on IMT damage and carotid atherosclerosis between the 2 treatment groups, coordinate and simply, by the results in Table 3.7: effect improved markedly on IMT and carotid atherosclerosis between coordinate Atorvastatin treatment group compared with aspirin alone treatment groups, respectively (paired t -2.06, p <0.05) and (t paired -3.04, p <0.01).

Research results have shown that taking Atorvastatin in patients with acute CI has antiinflammatory effects and improved carotid atherosclerosis damage clearly, that is the risk factor and recurrence prevention factor of acute CI in the future. Especially, Atorvastatin has improved status carotid atherosclerosis (p < 0.001), one of the leading causes of acute CI, and improve clinical symptoms.

This study is consistent with several studies in the world such as:

Blanco P. et al studied on 215 acute CI patients, including 89 patients receiving atorvastatin 20 mg/ day lasted for 3 months. The results obtained were compared with 126 acute CI patients without statin therapy. The results showed that group of 89 patients taking statin reduced the risk of acute CI, mortality and reduced the average infarct volume significantly.

Study of Ridker PM. shows one of the evidence that statin treatment in patients without hyperlipidemia that CRP reduction is quite clear. Past research also suggests that aspirin and statins to lower the risk of coronary heart disease and acute CI is not merely due to anti-platelet and lipid reduction, but also due to their anti-inflammatory effects. As well as the study of Blake GJ et al also showed that statins have anti-inflammatory treatment is completely independent of its lipidlowering effect.

Research of Krupinski J. about carotid atherosclerosis, pathogenesis and treatment serum CRP concentrations in acute CI showed: high CRP concentration related with acute CI rate, the severity of disease, loss of neurological and vascular events later. CRP as well as other endothelial factor is an acute phase protein, and thus its association with cerebrovascular disease reflects the contribution of embolism due to atherosclerosis, their acute phase condition or both. The study found that many drugs, especially statins independently reduce CRP levels, improve status of carotid atherosclerosis and the clinical symptoms.

Study by Amarenco P. et al showed that IMT, LDL-C reduction reduces the relative risk for acute CI. Reduction of 10% of LDL-C estimately reduces 15.6% the risk of acute CI and IMT of caritid decreased 0.73%, study results also showed that statins reduce the risk factors for stroke.

Recently, research of carotid atherosclerosis preventing of the Texas and the U.S. Air Force (AFCAPS / TEXCAPS) studied the effectiveness of statins in primary prevention of cardiovascular disease, cerebrovascular disease in patients having low and average risk (high levels of LDL-c and CRP), statins reduce meaningfull the risk of cerebrovascular and cardiovascular disease: the relative risk of only 0.53 and 0.58.

Research of Koutouzis M. on 114 acute CI

patients with 89 men and 25 women (mean age  $67 \pm 8$  years), 53 patients (46%) were treated with statins for at least 3 months and 61 patients (54%) not treated with statins, the results showed that patients taking statins lower serum total cholesterol (172 ± 50 vs. 194 ± 35 mg / dl, p = 0.014), serum hs-CRP (1.8 [1.1 to 3.4] vs 3.4 [1.3 to 4.9] mg / l, p = 0.03).

Thus, through this study we found that: before we only known lipid-lowering effects of statins and statin treatment as a mere group of cholesterollowering drugs, recent studies in the world as well as this study found that statins not only lower blood lipids but also have anti-inflammatory effects independent of its lipid-lowering effects, and improve carotid atherosclerosis in clinical. The study also found that statins reduce the incidence of acute CI and prevent many other cardiovascular risk factors. However, this is the first step of the study with few cases, study selected and excluded many other acute CI cases according to the standard, so more research is needed on this issue in the future.

#### **5. CONCLUSION**

Combination therapy Atorvastatin and Aspirin in patients with acute CI have anti-inflammatory effects and improve the status of carotid atherosclerosis is very clear, the risk factors of CI and improve the clinical symptoms, and simultaneously, prognostic factors and recurrence prevention factors in the future.

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