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ORIGINAL ARTICLE

Physiological and Clinico- Pharmacological Study of High sensitivity C-reactive protein, as a Prognosis Biomarker in Acute Coronary Syndrome and its Level in AtherostatinTreatment

Mohammad Reza HafeziAhmadi[1], Saeed Nafisi[2],Ehsan Hosseini[*3], Ali Mohammad Bahrami[3], Someyra Miss Ghavam[4]
1-Ilam university of Medical Sciences, department of pathology, Ilam, Iran
2.Faculty of Veterinary medicine, Urmia University ,Urmia, Iran
3- Faculty of Para-Veterinary Medicine, Ilam University, Ilam, Iran
4.Cardio-vasculae Specialist, Ilam medical Hospital

ABSTRACT
Inflammatory markers such as high-sensitivity C-reactive protein (hsCRP) are elevated in Acute Coronary Syndrome (ACS), but there is little information on its relationship to prognosis ACS in association with Atherostatin usage. The current was designed to assay the relationship between hsCRP and prognosis in patients with ACS consuming Atherostatin in two different doses.90 patients hospitalized with ACS diagnosis were selected for current study. The patients were randomly divided in to two groups in respect of hsCRP level: with hsCRP under 10 and with hsCRP further than 10 and then were taken under treatment of atherostatin 40 or 80 mg for 6 months. The patient with hsCRP more than 10 was sampled again 3weeks later to rule out infectious factors that increasehs CRP. After 6 months every two groups was examined for echocardiography, electrocardiography and follow-up the status of disease. Two groups with high dose (80 mg atherostatin) and moderate dose (40 mg atherostatin) showed a totally decrease about 26 %(p<0.05) in hsCRP level after 6 month treatment with atherostatin. However, the decrease amount of hsCRP in group 40 mg was higher than in 80 mg group but the number of renewed hospitalization during 6 month in 80 mg was lower than group 40 mg. On the base of this study, it was recommended that for alleviating the risks of cardiovascular events and decreasing repetitive hospitalization, statin with high dosage would rather administer to patients with acute coronary syndrome without consideration of cholesterol and hsCRP levels. Moderate dosage of Atherostatin is proposed to use, only when the side effect of high doses may happen.
Key words: Atherostatin, Acute Coronary Syndrome, Prognosis

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INTRODUCTION

High sensitivity C reactive protein (hsCRP) is a serum protein of acute phase, synthesized by hepatocytes. Serum levels of this proteins increases during infection, inflammation and tissue damage. HsCRP is produced mainly in hepatocytes and cytokines such asIL-6 increases its release [1]. Cytokines may stimulate synthesize of hsCRP in adipose tissue resulting in elevated plasma levels of hsCRP. Infiltration of macrophages in to the adipose tissue with release of cytokines and also insulin resistance are effective factors stimulating athroma formation in obese persons [2].Therefore, high plasma level of hsCRP is one of inflammation indexes especially in visceral adipose tissue and because of it's direct relationship with obesity, insulin resistance and dislipidemia,hsCRP may also be considered as one of the indicators of cardiovascular disease and metabolic syndrome[2].On the other hand, hsCRP may represent inflammatory status of vessels. One of the new notions in cardiovascular science is that macrophage infiltration in to the athroma and secretion of proteinase or rupture of plaques can be happened as inflammatory reflex in response to atherogenic lipoproteins retention in arterial wall of Acute Coronary Syndrome (ACS) patients with widespread atherosclerosis, leading to release of cytokines and increase of hsCRP synthesis by hepatocytes [3].Furthermore, it is likely that hsCRP is locally produced by Vessel wallcellsBut itseems unlikely that such low levels of hsCRP has major role in systemic level[3].There is some evidence indicating hsCRP can cause tissue damage. HsCRP bonds to its ligands and activates

complement system then causes sedimentation of C3 (one of the elements of complement system)[4].In animal model, this reaction result in expanding of infracted region after Acute myocardial infarction(AMI)[4].C3sedimentation and activation of complement system may exacerbate atherosclerosis process [4].HsCRP level obviously elevates in MI (Myocardial infarction) patients in first six hours and continues to increase during 50 hours after beginning of ischemia. The plasma level of hsCRP is an index of prognosis including death in AMI [5]. ACS patients with low level of hsCRP due to statin treatment are in lower risk for further MI rather than patients with high level of hsCRPand even with desirable LDL amount [6].As half of MI cases have normal lipid profile ,therefore measurement of inflammatory biomarkers like as hsCRP, fibrinogen, hemocyctein is important in indication of treatment and prognosis[6].It seems that anti-inflammatory treatment including statin in patients with high level of inflammatory biomarkers affecting prognosis can reduce mortality and heart failure in these patients[7]. The present study, was designed to determine the level of hsCRP in patients with ACS before and after treatment with two dose of atherostatin 40 and 80 mg, detection of it's effect in prognosis of patients on the base of cardiac output, mortality, further hospitalization and arrhythmia and also six months follow-up of patients after treatment with atherostatin and it's relationship with serum level of hsCRP.

PATIENTS AND METHODS

A single site cross-sectional study was conducted. Utilizing Statcalc software under Epi-info program, 83 cases were selected and for avoiding from design effect, finally 90 individuals were considered for present study. At first demographical information, clinical signs and electrocardiography of patients were obtained. Patients, which have atherostatin consumption, surgery, renal, hepatic, cerebrovascular disease, and malignant tumor during the past 4 weeks, were excluded. Accordingly, 90 patients with ACS diagnosis (According to the cardiovascular disease's diagnostic criteria of ISFC/WHO) hospitalized in Mustafa Khomeini hospital (ILAM Province, Iran) was selected for current study. Written informed consent was obtained from them. 5 ml blood sample was taken from patients in the first 24 hours of admission and sent to the lab for measurement of hsCRP and other biomarkers.The patients randomly were taken under treatment of atherostatin 40 or 80 mg for 6 months. The patients were divided in to two groups in respect of hsCRP level: with hsCRP under 10 and with hsCRP further than 10.The patient with hsCRP more than 10 was sampled again 3weeks later to rule out infectious factors that increase hsCRP. After 6 months every two groups was examined for echocardiography, electrocardiography and follow-up the status of disease.

Statistical analysis

The results were expressed as mean ± SEM. Differences between means analyzed using one- sample T-test. P-values of 0.05 or less were considered as statistically significant. Data were analyzed using version 15 of SPSS software.

RESULTS

This study was done on 90 patients with ACS hospitalized in Mustafa Khomeini hospital in year 2009-2010.52.2% were woman and 47.8% were man.The majority of them were married (96.7%) and urban (68.9%).The mean age of patients was 58.97±14.56 and only 17% of studied patients was under the age of 45.55.6% of patients had high blood pressure While the18.9% of them had a history of diabetes and blood glucose lowering drugs.17.8% of the cases were smokers and only27.8% of them reported a history of hyperlipidemia. The history of premature CHD (Chronic Heart Disease) among the first degree relatives of male and female was 20% and 11.1% respectively. Among The studied persons the history of CABG*(Coronary Artery Bypass Graft)*, PTCI (Percutaneous Transluminal Coronary Intervention) and MI(Myocardial Infarction) were respectively 4.4%, 5.6% and 21.1%.The most common complaints of patients were Angina (86.7%) and dyspnea (38.9%).The most prevalent kind of MI between patients with AMI were Distal MI and (36.8%) and Anteroseptal MI (21.1%).The mean BMI (Body Mass Index) of patients was 26.67±4.11 while mean BMI of women (27.42±4.51) in time of hospitalization was higher than men. However, most patients had normal blood pressure (Systolic and Diastolic) at admission and cardiac output in patients was in the standard range.

According to table 15 and 16 more than two-thirds of persons in the group treated with 40 mg of statin had hsCRP higher than 3 in the time of hospitalization

Whereas in group 80 mg, half of the individuals had hsCRP higher than 3.After treatment, cases in group40 with hsCRP higher than 3 showed 50% decrease in hsCRP whilst individuals with same condition in group 80 exhibit only 24.3% in hsCRP. The decreasing amount of hsCRP in group 40 was higher than group 80.There was no significant relationship between atherostatin and the level of hsCRP. Number of readmissions in group 80 during 6 month was lower than group 40. The correlation coefficient of phi between readmissions and arrhythmias on hospitalization approximately was %25(r=0.562)

exhibiting that with increasing of arrhythmias, the readmissions would elevate in patients whereas in group 80 there was not such significant relation (the phi coefficient was %4, r=0.293).There was not any report indicating hepatic enzymes elevation or myopathy during follow-up period in treatment groups. None of the subjects refused from study during the6 months and also, no mortality were reported due to cardiovascular side effects.

Table1.Frequency of subjects by sex**, residence** and marital status(Most of the patients(52.2%) were female, married (96.7%) and live in urban areas(68.9%))

Percentage	Abundance	Population studied
		Sex(N=90)
47.8%	43	Man
52.2%	47	Woman
		Residence
68.9%	62	City
31.1%	28	Village
		Marital status
3.3%	3	Single
96.7%	87	Married

Table2. The relative abundance of subjects according to age groups (The mean age of patients was58.97±14.56 and most of them was up to 45 years old)

>65	55-65	45-55	<45	Age / Sex
24.4	12.2	39	24.4	Man
40.4	23.4	25.5	10.6	Woman
33	18.2	31.8	17	Total

Table 3.Frequency and relative abundance of subjects based on history of hypertension

Without History of Hypertension		With History of Hypertension		
relative abundance	Frequency	relative abundance	Frequency	Sex
69.8%	30	30.2%	13	Man
42.6%	20	57.4%	27	Woman
55.6%	50	44.4%	40	Total

Table4. Subjects in terms of frequency and relative frequency of diabetes (Only18.9% of subjects had diabetes)

Without diabetes		With diabetes		
Relative abundance	Frequency	Relative abundance	Frequency	Sex
29.8%	40	7%	3	Man
70.2%	33	29.8%	14	Woman
81.1%	73	18.9%	17	Total

Table5.Frequency and Relative abundance of Subjects based on smoking history (The majority of patients(82.2%) were not smokers)

Non-smokers		Smoker		
relative abundance	Frequency	relative abundance	Frequency	Sex
76.7%	31	23.3%	12	Man
91.5%	43	8.5%	4	Woman
82.2%	74	17.8%	16	Total

Table6.Frequencyandrelativeabundanceofsubjectsbased on the history of hyperlipidemia (More than two-thirds of cases(72.2%) were Without of History of hyperlipidemia).

Without History of hyperlipidemia		With History of hyperlipidemia		Sex
relative abundance	Frequency	relative abundance	Frequency	
76.7%	33	23.3%	10	Man
68.1%	32	31.9%	15	Woman
72.2%	65	27.8%	25	Total

Table 7.Frequency and relative abundance of subjects based on history of heart disease in men of family (Only20% of subjects history of heart disease in men of family)**.**

Without History of heart disease		With History of heart disease		Sex
relative abundance	Frequency	relative abundance	Frequency	
79.1%	34	20.9%	9	Man
80.9%	38	19.1%	9	Woman
80%	72	20%	18	Total

Table8. Frequency and relative abundance of subjects based on history of heart disease in women of family (Only11.1% of subjects had history of heart disease in women of family)**.**

Without History of heart disease		With History of heart disease		Sex
relative abundance	Frequency	relative abundance	Frequency	
90.7%	39	9.3%	4	Man
87.2%	41	12.8%	6	Woman
88.9%	80	11.1%	10	Total

Table9.Frequency and relative abundance of subjects based on **CABG (***Coronary Artery Bypass Graft)* **(**Only4patients(4.4%), had a history of CABG**).**

Without History ofCABG		With History of CABG		Sex
relative abundance	Frequency	relative abundance	Frequency	
97.7%	42	2.3%	1	Man
93.6%	44	6.4%	3	Woman
95.6%	86	4.4%	4	Total

Table10.Frequency and relative abundance of subjects based on **PTCI (Percutaneous Transluminal Coronary Intervention) (**Only5patients (5.6%) had the history of the PTCI**).**

Without History of PTCI		With History of PTCI		Sex
relative abundance	Frequency	relative abundance	Frequency	
95.3%	41	4.7%	2	Man
93.6%	44	6.4%	3	Woman
94.4%	85	5.6%	5	Total

Table11.Frequency and relative abundance of subjects based on MI (Myocardial Infarction) **(**Only 21.1% of patients had a history of theMI).

Without History of PTCI		With History of PTCI		Sex
relative abundance	Frequency	relative abundance	Frequency	
65.1%	28	34.9%	15	Man
91.5%	43	8.5%	4	Woman
78.9%	71	21.1%	19	Total

Table12.Frequencyandrelativeabundanceofsubjectsbasedsite of MI in AMI (*Acute Myocardial Infarction).*(Majority of patients hospitalized due to MI had Inferior and Anterior MI respectively) .

Without MI in mentioned Site		With MI in mentioned Site		site of MI
relative abundance	Frequency	relative abundance	Frequency	
63.2%	12	36.8%	7	**Inferior**
73.7%	14	26.3%	5	**Anterior**
94.7%	18	5.3%	1	**Septal**
78.9%	15	21.1%	4	**Antroseptal**
94.7%	18	5.3%	1	**Lateral**
89.5%	17	10.5%	2	**Antrolateral**
78.9%	71	21.1%	19	Total

Table13.Frequency and relative frequency of signsinthe subjects (The most common complaint of patients hospitalized **were** Angina(**86.7%)** and dyspnea in rest(**38.9%)).**

Without mentioned sign		With mentioned sign		signs
relative abundance	Frequency	relative abundance	Frequency	
13.3%	12	86.7%	78	**Angina in rest**
83.3%	75	16.7%	15	Nausea
87.8%	79	12.2%	11	Vomiting
61.1%	55	38.9%	35	Dyspnea in rest
74.4%	67	25.6%	23	Epigasteric Pain
77.8%	70	22.2%	20	Dizziness
71.1%	64	28.9%	26	Cold sweat
81.1%	73	18.9%	17	*Heart-throb*
82.2%	74	17.8%	16	**Angina in activity**
82.2%	74	17.8%	16	Dyspnea in activity

Table14. Abundance **of** signs ofheart disease insubjects (Most of the patientshad aBMI and EFinthe normal range).

Total	Women	Men	Sign
26/67±4/11	27/42±4.51	25.69±3.33	**Body mass Index(BMI)**
78/26±18/43	80/46±21/80	75.70±13.36	**Heart beet**
126/59±26/83	130/73±26.83	121.68±23.25	**Systolic blood pressure(mmHg)**
77/48±14/94	78/65±15/01	76.08±14.94	**Diastolic blood pressure(mmHg)**
47/00±6/44	46/82±7/22	47.24±5.27	**Ejection fraction(EF)**

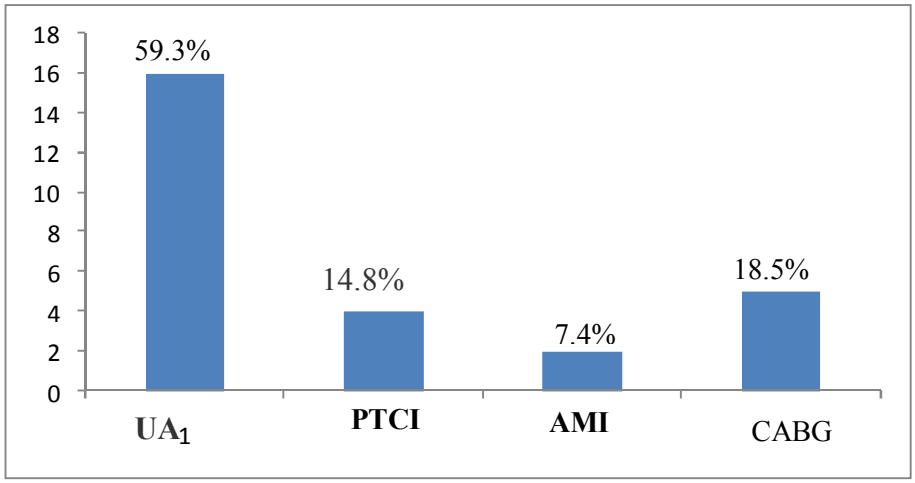
Table15.Quality comparison of hsCRP before and after treatment with statin 40 and 80 mg.

After Treatment			Before Treatment				
Total	Woman	Man	Total	Woman	Man		
35.7%	33.3%	40%	11.6%	13.6%	9.5%	<1	Statin 40mg
42.9%	44.4%	40%	16.3%	18.2%	14.3%	1-3	
21.4%	22.2%	20%	72.1%	68.2%	76.2%	>3	
11.1%	_	16.7%	10.3%	6.7%	14.3%	<1	Statin 80mg
55.6%	66.7%	50%	31%	33.3%	28.6%	1-3	
33.33	33.3%	33.3%	58.6%	60%	57.1%	>3	

Table 16.Quantitative comparison of hsCRP before and after treatment with statin40 and 80 mg.

After Treatment			Before Treatment			
Total	Woman	Man	Total	Woman	Man	
2.17±2.2[ab]	2.34±2.59	1.88±1.44	23.52±50.73[b]	34.6±66.39	11.32±19.56	Statin 40mg
22.74±10.56[a]	2.76±2.00	14.45±27.77	17.18±32.72	37.69±37.69	15.28±27.73	Statin 80mg

Fig 1.The number, percent and cause of renewed hospitalization during 6 month of study,UA(Unstable Angina)PTCI(Percutaneous Transluminal Coronary Intervention),AMI(Acute Myocardial Syndrome),CABG(Coronary artery bypass surgery)



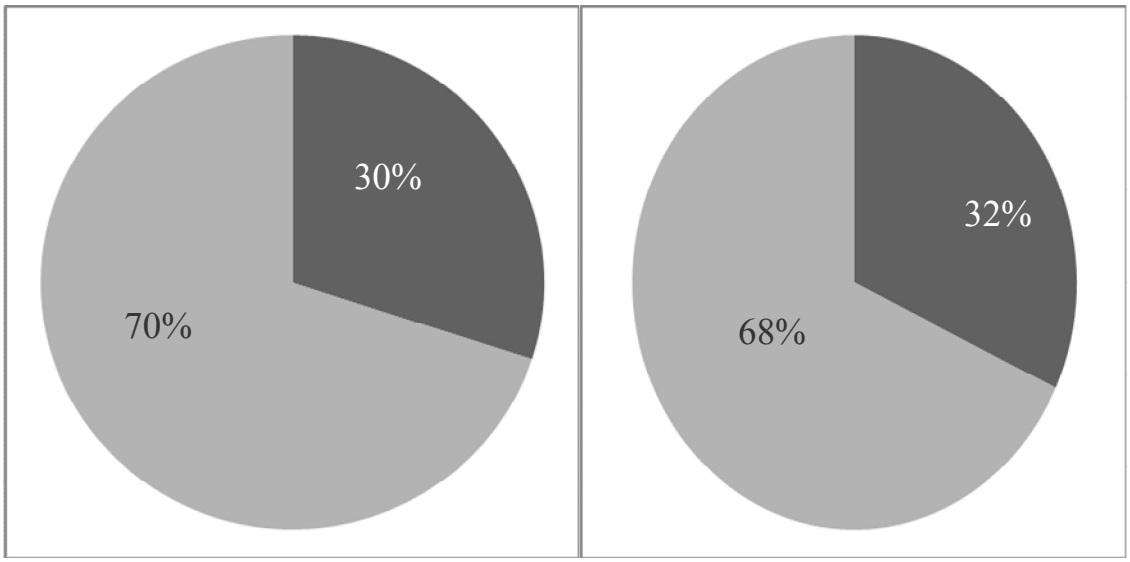


Fig.1.Relative abundance of renewed hospitalization in all studied cases

Fig.2.Relative abundance of renewed hospitalization of studied cases in 6 months following in Atherostatin treated groups

Table18. Relation between hsCRP and lipid profile.

Group1(Atherostatin 40mg)					Group2(Atherostatin 80mg)		
		UA(n=37)	AMI(n=8)	P Value	UA(n=34)	AMI(n=11)	P Value
hsCPR	<1	11.4%	21.5%	0.38	12%	-	0.19
	1-3	20.0%	-		36%	-	
	>3	68.6%	87.5%		52%	100%	
HDL	>50	73.5%	100%	0.30	75%	37.5%	0.09
	35-50	20.6%	-		20.8%	37.5%	
	<35	5.9%	-		4.2%	25%	
LDL	<35	5.9%	-	0.81	4.2%	-	0.50
	<70	11.8%	14.3%		66.7%	87.5%	
	70-130	55.9%	42.9%		29.2%	12.5%	

DISCUSSION

Effectiveness of lipid-lowering drugs, especially statins in prevention of primary and secondary coronary heart diseases was well documented. Therefore, recent studies have been focused on effective dose of statinson reduction of hsCRP levels and it's effectiveness on short- term and long-term follow-up of heart disease. It seems strict treatment with high doses of statins has better outcomes in reduction levels of hsCRP and prognosis of cardiovascular disease. In our study, effect of statins in lowering the levels of hsCRP and cardio-vascular prognosis on 90 patients hospitalized due to acute coronary syndrome in shahidmostafa Khomeini hospital (ILAM, Iran) during 2010 to 2011 was evaluated. Two groups with high dose (80 mg atherostatin) and moderate dose (40 mg atherostatin) showed a totally decrease about 26%($p<0.05$) in hsCRP level after 6 month treatment with atherostatin, on other hand in group of moderate dose two-third of cases has hsCRP higher than 3, exhibited 50% in hsCRP decrease and half of cases in high dose group has hsCRP higher than 3 that after treatment showed 24.3% falling in hsCRP level. This different result may be due to higher levels of hsCRP in moderate dose (40 mg atherostatin). A study was performed by NesarHosein and et al, short term treatment with atherostatin in three doses 20, 40 and 80 mg in patients with acute coronary syndrome was evaluated in this research that final decrease in hsCRP level in dose 40 mg was 30% after 6 month treatment and with dose of 80 mg was 40%[8], that showed the amount of decrease was higher than our study.However, the decrease amount of hsCRP in group treated with 40 mg atherostatin was higher than in 80 mg atherostatin group but the number of renewed hospitalization during 6 month treatment with 80 mg was lower than in group treated with40 mg. Also the correlation coefficient of fee and Cramer between renewed hospitalization and aretmia in start of hospitalization was positive and approximately 25%, representing the higher cases of aretmia the more cases of hospitalization. the correlation coefficient of fee and Cramer in group 80 atherostatin was positive and very low and only showed 4% correlation between data.Ridker and et al assayed the effect of Rosuvastatin in prevention from cardiovascular complications in women with CRP higher than 2mg/dL and LDL lower than 130 mg/dL [9]. This study showed Rosuvastatin was statistically effective in prevention of cardiovascular disease ($P<0.0001$) and also the rate of revascularization in treatment group was lower than placebo. Also Kandas and et al reported the considerably useful effect of atherostatin with dose 40 on cardiovascular complication and lipid profile [10]. In this research hsCRP level was less than of hospitalization starting ($P<0.001$) and also the LDL level decreased considerably. In a research fulfilled by Rosendo and et al on patients with high, moderate and mild risk of cardiovascular disease, it was not found profitable results from Simvastatin administration in decreasing hsCRP level [11] .Cannon and et al reported that however Atherostatin or Simvastatin with dose of 80 was along with attenuating the risk of cardiovascular events ($P<0.001$) and death ($P<0.001$), but it was concomitant with side effect of statins consumption [12]. Therefore the moderate dose of statins is preferred for treatment choice in most cases and higher doses is considered for patients with high risk of cardiovascular complication.In the present study high dose of atherostatin decreased the hsCRP level less than of moderate dose in 6 month following of patient and there was not reported any side effect of statin dose which is somewhat due to lack of complete information of patients aboutharmful effects of atherostatin dose or lack of correct reporting.

CONCLUSION

Previous studies represented that with increasing the dose of statin, thedecreasing amount of hsCRP was falled but the risk of cardiovascular complication was lowered. In our study, decreasing of hsCRP in Atherostatin 40 mgwas higher than of Atherostatin 80 during 6 month period; however atherostatin 40 mg did not improve cardiovascular risk prognosis. Therefore, it seems that starting Atherostatin administration at primary stages of hospitalization, being independently from the rate of decreasingthe hsCRPand cholesterol, is able to improve cardiovascular prognosis and decrease repetitive hospitalization and electrocardiography alterations. On the base of this study, it was recommended that for alleviating the risks of cardiovascular events and decreasing repetitive hospitalization, statin with high dosage would rather administer to patients with acute coronary syndrome without consideration of cholesterol and hcCRPlevels.Moderate dosage of Atherostatinis proposed to use, onlywhen the side effect of high doses may happen.

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