Original Article

EFFECT OF ROSUVASTATIN ON LEFT VENTRICULAR REMODELING IN PATIENTS WITH ELEVATED HS-C REACTIVE PROTEIN AFTER FIRST ST SEGMENT ELEVATION MYOCARDIAL INFARCTION (STEMI)

Kamran Rashid[a*], Irfan Majeed[b], Abdul Sattar[a], Nadeem Hayat Mallick[a]

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ABSTRACT:

OBJECTIVE: To assess the anti-inflammatory role of high dose Rosuvastatin therapy on post MI LV remodeling (LVR) in patients suffering from first ST segment elevation MI (STEMI).

MATERIALS AND METHODS: The study was conducted at the Cardiology Department, Punjab Institute of Cardiology, Lahore which is a 347 bedded tertiary care hospital dedicated to cardiac patients only from January 2016 till July 2016 (6 months).

Overall 120 patients presenting with first ST segment elevation MI, having Hs CRP level >3mg/l, were studied. These patients were divided into two groups on the basis of Rosuvastatin therapy, Group I: 60 patients having CRP levels >3mg/L received Rosuvastatin 20mg daily and Group II: 60 patients having CRP levels >3mg/L received Rosuvastatin 40mg daily. Patients were consented before start of the study. All patients underwent echocardiography for LV remodeling prior to discharge at 72 hours of admission and at 06 months follow-up. Occurrence of LVR on 6 months follow up was noted for every patient in the two groups. Any patient lost to follow-up was excluded.

RESULTS: Mean age of patients in Group I was 57.4±12.6 years while it was 56.6±12.3 years for Group II patients with non significant association. The proportion of males and females was similar in the two groups as there were 42(71.7%) males and 17(28.3%) females in Group I and there were 45(75%) males and 15(25%) females in Group II (p value 0.8415). There were more smokers 25(41.6%) in Group I as compared to 22(36.7%) Group II (p value 0.708). Diabetes mellitus was observed in similar proportions in the two groups as there were 21(35%) diabetics in Group II vs. 20(33.3%) in Group I (p value 1.00). Hypertension was present in 29(48.3%) in Group II and 28(46.6%) in Group I (p value 1.00). History of coronary artery disease was present in 22(36.7%) in Group II and it was 20(33.3%) in Group I (p value 0.841). Family history of coronary artery disease was 20(33.2%) in Group II and it was 19(31.6%) in Group I (p value 1.00). Dyslipidemia was 21(35%) in Group II and 20(33.3%) in Group I (p value 1.00). Stress was present in 9(15%) in Group II and 7(11.7%) in Group I.

Echocardiography done during admission revealed mean left ventricular end-diastolic volume (LVEDV) of 119.2±29.3 ml in Group I and it was 118.6±31.4 ml in Group II (p value 0.941). Mean left ventricular end-systolic volume (LVESV) was 67.1±22.4 ml in Group I and 69.5±24.3 ml in Group II (p value 0.8744). Mean ejection fraction was 42.3±6.3 for Group I and 41.5±8.4 for Group II (p value 0.96). Mean S' was similar in the two groups. E/E and E/E' ratios were similar in the two groups with non significant association. Mean Left ventricular mass was 143.2±36.2 gm in Group I and 142.4±33.6 gm in Group II. Mean Wall motion score Index was also similar in both groups. 06(10%) patients died in group I during hospital stay and 05 (8.3%) patients died in group II (p value 1.00). LVEDV increased from 119.2±29.3 to 122.4±26.3 (p value 0.049) in group I, while in group II LVEDV increased from 118.6±31.4 to 120.3±28.3 (p value 0.053).

CONCLUSION: There was trend towards lower mortality in high dose statin therapy as compared to moderate dose statin therapy during acute phase of STEMI. Furthermore high dose statin therapy leads to attenuation of inflammatory activity and hence lesser left ventricular remodeling at six months post MI follow-up.

KEY WORDS: Rosuvastatin, Left ventricle remodeling, HS-C reactive protein, ST elevation myocardial infarction.

[a]Punjab Institute of Cardiology, Lahore Pakistan.
[b]Waziarabad Institute of Cardiology, Waziarabad.

* Corresponding author:
Email:drskrashid@yahoo.com

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INTRODUCTION:

In acute myocardial infarction there is inflammatory response of the body. CRP is a marker of inflammation. It rises after first hour of MI and maximizes on second day [1]. As a result of which the damage is followed by repair process [2]. Increased levels of CRP are associated with increased mortality and morbidity [3]. Left ventricular remodeling often complicates acute STEMI. Damage due to acute MI is followed by remodeling influenced by mechanical neuro-hormonal and genetic mechanisms [4]. The heart dilates and becomes elliptical as a part of remodeling process [5]. LV remodeling, goes on well beyond the acute phase, for months and even years afterwards.

OBJECTIVE:

To assess the anti-inflammatory effects of high dose Rosuvastatin therapy on post MI left ventricular remodeling (LVR) in patients suffering from first ST segment elevation MI (STEMI).

INCLUSION CRITERIA:

Characteristic ischemic chest pain, duration of symptoms <12 h before hospital admission, ECG criteria of acute STEMI and all patients receiving Streptokinase therapy followed by standard post MI regimen including antiplatelets, beta blockers and ACE inhibitors.

EXCLUSION CRITERIA:

- History of revascularization.
- Patient in shock.
- Heart failure (class III or IV).
- LBBB.
- Atrial fibrillation.
- History of valvular heart disease.
- Idiopathic cardiomyopathy.
- High blood pressure, i.e. B.P.>180/110.
- Raised serum creatinine level >176.8 mmol/l.
- Acute or chronic infections causing raised CRP levels.
- Chronic inflammatory diseases/Autoimmune diseases on admission.
- Use of steroids or immunosuppressive drugs.
- Patients having previous h/o MI.

OPERATIONAL DEFINITIONS:

Left Ventricular remodeling (LVR):

LVR is defined according to the previously validated criterion that is >20% increase in end-diastolic left ventricular volume (LVEDV) by echocardiography seen at 6-month follow-up compared with the baseline.

C-reactive protein (CRP):

Normal CRP level is 0mg/L to 10 mg/L and hs CRP <3mg/L.

MATERIALS AND METHODS:

The study was conducted at the Cardiology Department, Punjab Institute of Cardiology, Lahore which is a 347 bedded tertiary care hospital dedicated to cardiac patients only from January 2016 till July 2016 (6 months).

Overall 120 patients presenting with first ST segment elevation MI, having Hs CRP level >3mg/l, were studied. Patients were divided into two groups on the basis of Rosuvastatin therapy, Group I: 60 patients having CRP levels >3mg/L received Rosuvastatin 20mg daily and Group II: 60 patients having CRP levels >3mg/L received Rosuvastatin 40mg daily.

Patients were consented before the start of study. History, physical examination and Echocardiography were performed. All patients received streptokinase therapy provided they did not have any contraindications to this therapy i.e. history of cerebro-vascular accident, bleeding peptic ulcer or uncontrolled hypertension (blood pressure more than 180/110 mm of Hg). Streptokinase was provided free of cost to all patients. All patients were treated according to the treatment protocol of the Cardiology Department. After reperfusion therapy all patients received same pharmacotherapy as per guidelines during hospital stay and afterwards. Baseline Lab. Investigations including LFTs and fasting lipid profile were done before discharge. Patients with higher lipid profile levels were assembled preferably in group that receive Rosuvastatin 40mg/day. Patients were closely and regularly monitored for side effects of Rosuvastatin especially for hepato toxicity and rhabdomyolysis. Patients developing more than three times higher levels of LFT,s and CK were dropped out of study. Regular follow up contact with study population was observed through periodic phone calls and home visit if necessary. Twenty additional patients were added to original sample size in order to compensate the anticipated drop out.

The primary endpoint was LVR and secondary endpoints were mortality and post MI complications. Date and time of death were noted in case of mortality. Mechanical complications were left ventricular failure (LVF), cardiogenic shock, mitral regurgitation and post MI ventricular septal defect (VSD), while electrical complications were heart blocks, 1st degree, 2nd degree or complete AV block and ventricular tachycardia or ventricular fibrillation.

During hospital stay all patients were followed

up daily. On 6 month follow up mortality and post MI complications were noted for all patients and compared between Group I & Group II.

All patients underwent echocardiography for LV remodeling prior to discharge at 72 hours of admission and at 6months follow-up. Occurrence of LVR on 6 months follow up was noted for every patient in the two groups. Any patient lost to follow-up was excluded.

SPSS 20.0 was used to analyze the data. Mean ± S.D were given for quantitative (age, CRP level, clinical and lab investigation, Echocardiography findings, etc.) variable. Frequencies and percentages were given for qualitative variables (gender, wall motion, risk factors, mortality, mechanical complication, electrical complications). Two independent sample t tests were applied to observe groups mean differences in quantitative variables i.e. age, CRP level and left ventricular remodeling (LVR). Pearson Chi-Square test was applied to observe the association of qualitative variables like risk factors, hospital mortality and morbidity between the two groups. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS:

Mean age of patients in Group I was 57.4±12.6 years while it was 56.6±12.3 years for Group II patients with non significant association. Table 1. The proportion of males and females was similar in the two groups as there were 42(71.7%) males and 17(28.3%) females in Group I and there were 45(75%) males and 15(25%) females in Group II (p<0.06). There were more smokers 25(41.6%) in Group I as compared to 22(36.7%) in Group II (p value 0.708). Diabetes mellitus was observed in similar proportions in the two groups as there were 21(35%) diabetics in Group II vs. 20(33.3%) in Group I (p value 1.00). Hypertension was present in 29(48.3%) in Group II and 28(46.6%) in Group I (p value 1.00). History of coronary artery disease was present in 22(36.7%) in Group II and it was 20(33.3%) in Group I (p value 0.841). Family history of coronary artery disease was 29(33.2%) in Group II and it was 19(31.6%) in Group I (p value 1.00). Dyslipidemia was 21(35%) in Group II and 20(33.3%) in Group I (p value 1.00). Stress was present in 9(15%) in Group II and 7(11.7%) in Group I. Table 1

Mean time from the beginning of symptoms till arrival to the hospital was 6.4±3.6 hours for Group I patients while it was 6.8±3.8 hours for Group II patients. Anterior wall myocardial infarction (AWMI) occurred in 35(58.3%) patients in Group I and 37.7% patients in Group II followed by Inferior wall myocardial infarction (IWMI) in 20(33.3%) in Group I and 19(31.7%) in Group II (p value 0.909). Table 1.

Mean CRP level was similar in the two groups, it was 8.4±3.9 in Group I and 8.3±3.6 in Group II. Table 2. Peak CK MB was also similar in the two Groups. Mean peak Trop T was 250.1±12.4 in Group I and 246.3±13.4 in Group II (p value 0.846). Mean cholesterol was higher in Group II 198.6±39.5 vs 195.9±38.8 in Group I (p valye 0.987). Mean Triglycerides were 197.3±142.3 in

Table 1 Baseline demographic characteristics.

Characteristics		Group I Rosuvastatin 20mg n=60	Group II Rosuvastatin 40mg n=60	p value
Age		57.4±12.6	56.6±12.3	0.7522
Gender	Male Female	43(71.7%) 17(28.3%)	45(75%) 15(25%)	0.8415
Smoking		25(41.6%)	22(36.7%)	0.7083
Diabetes Mellitus		20(33.3%)	21(35%)	1.000
Hypertension		28(46.6%)	29(48.3%)	1.000
H/O CAD		20(33.3%)	22(36.7%)	0.8415
F/H IHD		19(31.6%)	20(33.3%)	1.000
Dyslipidemia		20(33.3%)	21(35%)	1.000
Stress		7(11.7%)	9(15%)	0.791
Time from onset till arrival to hospital mean hours		6.4±3.6	6.8±3.8	0.555
Site of MI	AWMI IWMI Lat MI	35(58.3%) 20(33.3%) 5(8.3%)	37(61.7%) 19(31.7%) 4(6.7%)	0.9094
Streptokinase		60(100%)	60(100%)	1.0

AWMI=Anterior wall myocardial infraction; IWMI=Inferior wall myocardial infarction; LAT MI=Lateral wall myocardial infarction

Table-2: Laboratory parameters.

Characteristics	Group I Rosuvastatin 20mg n=60	Group II Rosuvastatin 40mg n=60	p value
CRP level mean	8.4±3.9	8.3±3.6	0.947
Peak CK MB	132.3±74.8	131.5±72.9	0.9268
Peak Trop T mean units	250.1±12.4	246.3±13.4	0.8466
Cholesterol mean mg/dl	195.9±38.8	198.6±39.5	0.9877
Triglyceride mean mg/dl	195.7±150.3	197.3±142.3	0.844
LDLC mean mg/dl	86.3±53.8	87.4±57.2	0.9711
HDLC mean mg/dl	35.1±17.8	41.1±33.2	0.2198
RBS mean mg/dl	172.5±22.6	177.6±21.5	0.2078

CRP=C reactive protein; CK MB=Creatine kinase MB fraction; LDLC=Low density lipoprotein; HDLC=High density lipoprotein; RBS=Random blood sugar

Table-3: Initial Echocardiographic variables and inhospital outcome.

Characteristics	Group I Rosuvastatin 20mg n=60	Group II Rosuvastatin 40mg n=60	p value
LVEDV	119.2±29.3	118.6±31.4	0.941
LVESV	67.1±22.4	69.5±24.3	0.8744
LVEF	42.3±6.3	41.5±8.4	0.9612
S'	6.87±7.2	6.9±7.1	0.9617
E/A Ratio	0.84±1.2	0.82±1.3	0.9304
E/E' Ratio	9.6±10.3	9.5±11.7	0.9604
LVM	143.2±36.2	142.4±33.6	0.923
Wall Motion Score Index	1.6±0.34	1.6±0.35	1.00
Mortality	6(10%)	5(8.3%)	1.000
VSR MR LV Pump Failure LV Aneurysm	0 4(6.7%) 5(8.3%) 5(8.3%)	0 3(5%) 4(6.7%) 4(6.7%)	0.999
Electrical complications VT VF Asystole Heart Block	 1(1.7%) 2(3.3%) 1(1.7%) 2(3.3%)	 1(1.7%) 1(1.7%) 2(3.3%) 1(1.7%)	0.802

LVEDV=Left ventricle end diastolic volume; LVESV=Left ventricle end systolic volume; LVEF=Left ventricle ejection fraction; LVM=Left ventricle mass; LV=Left ventricle; MR=Mitral regurgitation; VT=Ventricular tachycardia; VF=Ventricular fibrillation

Table-4:Six month follow-up lipid profile.

Characteristics	Group I Rosuvastatin 20mg n=60	Group II Rosuvastatin 40mg n=60	p value
Cholesterol mean mg/dl	130.3±19.6	129.1±20.4	0.7413
Triglyceride mean mg/dl	140±105.3	134.9±99.4	0.786
LDLC mean mg/dl	63.2±25.2	65.1±23.5	0.675
HDLC mean mg/dl	38.2±11.2	43.1±12.1	0.0231

LDLC=Low density lipoprotein; HDLC=High density lipoprotein

Group II and it was 195.7±150.3 in Group I (p value 0.844). Mean low density lipoprotein cholesterol (LDLC) was 87.4±57.2 in Group II and it was 86.3±53.8 in Group I (p value 0.971). Mean high density lipoprotein cholesterol (HDLC) was 41.1±33.2 in Group II and it was 35.1±17.8 in Group I with (p value 0.21). Mean random blood sugar at the time of presentation was 177.6±21.5 mg/dl in Group II and it was 172.5±22.6 mg/dl in Group I (p value 0.207). Table 2

Echocardiography done revealed mean left ventricular end-diastolic volume (LVEDV) of 119.2±29.3 ml in Group I and it was 118.6±31.4 ml in Group II (p value 0.941). Mean LV end-systolic volume (LVESV) was 67.1±22.4 ml in Group I and 69.5±24.3 ml in Group II (p value 0.874). Mean Left ventricular ejection fraction was 42.3±6.3 for Group I and 41.5±8.4 for Group II (p value 0.96). Mean S' was similar in the two

Table-5:Six month follow-up Echocardiographic variables and follow-up outcome.

Characteristics	Group I Rosuvastatin 20mg n=60	Group II Rosuvastatin 40mg n=60	p value
LVEDV	122.4±26.3	120.3±28.3	0.6745
LVESV	68.2±21.4	66.4±22.4	0.6535
LVEF	43.4±7.4	41.3±7.2	0.1178
S'	6.72±7.1	6.6±7.3	0.9272
E/A Ratio	0.82±1.1	0.83±1.3	0.9638
E/E' Ratio	9.4±11.3	9.5±10.7	0.9604
LVM	145.3±33.1	144.4±31.6	0.876
Wall Motion Score Index	1.6±0.32	1.6±0.35	1.000
LVR	13(21.7%)	11(18.3%)	0.8233
Mortality	1(1.7%)	1(1.7%)	1.00
Mechanical complications VSR MR LV Pump Failure LV Aneurysm	 0 5(8.3%) 4(6.7%) 5(8.3%)	 0 4(6.7%) 4(6.7%) 4(6.7%)	0.9952

LVEDV=Left ventricle end diastolic volume; LVESV=Left ventricle end systolic volume;
LVEF=Left ventricle ejection fraction; LVM=Left ventricle mass;
LVR=Left ventricle remodeling; LV=Left ventricle; MR=Mitral regurgitation

groups. E/E and E/E' ratios were similar in the two groups with non significant association. Mean Left ventricular mass was 143.2±36.2 gm in Group I and 142.4±33.6 gm in Group II. Mean Wall motion score Index was also similar in the two groups (Table 3). LVEDV increased from 119.2±29.3 to 122.4±26.3 (p value 0.049) in group I, while in group II LVEDV increased from 118.6±31.4 to 120.3±28.3 (p value 0.053).So there is significant increase in LVEDV in group I.

In-hospital mortality was higher in Group I 6(10%) as compared to Group II 5(8.3%) (p value1.00). Mitral regurgitation was seen in 4(6.7%) patients in Group I and 3(5%) patients in Group II. LV pump failure occurred in 5(8.3%) patients in Group I and 4(6.7%) patients in Group II. LV aneurysm was seen 5(8.3%) patients and 4(6.7%) patients in Group II (p value 0.99). Ventricular tachycardia occurred in one patient in each group. Ventricular fibrillation occurred in 2(3.3%) patients in Group I and 1(1.7%) patients in Group II.

Asystole occurred in 1(1.7%) patient in Group I and 2(3.3%) patients in Group II. Heart block occurred 2(3.3%) patients in Group I and 1(1.7%) patient in Group II (p value 0.802). Table 3

On six months of followup mean cholesterol was lower in Group II 129.1±20.4 vs 130.3±19.6 in Group I (p value 0.74). Mean Triglycerides was lower 134.9±99.4 in Group II and it was 140±105.3 in Group I (p value 0.786). Mean LDLC was 65.1±23.5 in Group II and it was

63.2±25.2 in Group I (p value 0.675). Mean HDLC was 43.1±12.1 in Group II and it was 38.2±11.2 in Group I with (p value 0.0231). Table 4

At six months followup mean left ventricular end-diastolic volume (LVEDV) was 122.4±26.3 ml in Group I and it was 120.3±28.3 ml in Group II (p value 0.674). Mean left ventricular end-systolic volume (LVESV) was 68.2±21.4 ml in Group I and 66.4±22.4 ml in Group II (p value 0.65). Mean Left ventricular ejection fraction was 41.3±7.2 for Group II and 43.4±7.4 for Group I (p value 0.117). Mean S' was similar in the two groups. E/E and E/E' ratios were similar in the two groups with non significant association. Mean Left ventricular mass was 145.3±33.1 gm in Group I and 144.4±31.6 gm in Group II (p value 0.876). Mean Wall motion score Index was also similar in the two groups. LV remodeling occurred less in Group II 11(18.3%) as compared to 13(21.7%) patients in Group I (p value 0.823). Table 5

On six months followup one patient died in each group. None of the patients had ventricular septal rupture on six months followup. Mitral regurgitation was seen in 5(8.3%) patients in Group I and 4(6.4%) patients in Group II. LV pump failure occurred in 4(6.7%) patients in Group I and 4(6.7%) patients in Group II. LV aneurysm was seen in 5(8.3%) patients in Group I and 4(6.7%) patients in Group II (p value 0.995). Table 5

DISCUSSION:

Release of inflammatory mediators lead to LV dysfunction, aneurysm formation and rupture. [1,2] Inflammation also effects non-infracted myocytes and coronary arteries.

In the current study LV remodeling occurred less in Group II (high dose statin group Rosuvastatin 40mg) as compared to patients in Group I (Moderate dose statin group Rosuvastatin 20mg).

This study has first time being done in this area which linked CRP concentration with post-infarct LV remodeling. We only included STEMI patients. Other studies included patients with acute coronary syndromes [6-8]. There is different mechanism and magnitude of rise in CRP levels in patients with STEMI vs. stable or unstable angina patients. [9,10]. In angina (stable or unstable) CRP levels reflect plaque vulnerability and in MI it predicts necrosis [11].

Aggelopoulos et al. investigated the relationship between level of CRP rise and left ventricle systolic dysfunction in patients admitted with acute ischemic event [6]. In this study there was significant increase (6%) in risk of LVSD in patients with raised CRP level i.e 10 mg/L.

Ørn et al. in his study showed raised level of CRP (at two days and one week) correlates with the LVEF measured by MRI.[12] Furthermore Uehara et al. showed a high association between the LVEF at 1 month after STEMI and peak in-hospital CRP levels. The conclusions in various studies may vary due to multiple confounding factors.[13] For example Brunetti et al. included unstable angina patients, so results showed lack of association between CRP levels and LV ejection fraction[8]. Our study showed that the patients who had raised CRP levels were also having LVSD. Similar to our findings, Arruda-Olson et al. showed comparable values of LVEF and WMSI in tertiles of CRP measured at 6.1 h after symptom onset [7]. Whereas, Suleiman et al., measured CRP 12–24 h after symptom onset, found inverse relations between CRP concentration and both LVEF and WMSI in patients with acute MI [3].

We observed LV remodeling (LVR) occurred in 11(18.3%) patients in Group II as compared to 13(21.7%) patients in group I, it is still an unsettled issue whether CRP directly relates to post-infarct LVSD and a potential therapeutic target, or it just shows an increased risk for untoward events[14,15]. Evidence suggests that CRP reflects both pronecrotic and proatherogenic features. Firstly, CRP binds to phosphocholine groups of necrotic cell membranes, leading to complement activation and inflammatory response, injury to the myocytes and increase in area of necrosis[16]. Secondly, increased CRP level was associated with an increase in ischemic/reperfusion injury in a rabbit model [17]. Thirdly, increased C-reactive protein level exacerbated LVSD and remodeling after MI in a mouse model [18]. The undesirable effect of CRP on post-MI left ventricular remodeling was linked to increased apoptotic rates, macrophage infiltration, monocyte chemotactic protein-1 expression and matrix metalloproteinase-9 activity in the border zone. Additionally, CRP decreases nitric oxide,and so suppresses angiogenesis. CRP also inhibits endothelial progenitor cell differentiation, function and survival [19].

The evidence of clinical benefits of rosuvastatin in subjects with elevated CRP levels was derived from JUPITER trial[20]. In the current study two different regimes of rosuvastatin dosing was used first standard dosing of 20mg daily and second moderate to high dosing i.e 40 mg rosuvastatin daily. Our results are in accordance with Erbs at al and Sposito et al studies.

Erbs et al showed that high dose Rosuvastatin enhanced ejection fraction. In CHF, rosuvastatin activates circulating endothelial progenitor cells that contribute to neovascularisation and to the enhancement of endothelial function[21].

Sposito et al showed that there are two mechanisms by which statins play their beneficial role. First, the study showed that regardless of the LDL cholesterol level, th benefit is more at high dose statin therapy. It means decrease in inflammatory activity and the improvement of NO production and endothelial vasomotor function. Second, maximum benefit with statin therapy is observed when it is initiated in the first hours after onset of MI [22].

Sposito et al observed in NSTEMI and in STEMI that this anti-inflammatory effect can be faster.

CONCLUSION:

There was trend towards lower mortality in high dose statin therapy as compared to moderate dose statin therapy during acute phase of STEMI. Furthermore high dose statin therapy leads to attenuation of inflammatory activity and hence lesser left ventricular remodeling at six months post MI follow-up.

Author's Contribution

KR: Conducted the study and wrote the article.
IM: Helped in conducting the study and gave frequent advice.
AS: Corrections and did final proof reading.
NHM: Consultant incharge and supervisor.

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