

# High and low dose atorvastatin effects on high sensitivity C-reactive protein in patient with acute coronary syndrome

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## Original Article

### Abstract

**Introduction:** The effect of statins in reducing the risk of acute cardiovascular events is not only due to their effect on serum cholesterol level but also from their anti-inflammatory effects, particularly those resulting from reducing of C - reactive protein (CRP), is important. Atorvastatin dose and duration of treatment display different effects. This study compared the effects of high and low doses atorvastatin in reducing serum level of high sensitivity C reactive protein (hs-CRP).

**Methods:** One hundred patients with unstable angina or Non ST Elevation Myocardial Infarction (NSTEMI) randomized into two groups. Group 1 (n=50) received atorvastatin 80, 20 and 20 mg in three days but group 2 (n=50) received atorvastatin 80 mg/day for three days. High sensitivity C-Reactive protein was measured at admission time and after three dose atorvastatin therapy.

**Results:** Hs-CRP significantly decreased from baseline to end of three doses treatment in both groups (P=0.0001). However, the reduced level was greater in the group2 than group1 (-39.5% vs -31.2%, P=0.0185).

**Conclusion:** We found that both treatment methods have significantly effect on hs-CRP in short term but high dose (80 mg/day) atorvastatin being associated with significantly greater reductions in hs-CRP concentration.

**Key words:** Atorvastatin, Acute Coronary Syndrome, CRP, NSTEMI

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### Introduction:

Coronary artery disease (CAD) is leading cause of death worldwide. The main pathology for CAD is atherosclerosis that known as a chronic inflammatory phenomenon. Acute Inflammatory response play an important role in the onset and

development of acute events (1-3). Atherosclerotic plaques which contain more inflammatory cells are more prone to rupture (4). These plaques known as vulnerable plaques. Reduction in serum concentrations of inflammatory marker decrease acute coronary events in both patients with or without history of CAD (2). C- reactive protein

(CRP) is involved in atherosclerotic processes so that increased CRP levels may increase the risk of coronary events (2,5-9). High Sensitivity C-Reactive Protein (hs-CRP) is one of the predictive factors for risk of acute coronary events (1,3,5,8).

Therefore CRP is one of the best markers available for inflammation evaluation in patients with CAD (3,7,10) hs-CRP level may use for stratifying patients to higher and lower risk groups. Elevated hsCRP levels in patients with acute coronary syndrome (ACS) show higher risk of recurrent events (8). Also LDL and oxidized LDL level has prognostic information but increased hs-CRP levels indicate a worse prognosis in patients with ACS (11,12).

Effect of statins in decreasing coronary event is not only due to decreasing cholesterol level but its anti-inflammatory effect is an important factor in these patients (13,14).

Atorvastatin is one of the statins drug groups that used widely in prevention and treatment of patients with ACS. Atorvastatin effects on hs-CRP serum level is dose dependent (5,14) and high dose being associated with greater reductions in hs-CRP concentrations (5). At the same time other studies showed that early treatment with low dose atorvastatin modifies inflammatory response after one week (15). It means that positive effect of low dose atorvastatin treatment can be achieved with long time of treatment duration. In patients with ACS, treatment with 10,20,40 and 80 mg of atorvastatin has controversial anti-inflammatory effect but this effect was independent of the change in cholesterol level (5,15-17]. A study from China in patients with hypercholesterolemia showed cholesterol lowering effect of statins with no significant effect on hs-CRP (18). There are general agreement that statins effects the hs-CRP and result in decreasing attacks of ACS but still there are doubt about the best recommended dose and duration of treatment to be continued (19). In the present study we compared the effect of short term high and low dose atorvastatin treatment on hs-CRP level in patients with ACS.

## Methods:

This trial was a Single blind-Randomized-Pro prospective study that was carried out on patients

admitted with Unstable Angina or NSTEMI in Shahid Mohammadi hospital (General educational medical center, Bandar Abass-Iran). 100 patients were included in our study by simple randomized sampling.

Exclusion criteria included ST Elevation Myocardial Infarction, diabetes mellitus, heart Failure, renal failure, uncontrolled hypertension, active infectious diseases, current use of statins, fibrates and other lipid lowering therapy, use of aspirin and other NSAID (nonsteroidal anti-inflammatory drug).

Patients were randomized in 1:1 manner into two treatment groups: group 1) 80mg atorvastatin at first day and continue with 20mg for two next days. Group 2) 80mg/day atorvastatin for three days.

We used a High Sensitivity assay for measurements of serum C- reactive protein (hs-CRP) with Immunoturbidometry method. For all patients, hs-CRP was assayed at admission and after treatment by three doses of atorvastatin.

All patients were treated with ACE inhibitors, heparin, aspirin, nitrates, beta blockers, (according to the American Heart Association guideline). The protocol was approved by the Research Ethics Committee. All patients gave written informed consent before entering the study.

Statistical analysis was performed by Epi Info for windows (V.3.5.3-2011). Continuous variables were expressed as mean $\pm$ SD. Comparison of variables between groups was performed using the Chi-square test and unpaired t-test. P-values of <0.05 were considered statistically significant.

## Results:

One hundred patients (58 males, 42 females) with an average age of 62.3 $\pm$ 10.9 years were include in this study. Baseline characteristics did not differ between the two groups (Atorvastatin 80-20-20mg and Atorvastatin 80-80-80 mg) (Table 1).

In both groups, the baseline hs-CRP levels were comparable (0.64 $\pm$ 0.96 vs 1.44 $\pm$ 3.11 mg/dl, P=0.0866) also at the end of 3 doses treatment were comparable (0.44 $\pm$ 0.72 vs 0.87 $\pm$ 2.07 mg/dl, P=0.1741). Hs-CRP significantly decreased from baseline to end of 3 doses treatment in group 1 (P=0.0001) as well as in group2 (P=0.0001) (Figure 1). However, the decrease was greater in

the group2 than group 1 (-39.5% vs -31.2%, P=0.0185) (Table 2).

**Table 1. Baseline characteristics**

|               | Group 1 (80, 20, 20 mg) |    | Group 2 (80, 80, 80 mg) |    | P-value* |        |
|---------------|-------------------------|----|-------------------------|----|----------|--------|
|               | N=50                    | %  | N=50                    | %  |          |        |
| Age (Mean±SD) | 62.4±11.1               |    | 62.3±10.8               |    | 0.9710   |        |
| Gender        | Male                    | 32 | 64                      | 26 | 52       | 0.1555 |
|               | Female                  | 18 | 36                      | 24 | 48       |        |
| History of    | Chronic hear disease    | 30 | 60                      | 25 | 50       | 0.2107 |
|               | Hypertension            | 21 | 42                      | 19 | 38       | 0.4192 |
|               | Hyperlipidemia          | 1  | 2                       | 0  | 0        | 0.5    |
|               | Stroke                  | 3  | 6                       | 1  | 2        | 0.3086 |
|               | Smoking                 | 25 | 50                      | 17 | 34       | 0.0778 |

\* P-values of <0.05 were considered statistically significant

**Table 2. Change of means and median of hs-CRP concentration after atorvastatin therapy**

|                      | Mean hs-CRP (mg/dl)    |                        | Median hs-CRP (mg/dl)        |                          | P-value |
|----------------------|------------------------|------------------------|------------------------------|--------------------------|---------|
|                      | Group 1                | Group 2                | Group 1                      | Group 2                  |         |
|                      | (80, 20, 20 mg)        | (80, 80, 80 mg)        | (80, 20, 20 mg)              | (80, 80, 80 mg)          |         |
| Admission time       | 0.64±0.96              | 1.44±3.11              | 0.3 (0.1, 6.1)               | 0.6 (0.01, 21.2)         | 0.0866  |
| After 3 dose therapy | 0.44±0.72              | 0.87±2.07              | 0.2 (0.01, 4.5)              | 0.3 (0.01, 14)           | 0.1741  |
| Change (%)           | -0.20±0.26<br>(-13.2%) | -0.57±1.06<br>(-39.5%) | -0.1 (-1.6, 0.1)<br>(-33.3%) | -0.3 (-7.2, 0)<br>(-50%) | 0.0185  |
| P-value**            | 0.001                  | 0.0001                 |                              |                          |         |

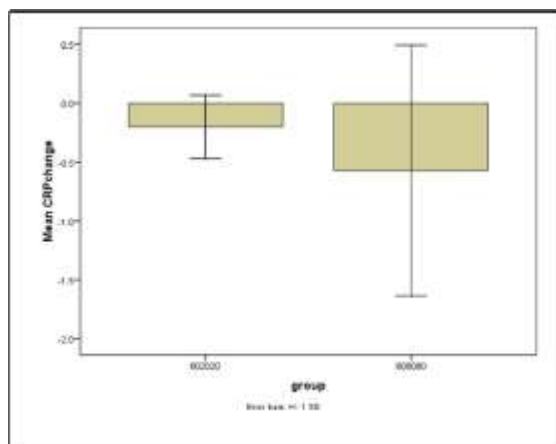
\* P values of <0.05 were considered statistically significant

\* P-value, group1 vs. group2

\*\* P-value, After 3 dose therapy vs. Admission time

**Table 3. Results of atorvastatin effect on CRP level in other studies**

| Study             | Dose (mg/day)                                  | Duration therapy          | Reducing (%) |
|-------------------|--|---------------------------|--------------|
| Ostad (18)        | 80   | 8 weeks                   | 61.2         |
| Naser Hossein (7) | 80   | 6 months                  | 40           |
| Recent study      | 80   | 3 day                     | 39.5         |
| Bonnet (5)        | 80   | 5 weeks                   | 36.4         |
| Gensini (1)       | 80   | 12 weeks                  | 33.6         |
| Recent study      | 80 (80 mg initially and continue<br>20 mg/day) | 3 day                     | 31.2         |
| Macin (6)         | 40   | 1 month                   | 84           |
| Macin (6)         | 40   | Discharge time (4±3 days) | 62           |
| Naser Hossein (7) | 40   | 6 months                  | 30           |
| Gensini (1)       | 40   | 12 weeks                  | 23.1         |
| Karaca (16)       | 20   | 4 weeks                   | 47           |
| Keles (17)        | 20   | 1 month                   | 37           |
| Keles (17)        | 20   | 3 months                  | 36           |
| Gensini (1)       | 20   | 12 weeks                  | 28           |
| Keles (17)        | 20 (every other day)                           | 3 months                  | 25.6         |
| Keles (17)        | 20 (every other day)                           | 1 month                   | 21           |
| Naser Hossein (7) | 20   | 6 months                  | 20           |
| Bonnet (5)        | 10   | 5 weeks                   | 25           |
| Gensini (1)       | 10   | 12 weeks                  | 20.8         |



**Figure 1. Mean of CRP change in both groups at three days atorvastatin therapy**

In this study, no complications of treatment were reported and both methods of treatment were tolerated by patients.

### Conclusion:

Plasma CRP level is elevated in the first days of ACS. It is due to systemic inflammatory response and have been associated with short and long term poor prognosis (6).

This study showed that both methods (low and high dose Atorvastatin) have significant effect on decreasing hs-CRP level in short term but reduction in high dose method was greater (-39.5% vs -31.2%,  $P=0.0185$ ). Although means of hs-CRP level after 3 days treatment was not significantly different between groups.

Other studies have been shown dose dependent effect of atorvastatin on reduction of hs-CRP level (5,7). Most studies evaluated atorvastatin administration effectiveness during several weeks to several months (13,15) but the effect of short term (several days) less investigated.

Nesar Hossein et al studied 20, 40 and 60 mg atorvastatin effect for 6 months. They showed reduction of plasma level of hs-CRP in most patients but significantly reduction in 80 mg group incident after 3 months treatment and after 6 months for other dosages (7). However our study showed significantly reduction of plasma level of

hs-CRP in both groups (80.80.80 mg and 80.20.20 mg) only after 3 days treatment.

Lower dose compare with 80 mg and 10 mg (add with 10 mg Ezctimibe) atorvastatin also showed significantly reduction in hs-CRP versus per-treatment after 8 weeks but did not significantly differ between two groups at pre-treatment and post-treatment (20). These findings were demonstrated in our study but in recent study mean absolute change was significantly different between groups. Walter et al demonstrated significantly effect of 30mg atorvastatin in hs-CRP concentration after 8 weeks (21).

Different doses at different duration of treatment have different effect. In recent study, 39.5% reduction is happened with 80mg per day atorvastatin after 3 days. However in Macin study, 62% reduction had been occurred with 40 mg per day atorvastatin at discharge (3±4 days) (6). High and aggressive dosages of atorvastatin (e.g. 80 mg) have similar effects in reduction of hs-CRP concentration (almost between 30% to 40%) (Table 3).

Therefore, administer of 80 mg atorvastatin is more effective than mild and moderate doses (1) Also, in recent study both methods therapy decrease hs-CRP between 30% to 40%. Our findings is near to results from a study done in an Iranian population (22).

In study of keles et al, comparing the effects of standard once daily 20 mg atorvastatin treatment with 20 mg administered every other day showed both methods have similar effects after one and three months treatment (17).

Meta analysis of PanPan proposed that difference effect may be due to a dosage effect rather than different statins (13).

Tousoulis et al showed that, statins required more than 1 week to significantly modify inflammatory response (15) findings of recent study and others studies display that statin effect is dependent to dosage, treatment duration and loading dose.

This study included only a limited number of patients from a single center and we have no data about clinical end-points because of short term follow-up period

Our findings showed that treatment with 80 mg atorvastatin for three days and 80 mg for first

day continued by 20 mg for next two days resulted in decreasing hs-CRP level in short term but the effect is more prominent in high dose group. We propose to use 80, 20 and 20mg dose for short term.

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## تأثیر تجویز داروی آتورواستاتین با دوزهای بالا و پایین بر سطح سرمی High sensitivity C-reactive protein در بیماران مبتلا به سندرم حاد کرونری

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### چکیده

**مقدمه:** اثر استاتین‌ها مانند آتورواستاتین در کاهش ریسک حوادث قلبی عروقی تنها ناشی از اثر آنها بر کاهش کلسترول نمی‌باشد بلکه اثر ضد التهابی آنها به ویژه ناشی از کاهش سطح سرمی C-Reactive Protein می‌باشد. مقدار و مدت زمان مصرف آتورواستاتین دارای اثرات متفاوت می‌باشد. هدف از این مطالعه، مقایسه تأثیر دوز بالا و پایین آتورواستاتین بر کاهش CRP می‌باشد.

**روش کار:** این مطالعه به صورت کارآزمایی بالینی یک سوکور بر روی ۱۰۰ بیمار بستری با تشخیص سندرم حاد کرونری انجام شد. به نیمی از بیماران آتورواستاتین ۸۰ میلی‌گرم روزانه تا سه روز تجویز شد و به نیمی دیگر ابتدا ۸۰ میلی‌گرم در روز اول و سپس روزانه ۲۰ میلی‌گرم تا روز سوم آتورواستاتین داده شد و برای همه بیماران High Sensitivity C-Reactive Protein (hs-CRP) قبل از شروع درمان و در روز سوم اندازه‌گیری شد.

**نتایج:** میانگین hs-CRP روز سوم در هر گروه به طور معنی‌داری کمتر از میانگین hs-CRP روز بستری در همان گروه است ( $P=0/001$ ). همچنین درصد کاهش میانگین hs-CRP در طی این سه روز در گروه بیماران دریافت‌کننده دوز بالاتر آتورواستاتین به طور معنی (۳۹/۵- درصد) بیشتر از گروه دریافت‌کننده دوز پایین‌تر آتورواستاتین (۳۱/۲- درصد) بدست آمد ( $P=0/185$ ).

**نتیجه‌گیری:** با توجه به اینکه هر دو روش درمانی سبب کاهش معنی‌دار سطح سرمی hs-CRP می‌شوند، استفاده از روش شروع درمان با تک دوز ۸۰ میلی‌گرم آتورواستاتین و ادامه آن با دوز ۲۰ میلی‌گرم پیشنهاد می‌گردد.

**کلیدواژه‌ها:** آتورواستاتین، سندرم حاد کرونری، CRP، سکتة حاد قلبی

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