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**Research Article**

# STATIN THERAPY AND HIGHLY SENSITIVE C - REACTIVE PROTEIN IN PATIENTS WITH ACUTE CORONARY SYNDROME

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**Abstract**: Background: Acute Coronary Syndrome (ACS) has taken an epidemic course in developing countries. Dyslipidemia is one of the causative factors for ACS. Statins are the preferred agents among hypolipidemic drugs. Apart from hypolipidemic action, statins have pleiotropic actions. Various studies have proved the anti-inflammatory action of statin by assessing inflammatory markers. Objective: To assess the effect of 40mg & 80mg of atorvastatin on inflammation by assay of highly sensitive – C Reactive Protein (hs-CRP) and to verify whether it is dose-dependent or dose independent. Methods: An open labelled, randomized study enrolling 20 patients of Acute Coronary Syndrome (ACS) conducted in M.S. Ramaiah Hospital, Bengaluru. Patients were randomized to either atorvastatin 40 mg alone once daily or atorvastatin 80mg once daily for 3 months. The hs-CRP was analysed both at starting as well as at end of the study. Results: The reduction in hs-CRP level between the atorvastatin 40mg and atorvastatin 80mg group from the baseline was 0.38 mg/dl and 0.30 mg/dl respectively. The reduction in hs-CRP before and after statin therapy irrespective of the dose was statistically significant (P=0.008). On comparing, it was significant in atorvastatin 40mg group (P =0.041), but was not significant in atorvastatin 80mg group (P =0.106). Statins have anti-inflammatory action, but the reduction of hs-CRP in patients with ACS on statin therapy is dose-independent. Conclusion: Treatment with statins augments the natural decline in inflammatory markers following ACS and is associated with better prognosis
Key**words:** Acute Coronary Syndrome; hs-CRP; Atorvastatin.

## INTRODUCTION

Statins are the most often preferred hypolipidemic agents. Several recent statin trials have suggested additional the benefits behind cholesterol lowering. Pleiotropic effects of a drug are actions other than those for which the agent was specifically developed. These effects may be related or unrelated to the primary mechanism of action of the drug, and they are usually unanticipated. Pleiotropic effects of statins include improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant properties, inhibition of inflammatory responses, and stabilization of atherosclerotic plaques [1].

Researchers and clinicians have turned to biochemical markers of inflammation as possible non invasive indicators of underlying atherosclerosis, the risk of first or recurrent cardio vascular events and the success of therapeutic and preventive interventions. Out of the basic sets of inflammatory markers, High Sensitive C-reactive protein (hs-CRP) is the most extensively studied one and is associated with the risk of adverse cardio vascular outcomes in patients with ACS [2].

Various studies have demonstrated that lower levels of hs-CRP is associated with a more favourable outcome, suggesting a role for hs-CRP in monitoring the response to statin therapy and other preventive interventions that influence inflammation [3]. Treatment with statins lowers the concentration of the hs-CRP by 13% to 50% compared with placebo and in retrospective analysis has shown to reduce the risk associated with elevated levels of this inflammatory marker [4]. Thus, the addition of CRP to standard cholesterol evaluation may provide a simple and inexpensive method to improve global risk prediction and compliance with preventive approaches [5].

The aim of the present study is to assess the effect of 40mg & 80mg of atorvastatin on inflammation by assay of hs-CRP and to verify whether it is dose-dependent or dose independent.

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Acute Coronary Syndrome (ACS) is one of the clinical manifestation of Coronary Artery Disease (CAD). CAD is invariably caused by a disease affecting the coronary arteries, the most prevalent being atherosclerosis, accounting for more than 90% of cases. Atherosclerosis is a chronic immunoinflammatory, fibro proliferative disease of large and medium-sized arteries fuelled by lipid. Atherosclerosis by itself is rarely fatal; it is thrombosis, superimposed on a ruptured or eroded atherosclerotic plaque that precipitates the life-threatening clinical events such as acute coronary syndromes [6]. Inflammation is an important contributor to atherogenesis and acute atherothrombosis [7].

In view of clinical application CRP seems to be a stronger predictor of cardiovascular events than Low Density Lipoprotein Cholesterol (LDL-C) and it adds prognostic information at all levels of calculated Framingham risk. Based on hs-CRP assay, CRP levels of less than 1, 1-3 and more than 3 mg/dl correspond to low-risk, moderate-risk, and high-risk groups for future Cardiovascular events. Measurement of hs-

CRP, an inflammatory biomarker independently predicts future vascular events and also improves global classification of risk, regardless of LDL-C level [5].

Statins are the most effective and best tolerated drugs among hypolipidemic agents. Act by competitive inhibition of HMG CoA reductase, enzyme catalyses an early, rate limiting step in cholesterol synthesis [8].

The Pleiotropic actions of statin can be classified as Isoprenoid dependent and Isoprenoid independent [1].

Isoprenoid dependent actions are:

1. Anti inflammatory - Decreases highly sensitive C - reactive protein (hs-CRP) production which is induced by Interlukin -1 (IL-1), Interlukin -6 (IL-6) and lipoproteins.

2. Immuno modulation - Regulates intracellular signalling, decreases the adhesion molecule expression and also IL-1, IL-6, Tumor Necrosis Factor (TNF).

3. Coagulation - Decreases tissue factor, increases protein-C and plasminogen activator.

4. Endothelium - Increases Nitric Oxide (NO) production, inhibits endothelial cell apoptosis.

5. Plaque stability - Inhibits metalloproteinases.

Isoprenoid independent actions are:

1. Major Histocompatibility Complex (MHC) restriction

2. Hemooxygenase inhibition

3. Interferes with leucocyte endothelial interaction.

## METHODOLOGY

**Study type**: Open label, Randomized controlled study.

**Source of data and Study population**: Patients with Acute Coronary Syndrome attending Emergency room or Out-Patient Clinic in the Department of Cardiology, M.S. Ramaiah Hospital, Bengaluru.

**Method of collection of data**: Patients were recruited based on the inclusion and exclusion criteria mentioned below.

Inclusion criteria:

1- Patients with Acute Coronary Syndrome.
2- Both male and female patients.
3- Age group of above 18 years.

Exclusion criteria:

1- Inflammatory diseases – Arthritis, Lupus, Inflammatory Bowel Diseases.
2- Patient on Immuno-suppressants, steroids.
3- History of active, ongoing or chronic infectious disease.
4- Severe liver dysfunction.
5- Renal failure.

**Study procedure**: The sample size was calculated from the study conducted by Ping Y L et al. [9], considering power of the test 90% with alpha error of 5% and difference of hs-CRP as clinically significant at 1mg, Number Needed to Treat (NNT) was 17. Considering 10% as attrition rate due to loss of follow-up, sample size of 20 was considered. The study was conducted as per the ICH-GCP guidelines. The study protocol was approved by the Ethics Review Board. Informed consent was obtained after fully explaining the procedure and the consequences in patients own language. The work up included a detail history taking as per the Proforma. The patients were randomized in 1:1 ratio to either of the Two - treatment groups. Group I received Atorvastatin 40mg/ once daily alone and the Group II received Atorvastatin 80mg/ once daily for 3 months.

Blood samples were collected before the randomization and hs-CRP was analysed by ELISA method at Central Research laboratory, M S Ramaiah Medical Collage, Bengaluru.

**Follow up:** hs-CRP was repeated at the end of 3rd month and any changes in the hs-CRP levels were compared between the 2 groups.

**Statistical analysis:** A Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis).

## RESULTS & DISCUSSION

The present study was an open labeled, randomized study to assess the effect of 40mg & 80mg of atorvastatin on inflammation by assay of hs-CRP and to verify whether it is dose dependent or dose independent. The present study involved 20 patients, 9 patients each in atorvastatin 40mg and 11 patients in atorvastatin 80mg group. The mean age in the atorvastatin 40mg group was 47.89 years and in atorvastatin 80mg group was 53.33 years. Out of 20 patients, 3 were female and 17 were male patients (TABLE 1). In atorvastatin 40mg group 3 (33%) were female and 6 (66%) were male patients. In atorvastatin 80mg group all 11 (100%) were male patients.

**Table 1: Comparison of age and sex distribution**

| Parameters | | Group I (Atorvastatin 40mg) | Group II (Atorvastatin 80mg) | 'P' Value |
|---|---|---|---|---|
| **Age in years** (Mean ± SD) | | 47.89± 9.558 | 53.33± 10.11 | 0.214 |
| **Gender** | Male (n) (%) | 6 (66%) | 11 (100%) | - |
| | Female (n) (%) | 3 (33%) | - | |

**Table 2: Effect of treatment on hs-CRP.**

| Parameter | Point of study | Group I (Atorvastatin 40mg) | Group II (Atorvastatin 80mg) | P value |
|---|---|---|---|---|
| Hs-CRP (mg/dl) | Before | 0.838±0.30 | 0.715±0.39 | |
| | After | 0.449±0.32 | 0.410±0.32 | |
| | Change | 0.388±0.48 | 0.305±0.56 | 0.008 |
| | P value | 0.041 | 0.106 | - |

The reduction in hs-CRP level between the atorvastatin 40mg and atorvastatin 80mg group from the baseline was 0.388 mg/dl and 0.305 mg/dl respectively. The reduction in hs-CRP before and after statin therapy irrespective of the dose was statistically significant (P=0.008) as shown in Figure 1. The reduction of hs-CRP levels in atorvastatin 40mg was from 0.838 mg/dl to 0.449 mg/dl, which was statistically significant (P =0.041) as shown in Figure 2. The reduction of hs-CRP levels in atorvastatin 80mg was from 0.715 mg/dl to 0.410 mg/dl, which was statistically not significant (P =0.106) in Figure 3.

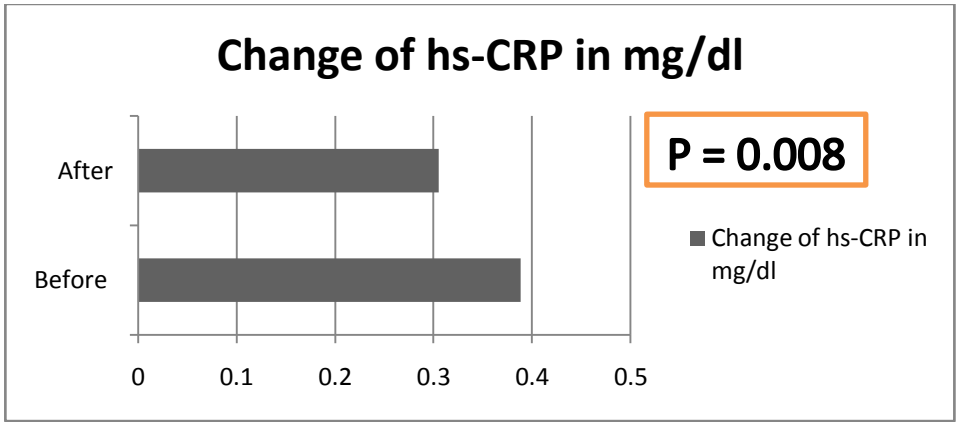


**Figure 1: Change in hs-CRP before and after statin therapy.**

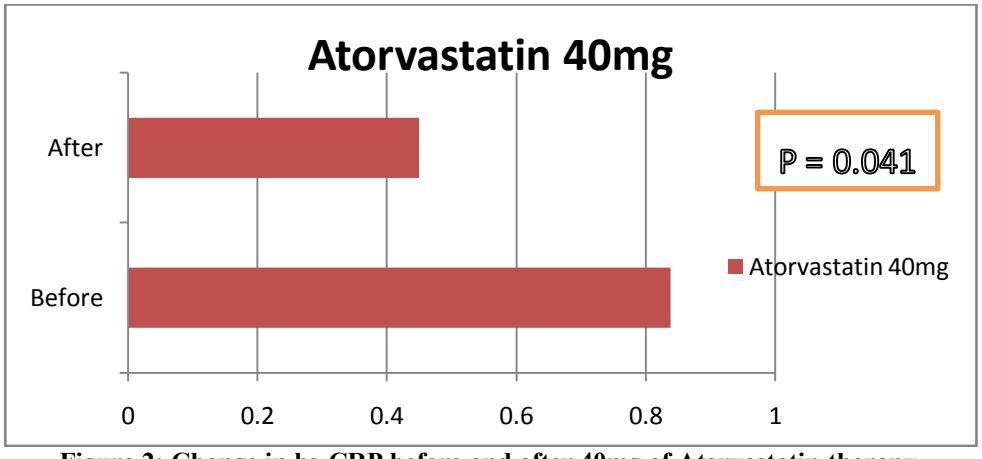


**Figure 2: Change in hs-CRP before and after 40mg of Atorvastatin therapy.**

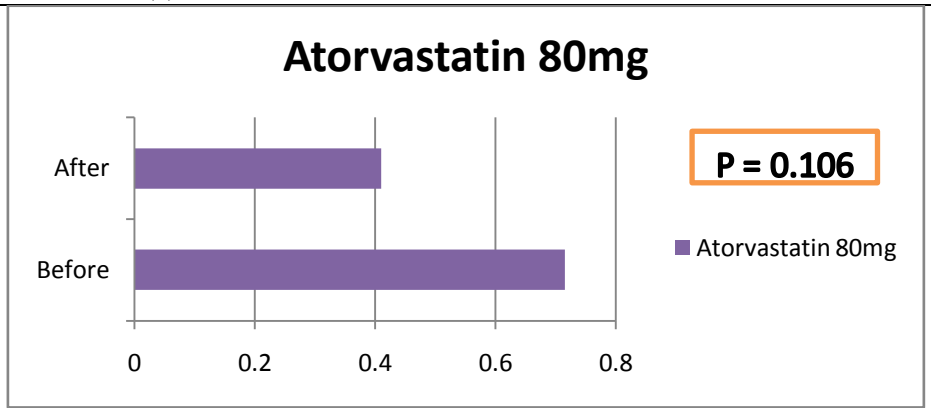


**Figure 3: Change in hs-CRP before and after 80mg of Atorvastatin therapy.**

Various studies have evaluated the anti-inflammatory action of Atorvastatin in the management of ACS.

In a study conducted by Ping Y L et al. [9], to assess pleiotropic action of statin, high dose statin monotherapy had greater effect on Rho associated coiled coil containing protein kinase and endothelial function but not on C-reactive protein, than lower dose statin plus ezetimibe.

In a study conducted by Paul M Ridker et al. [10], to assess the benefit of statin therapy in people with elevated hs-CRP levels but without hyperlipidemia, rosuvastatin significantly reduced the incidence of major Cardio-Vascular events.

## CONCLUSION

Dyslipidemia is one of the major risk factors for the development of ACS. Statins are the preferred agents among hypolipidemic drugs. Despite hypolipidemic action, statin has pleiotropic actions.

The present study demonstrates the anti-inflammatory action of statins, but it is dose independent. Further studies, involving larger patient population may provide greater in-sight for verification of dose-dependent anti-inflammatory action of statin.

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