

## FREQUENCY OF NON-RESPONDERS OF STATINS IN ACUTE CORONARY SYNDROME PATIENTS

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Date of Submission: 01-10-2022; Date of Acceptance: 08-11-2022; Date of Publication: 15-12-2022

### ABSTRACT:

**BACKGROUND:** *Acute coronary syndromes (ACS) includes non ST elevation (NSTEMI) or ST elevation myocardial infarction (STEMI) along with unstable angina and is associated with high morbidity and mortality despite advances in treatment. Statins is one of the pharmacological agent in the management of acute coronary syndrome (ACS). After remarkable advances in medical management over many years, a significant proportion of patients still do not respond to Statins.*

**AIMS & OBJECTIVE:** *To assess the frequency of non-responders of statins in acute coronary syndrome patients.*

**MATERIAL & METHODS:** *This cross-sectional study was carried-out at Punjab Institute of Cardiology, Lahore (PIC) from August 10, 2015 to February 10, 2016. Total 325 patients who fulfilled the inclusion criteria were enrolled and counseled about the details of the study. After taking consent, detailed history and examination was recorded. Details were recorded regarding age, gender of the patient. All patients received 10mg of rosuvastatin. Data stratification was done for age, gender and duration of ACS. Chi-square test was used after stratification to check the significance. p-value was taken as significant when less than 0.05.*

**RESULTS:** *The mean age of non-responders was 56.65±8.75 years. Out 325 patients, 81(24.90%) were non-responders. Mean LDL-C at baseline in non-responders was 197.58±19.08 mg/dl and mean LDL-C after statin therapy in non-responders was 154.64±17.77.*

**CONCLUSION:** *There is a significant number of patients with no response to statins. Lipid-lowering statin regimen gives individuals who have recently experienced ACS increased protection against mortality or experiencing serious cardiovascular events. Results show that such patients benefit from early and ongoing LDL cholesterol reduction.*

**KEY WORDS:** *Acute Coronary Syndrome, Statins, Non-responders.*

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**Author's Contribution:** OA: Wrote the article. MR: Conducting the study. ZA: Data analysis and corrections in manuscript. FU: Helped in data collection and analysis. AH: Manuscript proof reading. SM: Proof reading of the manuscript.

**INTRODUCTION:**

Unstable angina, NSTEMI and STEMI are included in the category of ACS which is associated with increased mortality and morbidity.<sup>1</sup> Reviewing the update report of Heart Disease and Stroke Statistics 2008 (AHA) there were 1,413,000 hospital discharges in US due to ACS in 2005.<sup>2</sup> Out of which 20% were due to ST elevation MI and rest were due to unstable angina and STEMI.<sup>2</sup> The estimated prevalence of NSTEMI-ACS is approximately 3 people out of 1000.<sup>2</sup> In the UK, about 114,000 patients with NSTEMI-ACS are admitted every year.<sup>1,3</sup> The treatment consists of antithrombotic regime and diagnostic coronary angiography followed by revascularization if required. Statins is one of the main ways to treat acute coronary syndrome (ACS). Despite advances in treatment over many years; a significant proportion of patients still do not respond to Statins.<sup>4</sup> Thus the problem of ACS treatment of these patients leads to re treatment.<sup>5</sup>

This study was done to estimate the frequency of statin therapy non-responders in ACS patients.

**METHODOLOGY:**

This cross-sectional observational study was carried-out at PIC, Lahore from August 10, 2015 to February 10, 2016. Total 325 patients who presented in the Punjab Institute of Cardiology, Lahore. Patients were enrolled according to inclusion criteria. Written consent was taken and detailed history was obtained. Details were collected regarding age, gender of the patient and data stratified as age, gender and duration of ACS. Chi-square test was applied to the data and p-value was taken significant if  $\leq 0.05$ . Sample size of 325 cases was estimated using 5% error margin and 95% confidence level, taking expected percentage of non-responders of statin, i.e. 30% in acute coronary syndrome.<sup>4</sup>

Patients of both sex groups with ages more than 30 years and less than 75 with ACS (It was assessed on symptoms of chest pain more than 30 minutes and ECG changes (ST elevation  $> 1\text{mm}$  in limb leads) cardiac enzyme level trop T  $> 0.1$ ) in PIC emergency department within or less than 72 hours of chest pain. Patients having hyperlipidemia having LDL-c  $> 160\text{mg/dl}$  (LDL-C  $> 160\text{ mg/dL}$  when presented). All patients were enrolled in the study after informed consent. ACS Patients having hyperlipidemia LDL-c  $< 160\text{ mg/dl}$ .<sup>3</sup> ACS patients who were non responders (patients were considered as non-responders if there were less than 30% reduction in LDL-C from the untreated baseline. Reduction was calculated

by subtracting the post treatment value after 6 months from present value) but their required data is not available in the record and patients already taking statins were excluded. Patients fulfilling the above mentioned inclusion criteria were counseled about the research. Patients were presented in PIC emergency having chest pain, ECG findings and cardiac enzyme positive treated with anti-ischemic drugs like aspirin, clopidogril and anti-thrombotics like streptokinase and heparin. Then moderate intensity statin rosuvastatin 10 mg was given. Patients were selected in which LDL-c level  $> 160\text{ mg/dL}$ . After taking rosuvastatin for 6 months LDL-c was checked again.

**DATA ANALYSIS PROCEDURE:**

The data was analysed using SPSS 23. Numerical variables i.e. age, LDL-C level before and after treatment and duration of ACS were presented by mean  $\pm$ SD and range. Categorical variables were presented i.e. gender and non-responders as frequency and percentage. Data stratification was done for age, gender and duration of ACS. Chi-square test was used after stratification to check the significance and p-value was taken as significant if  $< 0.05$ .

**RESULTS:**

Out of 325 ACS patients, 244 (75.10%) patients were males and 81 (24.90%) were females. Among these patients, 94(28.90%) were between 30-45 age group, while 158(48.60%), 73(22.50%) were between 46-60 and 61-75 age groups respectively. Mean age of the patients was  $52.16 \pm 9.93$  years. Mean LDL-C at baseline was  $196 \pm 19.93$  and LDL-C after statin therapy was  $119.29 \pm 28.89\text{ mg/dl}$ . Mean age of male patients was  $52.28 \pm 9.99$  years and mean age of female patients was  $51.82 \pm 9.77$  years. (Table-1)

Mean LDL-C at baseline in male patients was  $196.72 \pm 20.36\text{ mg/dl}$  and mean LDL-C after statin therapy in male patients was  $120.82 \pm 29.32\text{ mg/dl}$ . Mean LDL-C at baseline in female patients was  $193.86 \pm 18.71\text{ mg/dl}$  and mean LDL-C after statin therapy in female patients was  $114.67 \pm 27.17\text{ mg/dl}$ . (Table-2) With respect to gender there was no difference in non responders. (Table-3)

Mean age of non-responders was  $56.65 \pm 8.75$ . Mean LDL-C at baseline in non-responders was  $197.58 \pm 19.08$  and mean LDL-C after statin therapy in non-responders was  $154.64 \pm 17.77$ . Mean age of responders was  $50.67 \pm 9.86$  years. Mean LDL-C at baseline in responders was  $195.47 \pm 20.23\text{ mg/dl}$  and mean LDL-C after statin therapy in responders was  $107.55 \pm 21.29$

Table-1: Distribution of Gender, Age and Non-responders			
		Frequency (n)	Percentage (%)
Gender	Male	244	75.1
	Female	81	24.9
Age Groups	30-45 years	94	28.9
	46-60 years	158	48.6
	61-75 years	73	22.5
Non-Responders	Yes	81	24.9
	No	244	75.1

Table-2: Descriptive statistics				
Statistics	LDL-Cholesterol (Initial Value)	LDL-Cholesterol (After Therapy)	Age	Duration of ACS
Mean	196.00	119.28	52.16	38.14
Median	195	118	51	38
Std. Deviation	19.94	28.88	9.92	19.92
Minimum	161	50	30	6
Maximum	230	190	73	72

Table-3: Stratification of Non-responders with respect to Gender				
Gender	Non-Responders		Total	P-value
	Yes	No		
Male	66 (27.0%)	178 (73.0%)	244 (100.0%)	0.124
Female	15 (18.5%)	66 (81.5%)	81 (100.0%)	
Total	81 (24.9%)	244 (75.1%)	325 (100.0%)	

Table-4: Stratification of Non-responders with respect to Age and ACS duration					
		Non-Responders		Total	P-value
		Yes	No		
Age Groups	30-45	9 (9.6%)	85 (90.4%)	94 (100.0%)	0.000
	46-60	42 (26.6%)	116 (73.4%)	158 (100.0%)	
	61-75	30 (41.1%)	43 (58.9%)	73 (100.0%)	
Duration of ACS	6-24 hours	32 (33.0%)	65 (67.0%)	97 (100.0%)	0.090
	25-48 hours	24 (21.4%)	88 (78.6%)	112 (100.0%)	
	49-72 hours	25 (21.6%)	91 (78.4%)	116 (100.0%)	

mg/dl. Non responders are described according to the duration of ACS in Table-4.

It was also concluded that, out 325 patients, 81(24.90%) were non-responders and 244(75.10%) were responders.

**DISCUSSION:**

The use of high dose statins is associated with lower major adverse cardiac events than a moderate or low dose statin therapy. Previous

placebo controlled trials have indicated that a standard dose statins were beneficial.<sup>6</sup>

In the Heart Protection study, the use of statins resulted in reduction of LDL cholesterol level by was 40 mg per deciliter (1.03 mmol per liter) as compared to placebo group and was associated with a 25 percent reduction in major adverse cardiovascular events. In our study, the LDL cholesterol level was reduced by 33mg per deciliter

(0.85 mmol per liter) by use of the statins. This LDL lowering may be associated with a reduction of major adverse events i.e. a 20% reduction. However, the variability in the reduction may also be attributed to non-lipid-related pleiotropic effects, which may differ between the different types of statins.<sup>7</sup> New trials have focused on the effectiveness of different doses of statins. It is now suggested that high dose statins are associated with lower adverse events than lower doses. It is indicated in another study that statins in high doses are bound to reduce unstable angina events by 29% and a 14% reduction in revascularization procedures.

The reduction in mortality rate was of borderline significance (28 percent,  $P=0.07$ ), which suggests that use of high dose statins is more important to reduce future adverse cardiac events. This reduction in adverse events was more pronounced during first 30 days. This is similar to that reported placebo-controlled MIRACL trial<sup>8</sup> and in prior observational studies.<sup>9</sup> In our study, most of the patients of ACS were managed by early invasive treatment while rest of the study population received optimized medical treatment including statins. It was noticed that more intense statin therapy was associated lesser adverse cardiac events.<sup>6</sup> The early use of statins in patients prone to have cardiac problems is associated with more benefit and can stabilize the vulnerable plaques.<sup>10</sup>

The latest guidelines by ACC and AHA recommend starting lipid lowering treatment while discharging the patients admitted with ACS, considering that it will improve the patients'

outcomes.<sup>11</sup> The data of our study also favours this.

Apart from the early management of clinical events, we also assessed a continued benefit of intensive medical management with statin throughout the follow-up duration. However, it could not be rule-out from this research that long-term benefit was due to statin therapy or it was the result of an early management of acute event.

Additionally, it is unclear whether additional variations between the two statins utilised account for the noted therapeutic improvement. However, our results indicate that when high-dose statin medication is continued, patients with acute coronary syndromes who get early lipid-lowering therapy continue to benefit in the chronic phase of atherosclerosis.

Our findings that intensive lipid-lowering medication continues to benefit patients during the follow-up phase are consistent with studies demonstrating that this strategy slows the progression of atherosclerosis in people with stable coronary artery disease<sup>12</sup> or in those who undergo coronary-artery bypass grafting,<sup>13</sup> as well as in greater reductions in carotid intimal-medial thickening.<sup>14</sup>

#### **CONCLUSION:**

There is considerable number of patients who do not respond to standard hyperlipidemia treatment. A lipid-lowering statin regimen gives individuals who have recently experienced an acute coronary syndrome increased protection against mortality or experiencing serious cardiovascular events. Results show that such patients benefit from early and ongoing LDL cholesterol reduction. In older age group non responders are more than in younger age group.

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