

# Novel Risk Factors in Acute Coronary Syndrome (ACS) In Age Group Less Than 35 Years of Age –A Prospective Hospital Based Study.

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## ABSTRACT

**Background:** Although there are many studies of ACS in young, there are very few studies of ACS in age group less than 35 years. Besides there is hardly any data available about novel risk factors of our regional population in our young ACS patients less than 35 years of age. **Aim:** To study the novel risk factors in age group less than 35 years presenting as acute coronary syndromes. **Methods:** It was a prospective hospital based study. All patients with age less than 35 years presenting as acute MI from March 2012 to March 2014 were enrolled. Novel risk factors (Serum Lipoprotein – A [Lp(a)], homocysteine, Serum fibrinogen and Factor V Leiden, C-reactive protein) were analyzed. **Results:** Total of thirty patients were studied. The mean age of the patients was 30.87 years +3.72 (Range 21-35) years. All patients were males. Of these 14 patients had Anterior wall STEMI and other two had Anterior wall Non-STEMI. 14 patients had infarct of the inferior wall. Homocysteine (66.66%) and lipoprotein (a) (46.66%) were two major newer risk factors in the present study followed by CRP (33%) and fibrinogen (30%) No patient tested positive for factor V Leiden mutation. **Conclusion:** Homocysteinemia is present in two-thirds, lipoprotein (a) in half, CRP and fibrinogen in one third of very young ACS patients. Randomized controlled trials are needed to establish their causation in pathogenesis of CAD.

**Keywords:** Young ACS, Novel risk factors.

## INTRODUCTION

Coronary artery disease (CAD) affect Indians at a younger age sometimes with severe diffuse form of involvement and unrelenting course.<sup>[1]</sup> Half of the CVD related deaths (52% of CVDs) in India occur below the age of 50 years, and about 25% of acute myocardial infarction (AMI) in India occurs under the age of 40 years.<sup>[2]</sup> In general, myocardial infarction (MI) develops 5-10 years earlier in Asian Indians than in other populations, and its occurrence in patients under 40 is 5 to 10-fold higher. It is predominantly a disease of men. Although myocardial infarction (MI) in young patients is most often the result of coronary atherosclerosis, there are significant number of patients in whom there is no evidence of coronary atherosclerosis.<sup>[3,4]</sup> While the traditional risk factors (hypertension, diabetes, smoking, dyslipidemia and positive family history of premature (CAD) are associated with the development of CAD, a substantial number of CAD patients do not have identifiable conventional risk

factors. This has led to a search for newer risk factors, which might explain the development of coronary artery disease. The newer risk factors include Hyperhomocysteinemia, Lipoprotein-A (Lp (a)) Hyperfibrinogenemia, factor V Leiden and C-reactive protein (CRP). Elevated levels of homocysteine are associated with a modest increase in the risk of CAD.<sup>5</sup> Homocysteine, a thiol containing amino acid, is a product of methionine metabolism. Hyperhomocysteinemia could be due to heredity factors (like – Partial or severe deficiency of cystathioninesynthase) or acquired reasons like - chronic renal failure, hypothyroidism, psoriasis and cancer. Elevated Lp (a) level has been shown in number of clinical studies, to be an independent risk factor for CAD.<sup>[6]</sup> Lp (a) is an LDL like substances ten times more atherogenic than LDL containing a unique lipoprotein called Apo (a) In a study of 105 survivors of acute MI not receiving thrombolytic therapy, the only factor distinguishing those with persistent occlusion of the infarct related arteries (as opposed to those with patent infarct related arteries) was an elevated level of Lp (a) in the former.<sup>[7]</sup> Hyperfibrinogenemia and factor V Leiden increase blood viscosity and result in increased risk of thrombosis – a proposed link to atherosclerosis. C-reactive protein (CRP) is a protein found in the

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blood, the level of which rise in response to inflammation (i.e. C-reactive protein is an acute phase reactant). CRP During acute phase response, levels of CRP rapidly rise within two hours of insult reaching a peak at 48 hours. C-RP has been proposed as one of the most new potential addition to CVD risk screening Although there are many studies of ACS in young, there are very few studies of ACS in age group less than 35 years which describe various novel risk factors. Besides there is hardly any data available for our regional population in our young ACS patients less than 35 years of age.

### **Aims and Objectives**

To study the novel risk factors in age group less than 35 years presenting as acute coronary syndromes.

## **MATERIALS AND METHODS**

The study was conducted at Fortis Hospital Mohali (Punjab) between the period March 2012 to March 2014. This was a prospective study where thirty patients who presented with ischemic chest pain, evolutionary changes on serial ECG and elevated cardiac markers with clinical diagnosis of acute myocardial infarction in the department of emergency medicine and shifted to cardiac care unit were enrolled for the present study when they fulfilled the study criteria as mentioned below and underwent coronary angiography during the same hospital stay.

### **Inclusion Criteria**

1. Age equal to or less than 35 years.
2. Definite AMI at admission, i.e. having 2 of the following three (as per WHO definition of AMI).
  - a. Ischemic type chest discomfort.
  - b. Evolutionary changes on serially obtained EKG tracings.
  - c. Rise and fall of serum cardiac markers

### **Exclusion Criteria**

- (a) Age was more than 35 years.
- (b) Patients not willing for coronary arteriography.
- (c) Patients not having definite AMI (i.e. patients who did not fulfill WHO criteria of AMI).
- (d) Congenital valvular heart disease or cardiomyopathies.
- (e) End organ damage.

A detailed history was taken and thorough physical examination was carried out. All patients were investigated for the presence of novel coronary risk factors.

### **Newer Risk Factors included**

1. Serum Lipoprotein – A [Lp(a)] was estimated by ELISA technique. Values (>30mg/dl) were considered high.

2. Hyperhomocysteinemia: Fasting plasma homocysteine levels were estimated by high pressure liquid chromatography apparatus equipped with electrochemical detector. Level of 5-15nmol/ml was considered normal. Hyperhomocysteinemia was defined as values >15nmol/ml.
3. Thrombogenic factors (serum fibrinogen and factor V Leiden): Serum fibrinogen was estimated by manual methods (precipitation method) and values greater than (400mg/dl) were considered high. The presence or absence of factor V Leiden was recorded.
4. C-reactive protein: Blood sample was collected in a serum separating tube and measurement was done by spectrophotometry and values above 3mg/l were considered high

The study was approved by the Institute Ethics Committee.

### **Statistical Analysis**

Thirty (30) patients were taken for the study, the study sample was estimated on the basis of very low incidence of myocardial infarction in young (2%) with confidence interval of 95% and accuracy of 5%. COCHRAN Formula was applied for estimation of sample size. The data was analyzed by using SPSS Version 20. Mean and standard deviations were calculated for all quantitative data. Frequencies and percentages were calculated for all categorical data.

## **RESULTS**

Total of thirty patients were studied. The mean age of the patients was 30.87 years +3.72 and range was 21-35 years. All patients were males. The age and sex distribution of participants is shown in [Table 1] and [Figure 1]. None of the patient in the current study gave history of angina preceding acute coronary syndrome. 28 patients had STEMI, 14 patients had anterior wall MI, 14 had IWMI, 2 had Non-STEMI. Out of 28 patients who were eligible for thrombolysis, 5 were given streptokinase as initial reperfusion therapy, 21 out of 23 patients who had obstructive CAD underwent PCI (balloon angioplasty + stenting).

### **Novel risk factors**

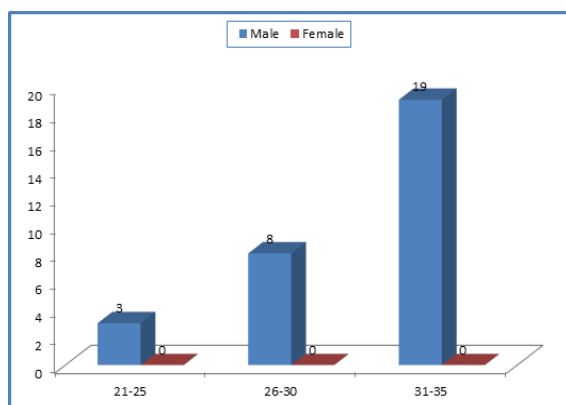
The novel risk factors are shown in [Table 2]. Homocysteine (66.66%) and lipoprotein (a) (46.66%) were two major newer risk factors in the present study followed by CRP (33%) and fibrinogen (30%). None of the patients tested positive for factor V leiden in our study.

**Table 1: Age and Sex distribution in studied patients**

Age (Years)	Male	Female	Total	Percentage
21 – 25	3	0	4	10%
26 – 30	8	0	6	26.66%
31 – 35	19	0	20	63.33%
Total	30	0	30	100%

**Table 2: Novel risk factors in 30 young MI patients**

Newer Risk Factors	No. of Patients	Percentage
Elevated lipoprotein(a)	14	46.66%
Hyperhomocysteinemia	20	66.66%
Factor V tested positive	0	0%
Hyperfibrinogenemia	9	30.00%
Elevated CRP	10	33.33%

**Figure 1: Age and sex distribution**

## DISCUSSION

There is a disturbing trend in recent times that shows that people in young age group are being affected by ischemic heart disease with increased frequency. It is now accepted that the development of premature CAD involves a complex interplay of physicochemical characteristics and metabolic alterations. These might be more evident or might have different implications in younger patients.

### Newer Risk Factors

#### Lipoprotein (a) [Lp (a)]

Lp (a) is an LDL like particle having structural homology to plasminogen. By displacing plasminogen, it reduces the formation of endogenous tissue plasminogen activator and hence confers the risk of thrombosis and atherosclerosis. In the present study 14 (46.66%) patients had elevated Lp (a) levels which is similar to other studies.<sup>[8-12]</sup> Lp (a) levels in excess of 20 mg/dl have been shown to be independent risk factor for MI and premature CAD.<sup>[13,14]</sup> Serum LP (a) level is not dependent on serum total cholesterol level and thus LP (a) had been an independent risk factor for the young patients with MI. Though, there have been studies correlating the elevated LP (a) levels and severity of coronary artery disease still there is a need to probe for more studies to assess the role of LP (a) as a risk factor to MI, especially in young patients. The measurement of LP (a) could be useful in informing the treatment of patients at high risk for ischemic heart disease and defining a suitable clinical target for LP (a) reduction.

#### Hyperhomocysteinemia

Hyperhomocysteinemia has been established as an independent risk factor for Coronary artery disease,

Cerebrovascular accident and peripheral vascular disease.<sup>[15-17]</sup> In a more recent review of 43 studies, Christen et al<sup>18</sup> have concluded that in contrast to cross-sectional and case control studies, results of prospective studies indicate less or no predictive ability for plasma homocysteine in causation of cardiovascular disease. Instead, elevated homocysteine level may be an acute phase reactant that is predominantly a marker of atherogenesis, or a consequence of other factor more closely linked to the risks of cardiovascular disease. Hyperhomocysteinemia increases the risk for coronary artery disease more in the presence of any other risk factor like smoking or hypercholesterolemia.

Our findings elevated homocysteine levels in 60% of the participants were comparable with the findings of other studies reported till date. However, large prospective studies are necessary to test whether lowering homocysteine level will decrease the risk of cardiovascular disease. The reason behind the high prevalence of hyperhomocysteinemia in our patients could be their diet as vegetarians have three times higher risks of hyperhomocysteinemia as compared to non-vegetarians and considering that majority of people adhere to vegetarian diet in Punjab.

### Thrombogenic factors

#### Factor V Leiden

None of our patients tested positive for the presence of factor V Leiden. This was in parallel with the findings of the study by Ricker et al,<sup>[19]</sup> who failed to find any relationship between the presence of factor V Leiden and the risk of Myocardial infarction or stroke. Similarly, the Physicians Health Study failed to establish any association between the presence of factor V Leiden and subsequent development of Myocardial infarction or stroke. Thus our results support the view that, though factor V Leiden leads to a hypercoagulable state (and is associated with venous thrombosis), it is not associated with Myocardial infarction in young.

#### Hyperfibrinogenemia

In the present study 9 (30%) of the 30 participants had hyperfibrinogenemia. This was similar to other studies.<sup>[20-23]</sup> Thus hyperfibrinogenemia is an important coronary risk factor in young MI patients. Elevated plasma fibrinogen levels cause a hypercoagulable state that could influence the degree and duration of thrombus formation at the time of coronary injury. The role of plasma fibrinogen levels in premature coronary artery disease is less clear. Therefore, further studies are needed for better understanding.

#### Elevated CRP levels

Elevated CRP levels were found in 10 patients (33.33%) in the present study. However studies like Honolulu Heart Program,<sup>[24]</sup> Physicians Health study and Multiple risk factor on intervention trial

(MRIFT) on middle aged men and Cardiovascular Health study 25 and Rural Health promotion project<sup>26</sup> on elderly men and women had shown that that CRP is a strong and robust independent risk factor. The possible reason for such a difference could be usage of statins before referral to higher centers and small number of patients in the present study. Therefore further studies with large number of patients and high- sensitivity CRP assay would be required to clarify the role of CRP in this group of patients. CRP's predictive power for vascular risk detection resides between 0.1 to 0.5 mg/dl – a level which is present in most of the healthy individuals without inflammation; hence a high sensitive assay is required. High sensitive CRP (hs-CRP) is well standardised and it has limits of detection as low as 0.02g/dl.

## CONCLUSION

Homocysteinemia is present in two thirds, lipoprotein (a) in half, CRP and fibrinogen in one third of very young ACS patients. Larger multicenter randomized control studies are needed in our country to confirm these findings and plan strategies for prevention and treatment of early and aggressive CAD in south Asians.

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