

Role of Statin and Frank Sign in Patients Experiencing PRE-ACS Pain to Predict Major Adverse Cardiovascular Events

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Introduction

A range of clinical manifestations including plaque formation in coronary vessels, its disruption, thrombosis, or embolization constitutes acute coronary syndrome (ACS).¹ It may lead to varying degrees of obstruction to coronary blood flow. It encompasses conditions like unstable angina, myocardial infarction (ST-elevation MI or non-ST elevation MI).² As the disease burden is increasing there is need for simple and reliable signs of atherosclerosis to prevent major adverse cardiovascular events (MACE).³

The pathological basis of developing acute coronary syndrome lies in the development of atherosclerosis in coronary arteries leading to complete or incomplete obstruction of coronary blood flow.³ The exact diagnosis of acute coronary syndrome rests on clinical manifestations, ECG findings, and biomarkers of necrosis.²

ABSTRACT

Objective: to assess the role of statins and Frank's sign in predicting major adverse cardiovascular events (MACE) among patients experiencing pre-acute coronary syndrome (pre-ACS) pain.

Methodology: A cross sectional study was conducted at KRL Hospital from Oct 2021 to March 2022. One hundred and one patients of both genders, using statins for at least 1 year due to Hypercholesterolemia, hospitalized for ACS, with or without ST-segment elevation, with an onset of symptoms during the previous 24 hours were included in our study.

Data was analyzed using SPSS 26.0. Chi square test was applied to see the association considering P values less than 0.05 as significant. Odds Ratio was calculated to see the risk of disease

Results: Males were predominant with more than half of the study population. Frank sign was observed in 56 patients out of which 29 patients (51.78%) developed Pre-ACS Pain having a p value of 0.20. Patients with Frank sign have a 0.5 times risk of developing Pre-ACS pain. 48 (47.52%) patients reported no Frank sign out of which 38 (79.16%) were taking Atorvastatin & 10 (20.84%) are taking Rosuvastatin. Rosuvastatin.

Conclusion: Prescribing statins should be done on an individual basis based on expert clinical opinion. Frank's sign has an extremely high correlation with pre-ACS pain. As a main preventive measure, prescribe statins to reduce the risk of post-acute aches and pains.

Keywords: Frank sign, Pre-Acs pain, Acute Coronary syndrome, Primary Prevention.

In developed high-income countries the prevalence of coronary artery disease is declining possibly due to better understanding of the disease process and treatment strategies. Whereas in developing countries of Southeast Asia like Pakistan this burden is continuously rising over the last decade.⁴ With men being considered the predominant target of the disease burden, a rise in women cases is also seen. delay in reporting and attribution of symptoms to be important or related to cardiac or non-cardiac causes is the major cause of mortality.⁵

American Heart Association (AHA) and the European Society of Cardiology (ESC) define "typical" symptom of ACS as pressure or squeezing pain in the center of the chest that lasts for at least 10 minutes and it may spread to the arms, neck, or jaw.⁶⁻⁷ This typical pain is also termed as Pre -ACS pain as it indicates impeding blood flow to the coronary arteries and needs to be evaluated clinically to reduce

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the deadly complication of Myocardial infarction (MI).⁵

While the atypical symptoms are “dyspnea, nausea, syncope, epigastric pain”. It is also seen that women present more with atypical symptoms, thus delay in seeking treatment.⁸

ACS represents a wide group of phenomena including inflammation, spasm, thrombosis, platelet aggregation following plaque formation. Cholesterol-lowering drugs such as Statins are originally designed to stabilize this process. Statins are more frequently prescribed in patients with hypercholesterolemia even if CAD is nonexistent. High levels of LDL cause thickening and narrowing of coronary arteries that can be reduced by statin use. Many studies demonstrate that high LDL cholesterol and non-HDL cholesterol and low HDL cholesterol levels are related to an increase risk of cardiovascular disease.⁹

There are certain physical signs that are predictors of atherosclerosis such as xanthelasma, corneal arcus and diagonal ear lobe crease or “Frank’s sign”.¹⁰ It’s a diagonal ear lobe crease that may vary in length and depth among patients but it’s typically present among older patients with coronary artery disease. Though its reliability is highly doubted. Studies also suggest that Frank sign can be considered another risk factor besides hypertension, diabetes, old age, smoking, and high cholesterol in predicting heart disease.⁴

This study aims to assess the role of statins and frank sign in patients experiencing PRE-ACS pain to predict major adverse cardiovascular events.

Methodology

A cross sectional study was conducted at KRL Hospital during the period of Oct 2021 to March 2022. A sample size of 101 patients was calculated using Rao soft calculator keeping confidence interval 95% & margin of error 5%. Convenience non-probability sampling was used.

All patients of both genders, using statins for at least 1 year due to Hypercholesterolemia, who were hospitalized for ACS, with or without ST-segment elevation, with an onset of symptoms during the previous 24 hours were included in our study. Patients who did not give consent and presented with history of COPD, Pneumonia, TB and asthma were excluded from the study.

Data was collected after the approval from ethical review committee of KRL Hospital and obtaining informed consent. The diagnosis of patients was made on ECG changes. Cholesterol, LDL levels, CRP, statins prescribed, Pre-ACS pain & frank sign were assessed. Patients with hypertension & diabetes were also noted as well as their diabetic control was checked.

IBM SPSS 26.0 was used to analyze data. Quantitative variables were presented as frequencies and percentages. Chi square test was applied to see the association considering P values less than 0.05 as significant. Odds Ratio was calculated to see the risk of disease.

Results

101 participants were included in the research, of which males were predominant with more than half of the study population. Mean age of patients was 54.83 ± 11.19 years. Patient Demographics are given in Table I.

Variables	Frequency	Percentages
Age		
24-50 years	33	32.68
51-80 years	68	67.32
Gender		
Male	77	76.23
Female	23	23.77

49 patients in our study had diabetes Mellitus (48.52%) whereas 52 (51.78%) patients had Hypertension. 31 patients (30.96%) patients had borderline cholesterol whereas 27 (26.47%) had high cholesterol levels having a mean of 180.18 ± 38.97 . 23 patients (22.77%) patients had borderline high triglycerides whereas 34 (33.66%) had high triglyceride levels having a mean of 184.19 ± 82.91 . 60 patients (59.40%) patients had low HDL levels whereas 41 (40.6%) had normal HDL levels having a mean of 38.86 ± 11.21 . 40 patients (39.60 %) patients had optimal high LDL levels whereas 09 (8.72%) had borderline high LDL levels having a mean of 117.37 ± 38.61 , as shown in Table II.

Out of 101 patients 20 had the established diagnosis of ACS and 27 had NSTEMI. 5 with angina and rest with different forms of MI. only 13% patients experienced pre -acs pain, while all of them use statin, either atorvastatin or rosuvastatin. Pre-acs pain was present in 4 patients with ACS and 5 patients with NSTEMI. Pre-ACS pain was present in

13.3% of the diabetic population and 3.22% of the hypertensive population. Pre-ACS pain was associated with ACS in 20% of the cases, whereas it was associated with NSTEMI in 18.5%, as shown in Table III.

Variables	N	%
Co-Morbid		
DM	49	48.52
HTN	52	51.78
Cholesterol		
Normal (below 170 mg/dL)	43	42.57
Borderline (170 to 199 mg/dL)	31	30.96
High (200 mg/dL or greater)	27	26.47
Triglycerides		
Normal (less than 150 mg/dl)	43	42.57
Borderline High (150–199 mg/dl)	23	22.77
High (200–499 mg/dl)	34	33.66
Very High (500 mg/dl and above)	01	1
HDL		
Low (Less than 40 mg/dL)	60	59.40
Normal (greater than 40 mg/dL)	41	40.6
LDL		
Optimal (Less than 100mg/dL)	40	39.60
Near Optimal (100-129mg/dL)	32	31.68
Borderline high (130-159 mg/dL)	9	8.72
High (160-189 mg/dL)	20	19.80

Frank sign was observed in 56 patients out of which 29 patients (51.78%) developed Pre-Acs Pain having a p value of 0.20. Patients with Frank sign have a 0.5 times risk of developing Pre ACS pain.

Diagnosis	N	%
AWMI	14	13.9
ACS	20	19.8
NSTEMI	27	26.7
INF MI	11	10.9
LAT MI	1	1.0
ANT MI	4	4.0
POST MI	2	2.0
EXT ANT MI	1	1.0
IWMI	9	8.9
ANGINA	5	5.0
IHD	1	1.0
USA	6	5.9

Since the p-value is less than our chosen significance level $\alpha = 0.05$, we can reject the null hypothesis, and conclude that there is an association between Pre-ACS pain in patients taking statins and patients having Frank Sign who are taking statins. There was a significant association between Pre-ACS pain in patients taking statins and patients having Frank Sign who are taking statins ($\chi^2(1) = 5.379$, $p = 0.020$), as shown in Table IV.

88 (87.12%) patients reported no pre-ACS pain out of which 68(77.27%) were taking Atorvastatin & 20 (22.73%) were taking Rosuvastatin. There is 2.91 times less risk of developing Pre-ACS pain in patients on Statins (OR = 2.914, 95% CI = 0.879-9.666). 48 (47.52%) patients reported no Frank sign out of which 38 (79.16%) were taking Atorvastatin & 10 (20.84%) were taking Rosuvastatin. There is 1.64 times less risk of developing Frank Sign in patients on Statins (OR = 1.643, 95% CI = 0.661-4.085), as shown in Table V.

Pre-ACS Pain	Frank Sign		P-value	Odds ratio	Confidence Interval
	Yes	No			
No	33	23	0.020	0.500	0.375 - 0.668
Yes	29	16			

Pre-ACS Pain	Statins		P-value	Odds ratio	Confidence Interval
	A	R			
No	68	20	0.071	2.914	0.879 - 9.666
Yes	7	06			
			Frank Sign		
No	38	10	0.283	1.643	0.661- 4.085
Yes	37	16			

88 (87.12%) patients reported no pre-ACS pain out of which 68 (77.27%) were taking Atorvastatin & 20 (22.73%) were taking Rosuvastatin. 13 (12.88%) patients reported pre-ACS pain out of which 07 (53.84%) were taking Atorvastatin whereas Rosuvastatin was taken by 06 (46.16%) patients, as shown in Figure I.

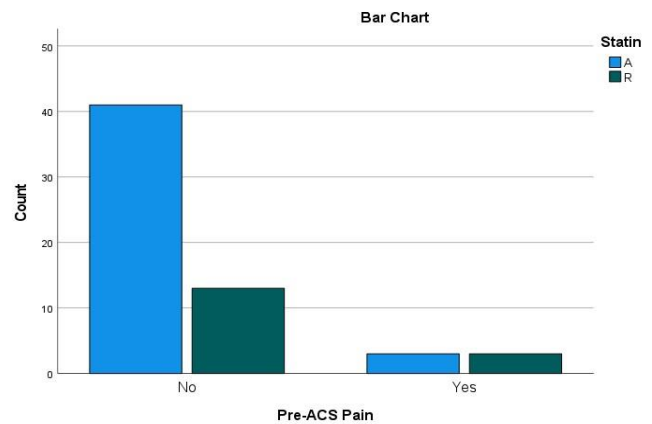


Figure I. Frequency of Patients on Statins with Pre-ACS Pain.

48 (47.52%) patients reported no Frank sign out of which 38 (79.16%) were taking Atorvastatin & 10 (20.84%) were taking Rosuvastatin. 53 (52.47%)

patients reported Frank sign out of which 37 (69.81%) were taking Atorvastatin & 16 (30.19%) were taking Rosuvastatin, as shown in Figure II.

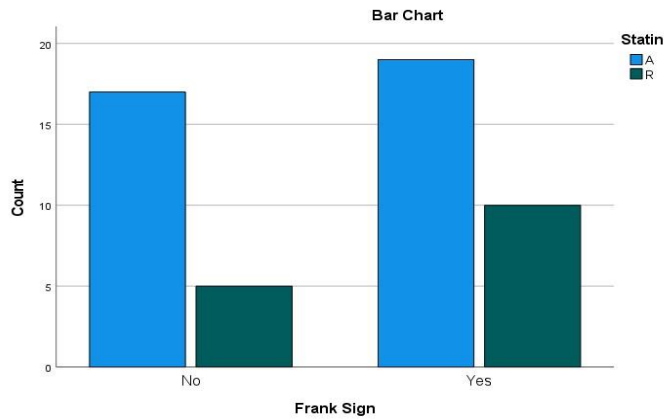


Figure II: Frequency of Patients on Statins with Frank Sign.

Discussion

Chest pain is classic presentation of acute coronary syndrome and remains a reliable predictor of clinical outcomes related to it. In a multinational prospective study chest pain is properly classified as 'typical', 'atypical' or 'dyspnea'.⁶ If the patients are diagnosed with pre-ACS pain they should be promptly managed to prevent MI or mortality related to it. In the same study patients who didn't present with chest pain were less likely to receive immediate interventions and were more likely to develop heart failure and in worse cases death.⁶

Following hospital discharge in patients with ACS, high potency statins are perceived to reduce further cardiovascular events. All patients in our study were already using statins (either atorvastatin or rosuvastatin). We concluded that there is significant association of statin use and pre-ACS pain ($p=0.71$). There is 2.94 times less risk of developing pre-acs pain in patients taking statins having a confidence interval of 0.87-9.66. Any patient either in -hospital or emergency ward with the complaint of chest pain and receiving statins followed by the diagnosis of ACS is considered emergent. A study done in Sweden observed that all-cause mortality (non-CVD and CVD) related events were reduced using statin use.⁷ Loannou A et al studied the pleotropic effects of statins on reducing inflammation, oxidative stress, and coagulation factors related to stable angina.¹¹

They concluded that not only effective in the management of acute symptoms of angina but also an excellent drug to prevent atherosclerotic disease. A meta-analysis studying randomized control trials

suggests the effect of statins (A and R) on patients with angina and ACS who are undergoing PCI to detect Major adverse cardiac events (MACE). They didn't find any clear association between statin dose and long-term outcome but considered it safe and healthy.⁸

A study done in Korea suggests that statin therapy did not reduce adverse cardiovascular events such as acute coronary syndrome, new-onset arrhythmia or cardiac death in a 3-year follow-up.¹² The adverse outcomes using statins use can be regarded as nonadherence, dose reduction, or switching to another alternative statin after NSTEMI-ACS.¹³ European heart journal reported that patients who did not adhere to statin treatment following 1 month of NSTEMI had higher chances of developing high lipid levels and inflammation related to cardiovascular disease.¹⁴

Our study suggests there is significant association between statin use and Frank sign in ACS patients. That shows that patients who take statins, either due to CAD or dyslipidemia are 1.64 times less risk of developing Frank's sign. It was supported by Oda N et al who studied the relation of endothelial dysfunction and Frank's sign. According to parameters patients using statin were less likely to develop ear lobe crease with $p<0.001$.¹⁵ It was first described by Dr. Sonders T. Frank in 1973 but during the last decade it has become an important physical sign for clinicians to diagnose cardiovascular disease. A study done in CMH, Lahore concludes that Frank sign has a positive predictive value of 68.5% and sensitivity of 50.7%, as a predictor of atherosclerotic disease.¹⁶

According to our study, 48 Patients with no Frank sign were also taking statins OR = 1.643, 95% CI = 0.661-4.085. Nazal et al support the notion that patients with Frank sign had an increased risk of CAD and were cautioned even before being diagnosed with CAD.¹⁷ Considering the pathophysiology of earlobe crease and CAD are similar such as pre-arteriole wall thickening and the presence of the same scavenger receptors of macrophages from the atheromatous plaque on the peptide chain of earlobe collagen.¹⁸ Frank's sign should be considered an individual and independent risk factor in patients with ACS. A case report showed a patient with chest pain and bilateral diagonal ear lobe crease to have significant coronary artery disease on angiography.¹⁹ Statins improve endothelial function, reduce the

inflammatory response, decrease adhesion molecule's expression to vascular endothelium and decrease apoptosis.²⁰

These characteristics not only reduce MACE but also reduce the development of Earlobe crease. Further cohort studies are needed to find similar associations considering the same characteristics of patients. One of the causes of discrepancies in finding an association between Frank's sign and statin use in patients experiencing pre-ACS pain is age. As Frank's sign and CAD are associated with older age.

The current study has certain limitations. First, the study was conducted at only one center in Islamabad; therefore, the findings of this study should be confirmed in other prospective clinical trials with long-term clinical follow-ups. Second, the

current study included a population in Pakistan only; thus, it might not be possible to generalize our findings to other regions.

Considering the current study results, it is important to carry out future studies in a larger sample size and involve more study sites to assess whether statin therapy is effective enough to reduce the probability of pre-ACS pain and Frank's sign.

Conclusion

According to our findings, statin medication is beneficial enough to minimize the risk of preACS pain and Frank's sign has an extremely high correlation with pre-ACS pain. As a main preventive measure, prescribing statins should be done on an individual basis based on expert clinical opinion.

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