

# A CLINICAL STUDY OF LIPID ABNORMALITIES AND ANGIOGRAPHIC PROFILE IN PATIENTS OF CORONARY ARTERY DISEASE ON STATINS UNDERGOING CORONARY ANGIOGRAPHY

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## ABSTRACT

**Background:** The traditional risk factors of coronary artery disease (CAD) are Age, Genetic factors, Smoking, Hypertension, Diabetes and Dyslipidemia occurrence of each of which influence the presentations of the disease and its severity of the angiographic profile. With changing scenario of risk factor assessment due to global increase in CAD and starting the statins quite early for patients with risk factors without the CAD, we want to see the present status of lipids in patients undergoing coronary angiogram (CAG).

**Objective:** We aim to evaluate the occurrence of various risk factors especially lipid abnormalities and correlate them with angiographic severity in patients presenting with CAD and undergoing CAG

**Methods:** We evaluated 504 consecutive patients already on statins presenting with CAD and undergoing coronary angiogram between August 2015 to December 2016 at our center. We obtained the detailed clinical, biochemical and angiographic profile from the records and analyzed the occurrence of risk factors and correlated the lipid abnormalities and angiographic profile for any statistical significance using Minitab 17 software.

**Results:** Of the total 504 patients 331 (65.6%) were males. 347 (68.8%) had Hypertension, 258 (51.1%) had DM, 370 (73.4%) had Dyslipidemia and 128 (25.3%) had LV dysfunction. 303 (60.1%) had abnormal coronary angiograms. Of these 148 (48.8%) had single vessel disease (SVD), 85 (28%) had double vessel disease (DVD), 70 (23.2%) had triple vessel disease (TVD). Abnormal CAG is significantly found in Males ( $p = 0.03$ ), Hypertension ( $p = 0.00$ ), DM ( $P = 0.01$ ) and LV dysfunction ( $p = 0.00$ ). Dyslipidemia had tendency for correlation with abnormal CAG but not statistically significant ( $p = 0.07$ ). The levels of LDL, HDL and triglycerides didn't correlate with the angiographic abnormality. In patients with severe CAD i.e. TVD the determinants are age ( $p = 0.01$ ), male sex ( $p = 0.01$ ), smoking ( $p = 0.02$ ), HTN ( $p = 0.002$ ), DM ( $p = 0.03$ ), LV dysfunction ( $p = 0.006$ ). Neither

Dyslipidemia ( $p = 0.2$ ) nor levels of Total cholesterol, HDL, LDL, TG determined the occurrence of TVD. Occurrence of DVD correlated significantly with age ( $p = 0.001$ ), male gender ( $p = 0.002$ ) and LV dysfunction ( $p = 0.02$ ). In SVD Male gender ( $p = 0.003$ ), HTN ( $p = 0.001$ ), LV dysfunction ( $p = 0.00$ ), TG ( $p = 0.03$ ) had showed significant correlation. Occurrence of Dyslipidemia didn't show any correlation with the occurrence of SVD ( $p = 0.26$ ) or DVD ( $p = 0.43$ ). High levels of individual lipid components except TG in SVD didn't show any correlation in occurrence of DVD or SVD.

**Conclusion:** In patients presenting with CAD on statins with abnormal CAG, age, male gender, HTN, DM and LV dysfunction of any severity are the determinants but not the occurrence of Dyslipidemia or the levels of Total cholesterol of LDL, HDL or TG. The occurrence of Dyslipidemia or levels of individual lipid component abnormalities except for high levels of TG in SVD didn't show any significant correlation with the occurrence of SVD, DVD or TVD.

**Keywords:** Dyslipidemia, Coronary Artery Disease

## INTRODUCTION:

The traditional risk factors for Coronary artery disease (CAD) are age, genetic factors, smoking, hypertension (HTN), diabetes (DM) and dyslipidemia. The occurrence of each of these risk factors may influence the presentation of the disease and severity of the angiographic profile. Dyslipidemia including high LDL cholesterol and low HDL is one of the most commonly associated and frequently addressed risk factors of present CAD. Use of the statins to control dyslipidemia is an important component of today's therapy in patients presenting with or having risk factors for CAD. Benefit of statins in secondary prevention of the cardiovascular disease is proved beyond doubt in many clinical trials. But the use of statins in the primary prevention of cardiovascular disease in asymptomatic patients is less well established[1]. At least five authoritative guidelines, including the recent publication from the US Preventive Services Task Force addressed this issue[2-7]. Their differing recommendations, however, suggest considerable uncertainty in the underlying data, creating

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confusion for both clinicians and patients. With the changing scenario of risk factor assessment due to global increase in cardiovascular disease and there is a trend towards the use of statins quite early in asymptomatic people with risk factors but without the established CAD. There may be a change in disease profile of CAD in patients taking statins early in the course of the disease, severity of which may correlate with the control of various lipid components.

The aim of the present study is to evaluate the present status of the lipids and their correlation with the angiographic profile of the patients presenting with stable CAD or acute coronary syndromes (ACS) undergoing coronary angiography (CAG) who is already taking statins either for secondary or primary prevention.

#### **MATERIALS & METHODS:**

We have retrospectively analyzed the data of 504 patients who are already using statins either for primary or secondary prevention of cardiovascular disease presenting with symptoms of CAD and undergoing CAG in the Nizam's Institute of Medical Sciences, Hyderabad, India between August 2015 to December 2016. We included both chronic stable angina (CSA) or acute coronary syndrome (ACS) i.e. unstable angina (UA), myocardial infarction (STEMI/NSTEMI) patients in our study. We excluded patients with significant renal, hepatic & other systemic dysfunction and patients who are in severe cardiogenic shock.

Institutional ethical guidelines were followed. Informed consent was taken from all the patients before inclusion into the study. All patients were evaluated after a detailed history, physical examination, and biochemical investigations including fasting lipid profile. Demographic and clinical characteristics of patients were documented.

All patients were pre-treated with oral sedation and antihistamine before CAG. It was done through either radial or femoral route. All the patients were classified according to their angiographic profile as single vessel disease (SVD) i.e. > 70% stenosis involving one epicardial coronary artery or double vessel disease (DVD) i.e. > 70% stenosis in 2 epicardial coronary arteries or triple vessel disease (TVD) i.e. > 70% stenosis of 3 epicardial coronaries or 2 epicardial coronaries + > 50 % stenosis of the left main coronary artery (LMCA).

Patients have monitored for any route related complications like hematoma or bleeding for 24 hrs. ECGs or cardiac enzymes were performed in patients complaining of chest pain after the procedure. They were discharged after 24 hours in a stable condition if CAG is normal or shows mild disease. Patients having significantly abnormal CAGs are planned for early revascularization either with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

These patients are divided into two subgroups depending on whether having dyslipidemia or not. Dyslipidemia in patients who are on statins is defined as patients having one or more of the following i.e. Total cholesterol (TC) > 200 mg/dl, LDL cholesterol (LDL) > 130 mg/dl, Triglycerides (TG) > 150 mg/dl, HDL cholesterol (HDL) < 40 mg/dl in males and < 50 mg/dl in females. Most of the baseline demography, risk factors, biochemical variables, clinical and angiographic profiles and complications were compared between these.

#### **Statistical Analysis:**

Data analysis was performed using Minitab version 17 software. The frequency of abnormal results was determined for each marker and compared by the *Fisher's exact test*. Continuous variables were expressed as mean  $\pm$  SD and were compared by the ANOVA test. Multiple regression analysis was performed to test the significance between two subgroups of normal Vs abnormal CAG for different variables including dyslipidemia, individual lipid components and non-lipid variables with occurrence of SVD, DVD or TVD. Categorical variables were compared using chi-square test. Results with a 'p' value < 0.05 are considered to be significant.

#### **RESULTS:**

Totally 504 patients presenting with CAD undergoing CAG between August 2015 to December 2016 were included in the study. Of the total 504 patients, 331 (65.6%) were males. Average age at presentation is 56.50  $\pm$  11.25 years. Of them 347 (68.8%) had Hypertension, 258 (51.1%) had DM, 370 (73.4%) had Dyslipidemia and 104 (20.6%) are smokers. 425 (84.3%) presented with CSA and 79 (15.6%) with ACS. 128 (25.3%) patients had LV dysfunction. Mean hemoglobin is 12.78  $\pm$  1.95 gm/dL.

Baseline demographic characteristics of the patients are depicted in Table 1.

Table 1: Baseline Demographic Characteristics

Parameter	Value
Age	56.50 ± 11.25
Males	331 (65.6 %)
Hypertension	347(68.8 %)
Diabetes	258(51.1 %)
Smoking	104(20.6 %)
CSA	425(84.3 %)
ACS	79(15.6 %)
LV dysfunction	128(25.3 %)
Hemoglobin	12.78 ± 1.95
Dyslipidemia	370(73.4 %)
TC (mg/dl)	147.16 ± 93.72
LDL (mg/dl)	76.89 ± 39.40
TG (mg/dl)	133.88 ± 61.60
HDL (mg/dl)	42.23 ± 16.60

Of the total patients 303 (60.1%) had abnormal coronary angiograms. Of these 148 (48.8%) had single vessel disease (SVD), 85 (28%) had double vessel disease (DVD), 70 (23.2%) had triple vessel disease (TVD). Basic angiographic profile of the patients is depicted in Table 2.

Table 2: Basic Angiographic Profile

CAG	n = 504
Normal	201(39.8 %)
SVD	148(29.3 %)
DVD	85(16.9 %)
TVD	70(13.9 %)

Binary logistic regression analysis correlating the abnormal CAG with various patient characteristics showed that abnormal CAG is significantly found in Males (p = 0.03), Hypertension (p = 0.00), DM (p = 0.01) and LV dysfunction (p = 0.00). Dyslipidemia had a tendency for correlation with abnormal CAG but not statistically significant (p = 0.07). The levels of TC, LDL, HDL and triglycerides didn't correlate with the angiographic abnormality (Table .3).

Table 3: p Value correlating the abnormal CAG

Variable	p Value
Age	0.15
Male sex	0.003
HTN	0.00
DM	0.011
Smoking	0.62
LV dysfunction	0.00
Dyslipidemia	0.07
ACS/CSA	0.15
TC (mg/dl)	0.24
LDL (mg/dl)	0.27
HDL (mg/dl)	0.32
TG (mg/dl)	0.84
Hemoglobin (gm /dl)	0.72

In the patients having dyslipidemia there is no significant difference from patients not having dyslipidemia in occurrence of abnormal CAG (p = 0.5) or its severity in form of SVD (p = 0.32), DVD (p = 0.78) and TVD (p = 0.88) (Table 4).

Table 4: CAG in Dyslipidemia+ vs No Dyslipidemia

CAG	Dyslipidemia+	No Dyslipidemia	p Value
Normal Coronaries	151 (40.8%)	50 (37.3%)	0.537
SVD	104 (28.1%)	44(32.8%)	0.320
DVD	64(17.2%)	21(15.6%)	0.788
TVD	51(13.7%)	19(14.1%)	0.885

Using Multiple logistic regression analysis we have compared the occurrence of various risk factors including dyslipidemia along with individual lipid components and other important characteristics in patients with normal CAGs Vs those who are having different severities of CAD in the form of SVD, DVD or TVD. In patients with severe CAD i.e. TVD the determinants are age (p = 0.01), Male sex (p = 0.01), smoking (p = 0.02), HTN (p = 0.002), DM (p = 0.03), LV dysfunction (p = 0.006). Neither Dyslipidemia (p = 0.2) nor levels of Total cholesterol, HDL, LDL, TG determined the occurrence of TVD.

Occurrence of DVD correlated significantly with age (p 0.001) male gender (p = 0.002) and LV dysfunction (p = 0.02). Neither dyslipidemia (p = 0.43) nor the individual

lipid components had showed significant correlation. HTN ( $p = 0.069$ ) and DM ( $p = 0.074$ ) have tendency for correlation with occurrence of DVD but not statistically significant.

In SVD, male gender ( $p = 0.03$ ), HTN ( $p = 0.01$ ), LV dysfunction ( $p = 0.00$ ) had showed significant correlation. High levels of TG showed significant correlation with the occurrence of SVD with  $p$  value of 0.03. Occurrence of Dyslipidemia ( $p = 0.2$ ) and other lipid component have not shown any correlation with the occurrence of SVD.

Multiple logistic regression analysis and  $p$  values for different variables in normal Vs abnormal CAGs depicted in Table 5.

Table 5:  $p$  values for different variables in normal Vs abnormal CAGs

Variable	SVD	DVD	TVD
Age (Yrs)	0.07	0.001	0.01
Male sex	0.03	0.002	0.01
Smoking	0.63	0.52	0.02
HTN	0.01	0.069	0.002
DM	0.89	0.074	0.03
LV dysfunction	0.003	0.02	0.006
Dyslipidemia	0.26	0.43	0.27
TC (mg/dl)	0.17	0.71	0.99
LDL(mg/dl)	0.77	0.78	0.54
TG (mg/dl)	0.03	0.29	0.65
HDL (mg/dl)	0.74	0.77	0.49

## DISCUSSION:

Use of statins has become part and parcel of routine cardiology practice in the treatment and prevention of the cardiovascular diseases (CVD) especially CAD. The benefits of statin therapy are attributed to pleiotropic effects that are independent of a lowering of the LDL-cholesterol level. These effects include improved endothelial function [8], reduced vascular inflammation [9, 10, 11] and reduced platelet adhesion and thrombosis [12].

The efficacy of the statins in the secondary prevention of the CVD is proved beyond doubt in number of well conducted randomized clinical trials (RCTs) including 4S (Scandinavian Simvastatin Survival Study<sup>13</sup>, HPS (Heart Protection Study) [13], CARE (Cholesterol And Recurrent Events)[14], LIPID (Long- Term Intervention

with Pravastatin in Ischaemic Disease) [15]. Thus use of statins became a standard therapy for the secondary prevention of cardiovascular events in patients with CVD and has a high risk of recurrent cardiovascular events.

In addition to start statin as early as possible, it was proved in many trials to titrate the dose of statins to the maximum to obtain best results in secondary prevention. According to (PROVE-IT [Pravastatin or Atorvastatin Evaluation and Infection Therapy][16], TNT [Treating to New Targets] [17], IDEAL [Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering][18] the target dose for an individual patient should be selected as a dose close to or at the highest level the individual patient tolerates without side effects. Most of the standard guidelines advocate using of statins and titration to the maximum tolerated dose in secondary prevention of the CVD.

But the scenario was not same in all patients. Results of multiple randomized trials completed since 2005 do not support the notion that statin therapy has constant relative benefits across all risk groups, yet this assumption remains the fundamental justification for arguments to base therapy on absolute risk. The four important trials, CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure)[19], AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) [20], 4D (German Diabetes and Dialysis Study) [21], and GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell' Insufficienza Cardiaca-Heart Failure) trials [22], in total included 13,613 patients and were reported between 2005 and 2009. All four of these well-conducted trials enrolled high-absolute-risk patients who achieved large low density lipoprotein (LDL) cholesterol reductions with statin therapy. Yet none showed significant clinical benefit in the secondary prevention of CVD.

Adding to the confusion created by these four trials some more important RCTs had shown significant benefit of using statins in primary prevention that are at very low risk of CVD. On the basis of high-quality randomized trial data, statin therapy can be considered as an adjunct to diet, exercise, and smoking cessation in the setting of primary prevention for those aged 50 and over with either diabetes (CARDS [Collaborative Atorvastatin Diabetes Study][23], elevated LDL cholesterol (WOSCOPS [West of Scotland Coronary

Prevention Study [24], MEGA) [25], low HDL cholesterol (AFCAPS)[26], or elevated hsCRP (JUPITER)[27]. These trials included 32,621 primary prevention patients and were published between 1998 and 2008, enrolled low-absolute-risk patients, most of whom would not qualify for statin therapy under any current guideline issued in the United States or Europe. Yet each showed the marked benefit of statin therapy.

According to the accumulated data and most of the standard guidelines now the scenario has changed to start the statins as early as possible especially in the primary prevention of the CVD. Most of the physicians are starting statins at least in low dose as soon as the detection of risk factors before developing CVD. Most of the patients were started on statins for high TC, LDL or low HDL as a part primary prevention. Yet many of the patients present with CAD in whom it is very difficult to predict the lipids as a risk factor as most of them would already be regularly taking statins and have altered or suppressed levels of lipids. Only few of them are qualified to be called as having dyslipidemia. In this scenario, we want to study the effect of dyslipidemia in patients who are already on statins and presenting with CAD, undergoing CAG in our institution and correlating the severity of CAD with lipids and other risk factors.

We have enrolled 504 consecutive patients regularly taking statins presenting with stable or unstable CAD in the study undergo CAG in whom lipid parameters might have been altered by the time of presentation. We have correlated the angiographic profile with the occurrence of lipid and non-lipid risk factors and tested for any significance. In all previously mentioned primary and secondary prevention trials the primary and secondary endpoints were CV mortality and occurrence of recurrent CV events and none of the studies had correlated the angiographic severity of the CAD with the lipid levels. Two recent trials had addressed this issue and correlated the consequences of intensive lipid lowering with high dose statins on angiographic regression of the atheromatous plaque. Intensive lipid-lowering therapy with statins not only improves survival rates and clinical outcomes but also reduces the progression of atherosclerosis [28-31]. The recent REVERSAL of Atherosclerosis with Lipitor (REVERSAL) study [29] showed that progression of the atheroma plaque volume was less with an aggressive dose of statin than with a moderate dose of statin.

Another study, the ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-derived Coronary Atheroma Burden) trial [32], demonstrated that intensive statin therapy with 40 mg Rosuvastatin daily could induce regression of coronary atherosclerosis. Furthermore, a very strong linear relationship was found between the LDL-cholesterol levels achieved and the course of atherosclerosis. But our study is not an interventional study and it is intended to see the correlation on dyslipidemia with the angiographic profile of the patients undergoing CAG.

Of the total 504 patients 331 (65.6%) were males. Average age at presentation is  $56.50 \pm 11.25$  years. 347 (68.8%) had Hypertension, 258 (51.1%) had DM, 370 (73.4%) had Dyslipidemia and 104 (20.6%) are smokers. 425 (84.3%) presented with CSA and 79 (15.6%) with ACS. 102 (20.2%) patients had LV dysfunction. Of these 128 patients, 45(35.1%) had mild, 37 (28.9%) had moderate and 46(35.9%) had severe LV dysfunction. Most of the patients presenting with ACS had some degree of LV dysfunction and most of the patients with moderate to severe LV dysfunction had TVD in CAG. Mean hemoglobin is  $12.78 \pm 1.95$  gm /dl. Mean Total cholesterol is  $147.16 \pm 93.7$  mg/dl, Triglycerides  $133.88 \pm 61.60$  mg/dl, LDL  $76.89 \pm 39.40$  mg/dl and HDL  $42.23 \pm 16.60$  mg/dl. A subgroup analysis is performed between males Vs females and diabetics Vs non-diabetics for mean lipid parameters. There is no significant difference is found among these groups in any of the individual lipid components. The occurrence of LV dysfunction is more in males (30.8% Vs 15.0%  $p = 0.000$ ), females more commonly presented with CSA (80.6% in males Vs 91.3% in females;  $p = 0.00$ ), and males with ACS (19.3% in males Vs 8.6% in females). CAG was done in 393 (77.9%) via radial route and in 111 (22.1%) via femoral route. Again there is no significant difference between the male and female subgroups ( $p = 0.17$ ). More number of catheters were required in males ( $1.47 \pm 0.59$  Vs  $1.25 \pm 0.47$ ;  $p = 0.03$ ). The average amount of contrast used was  $48.12 \pm 7.24$  ml.

At least one of the epicardial coronaries showing > 70% stenosis was defined as abnormal CAG. In the total 504 patients undergoing CAG 303 (60.1%) had abnormal CAGs. Of the patients having abnormal CAG, 148 (48.8%) had single vessel disease (SVD), 85 (28%) had double vessel disease (DVD), 70 (23.2%) had triple vessel disease (TVD). Females had more incidence of normal coronaries in the coronary angiogram (33.8% in males Vs

51.4% in females)  $p = 0.00$ , There is no significant difference between male and female subgroups in the occurrence of SVD, DVD or TVD.

We have subdivided the patients depending on having dyslipidemia or not, defined as having at least one of the following i.e.  $TC > 200\text{mg/dl}$ ,  $TG > 150\text{ mg/dl}$ ,  $LDL > 130\text{ mg/dl}$  and  $HDL < 40\text{ mg/dl}$  in males,  $50\text{ mg/dl}$  in females. According to this criteria, 370 (73.4%) are qualified to be having dyslipidemia. We have compared the angiographic profile between these two subgroups. By using binary logistic regression we couldn't find in any difference of occurrence of normal CAGs ( $p = 0.53$ ), SVD ( $p = 0.32$ ), DVD ( $p = 0.78$ ) and TVD ( $p = 0.88$ ) between these subgroups.

We have divided the patients into two groups depending on having normal Vs abnormal CAG. Patients having abnormal CAG were again subdivided into SVD, DVD or TVD. We have compared these subgroups using multiple logistic regression for different baseline characteristics and risk factors including dyslipidemia and individual lipid components, tested for the significance. In patients presenting with severe CAD i.e. TVD there is a significant correlation between age ( $p = 0.01$ ), male sex ( $p = 0.01$ ), smoking ( $p = 0.02$ ), HTN ( $p = 0.002$ ), DM ( $p = 0.03$ ), LV dysfunction ( $p = 0.006$ ). Neither Dyslipidemia ( $p = 0.2$ ) nor levels of Total cholesterol, HDL, LDL, TG determined the occurrence of TVD. Occurrence of DVD correlated significantly with age ( $p = 0.001$ ) male gender ( $p = 0.002$ ) and LV dysfunction ( $p = 0.02$ ). In patients presenting with DVD also neither dyslipidemia ( $p = 0.43$ ) nor the individual lipid components had shown significant correlation. HTN ( $p = 0.069$ ) and DM ( $p = 0.074$ ) have tendency for correlation with occurrence of DVD but not statistically significant. Male gender ( $p = 0.03$ ), HTN ( $p = 0.01$ ), LV dysfunction ( $p = 0.00$ ) are the primary determinants of occurrence of SVD. High levels of TG showed significant correlation with the occurrence of SVD with  $p$  value of 0.03. Occurrence of Dyslipidemia ( $p = 0.2$ ) and other lipid component didn't show any correlation with the occurrence of SVD. Occurrence of dyslipidemia on a whole didn't show any significant correlation for the occurrence of any degree of CAD.

#### CONCLUSION:

In patients who are already on statins and presenting with CAD and found to be having abnormal CAG,

primary determinants factors for the occurrence of CAD are age, male sex, HTN, DM and LV dysfunction of any severity but not dyslipidemia or the levels of TC, LDL, HDL or TG. Occurrence of dyslipidemia or levels of individual lipid component abnormalities except for high levels of TG in SVD didn't show any significant correlation with the occurrence of SVD, DVD or TVD.

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