## Original Articles

# High Fibrinogen Level is An Independent Predictor of Presence and Severity of Coronary Artery Disease

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***Key Words:*** *Fibrinogen, Coronary artery disease.*

**Abstract:**

***Background:*** *Fibrinogen has been identified as an independent risk factor for cardiovascular disease and associated with traditional cardiovascular risk factors. Few reports have so far investigated the relationship between fibrinogen levels and the extent of coronary artery disease (CAD) as evaluated by coronary angiography. Therefore the current study was carried out to evaluate the relationship between fibrinogen levels and the extent of CAD as evidenced by coronary angiography.*

***Method:*** *A total of 210 patients having ischemic heart disease including chronic stable angina, unstable angina, non-ST elevated myocardial infarction & ST elevated myocardial infarction were evaluated in National Institute of Cardiovascular Disease (NICVD), Dhaka with a view to find out the relationship between fibrinogen levels and the extent of CAD undergoing coronary angiography. Patients were divided in 3 groups according to fibrinogen levels: Group I = fibrinogen levels <400 mg/dl, Group II = fibrinogen levels (400-600) mg/dl, Group III = fibrinogen levels > 600 mg/dl. In this study, angiographic severity was assessed by vessel score, stenosis score and lesion morphology and tries to find out their relationship with angiographic severity and fibrinogen level.*

***Result:*** *Using a prospective analytic design we studied 210 patients who were divided into 3 groups : Vessel score in Group I, Group II & Group III were 1.14 ± 0.56, 2.24 ± 0.58, & 3.00 ± 0.65 respectively which was statistically significant ($p < 0.01$) and Stenosis score in group- I, group- II & group- III were 6.00 ± 4.19, 18.72 ± 4.94, & 32.41 ± 15.75 respectively which was statistically significant ($p < 0.01$). Regarding morphology of the lesions, complex lesions in group I, group II & group III were 21%, 32% & 39% respectively (statistically significant; $p < 0.01$).*

***Conclusion:*** *High fibrinogen level is independently and significantly associated with more severe coronary artery disease. Serum fibrinogen can be used as a new and even simpler tool for risk stratification in acute coronary syndrome.*

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**Introduction:**

Numerous evidence suggests that thrombosis, endothelial dysfunction and inflammation are strongly associated with coronary artery disease (CAD). Inflammation plays a crucial role in characterizing the formation of atheromatous plaque, as well as its progress. [1-4] The secretion of proinflammatory cytokines from the vascular endothelium as well as from macrophages induces the production of inflammatory molecules that are measured in the circulation, such as C-reactive protein (CRP), serum amyloid A and fibrinogen.[1.3] More than 20 years ago, the Northwick Park Heart Study,[5] a prospective study of middle-aged men, reported that elevated levels of fibrinogen, factors VII (FVII) and VIII (FVIII), and von Willebrand factor (vWF) predicted future coronary events. Elevated fibrinogen levels might therefore be an indicator of, and contribute to, the formation and progression of atherosclerotic plaques. Increased fibrinogen levels have also been identified as an important risk factor for future cardiovascular events in several prospective long-term studies of apparently healthy individuals[6-10] and patients with stable coronary

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artery disease.[11] However, the prognostic influence of increased fibrinogen levels in acute coronary syndromes has been investigated in only a few studies and with conflicting results.[12,13] In unstable coronary artery disease (ie, unstable angina or non–Q-wave myocardial infarction), plaque rupture with a superimposed thrombus seems to be the main pathophysiological mechanism.[14] Fibrinogen participates in platelet aggregation and is the substrate for fibrin formation. Plasma fibrinogen is an important component of the coagulation cascade, as well as a major determinant of blood viscosity and blood flow. Increasing evidence from epidemiological studies suggests that elevated plasma fibrinogen levels are associated with an increased risk of cardiovascular disorders, including ischaemic heart disease (IHD), stroke and other thromboembolism.[15] This increase in plasma fibrinogen levels may promote a prothrombotic or hypercoagulable state, and may, in part, explain the risk of stroke and thromboembolism in conditions such as atrial fibrillation (AF). Nevertheless, the relationship between hyperfibrinogenemia, atherosclerosis and thrombosis is complicated. As the process of thrombogenesis is very closely related to atheroma formation (atherogenesis), it follows that specific thrombogenic factors such as fibrinogen may play key roles in the process of atherosclerotic lesion formation, with subsequent effects on cardiovascular diseases.

Several studies have focused on fibrinogen, demonstrating a strong association with the presence of CAD. The Gothenburg Study[16] reported that plasma fibrinogen levels represent an independent risk factor for myocardial infarction (MI) and stroke in univariate analysis. Similarly, the Framingham study[17] demonstrated that the risk for MI and stroke increased progressively along with fibrinogen levels. The effect of fibrinogen levels on cardiovascular risk was even greater in young individuals and was similar to the effect of known risk factors such as hypertension, diabetes mellitus, and smoking. Repeated meta-analyses and reviews have shown that increased concentrations of fibrinogen are associated with the development or presence of atherothrombotic disease. Few reports have so far investigated the relationship between fibrinogen levels and the extent of coronary artery disease (CAD) as evaluated by coronary angiography. Thus, the aim of the current study was to evaluate the relationship between fibrinogen levels and the extent of CAD undergoing coronary angiography.

**Methods:**

A total of 210 consecutive patients undergoing coronary angiography were included in the study between January 2010 and December 2011 at National Institute of Cardiovascular Disease (NICVD), Dhaka. Informed consent was obtained from all patients before angiography. The study was approved by our local ethical committee. All demographic and clinical data were prospectively collected in a dedicated database. No exclusion criteria were applied. Blood sample was drawn for serum fibrinogen level before angiographic procedure. Patients were divided in 3 groups according to fibrinogen levels: Group I = fibrinogen levels <400 mg/dl, Group II = fibrinogen levels (400-600) mg/dl, Group III = fibrinogen levels > 600 mg/dl. Level of fibrinogen was measured in a blood sample collected in sodium citrate tube. Samples of citrate plasma were analyzed within 2 h of venipuncture by an automatic coagulometer (Multifibren, BCS, Siemens Healthcare Diagnostics). The expected values for fibrinogen in our laboratory ranged from 200 to 400 mg/dl. Coronary angiography was routinely performed by an experienced interventional cardiologist to assess severity of coronary artery disease. In this study angiographic severity of coronary artery disease was assessed by vessel score, stenosis score and lesion morphology.

- Vessel score:[18] This was the number of vessels with a significant stenosis (70% or greater reduction in lumen diameter). Scores ranged from 0 to 3, depending on the number of vessels involved.
- Stenosis score:[19] The evaluation of degree of stenosis relates to the percentage reduction in the diameter of the vessel. By Gensini score, the lesions are roughly classified by visual estimation of reduction of luminal diameter. Briefly, the most severe stenosis in each of eight segments was graded according to severity, that is; a grade of 1 for 1% to 49% reduction in lumen diameter, 2 for 50% to 74%, 3 for 75% to 99 %, and 4 for total occlusion. The scores in each of the eight segments were added together to give a total score out of a theoretical maximum of 32.
- Lesion morphology:[20] Type A, Type B and Type C lesion established by a joint ACC/AHA

task force. Type A lesion was defined as simple and Type B & C as complex lesion.

**Statistical analysis**

Statistical analysis was performed using SPSS 12.0 statistical package. Continuous data were expressed as mean ± SD and categorical data as percentage. Analysis of variance and the $c^2$ tests were used for continuous and categorical variables respectively. Multiple logistic regression analysis was performed to evaluate the relationship between fibrinogen levels and coronary artery disease, after correction for baseline confounding factors. A P value < 0.05 was considered statistically significant.

**Results:**

Patients were divided in 3 groups according to fibrinogen levels: Group I = fibrinogen levels <400 mg/dl, Group II = fibrinogen levels (400-600) mg/dl, Group III = fibrinogen levels > 600 mg/dl. Fibrinogen levels were normally distributed among the 3 groups (p = 0.4). Out of 210 patients 179 (85.23%) were male & 31 (14.76%) were female having a male and female ratio of roughly 6: 1. The mean age of the sample was 51 ± 6.97 (range 35 to 70 years). Among the important risk factors of CAD, 54.76% patients were smoker, 40.96% patients were hypertensive, 34.28% patients were diabetic, and 20.47% patients were dyslipidaemic and 16.19% had family history of IHD.

Baseline characteristics according to fibrinogen levels are shown in Table I. Patients with higher fibrinogen were associated with smoker, diabetes, female, hypertensive, having family history of CAD and presented with ACS (statistically significant; p < 0.001). But patients with higher fibrinogen were not associated with increasing age, dyslipidaemia and presented with chronic stable angina (statistically not significant; p > 0.05). Distribution of clinical presentation between stable angina and acute coronary syndrome (Unstable angina, non-STMI, STMI) were statistically significant among the study groups (p < 0.01).

Angiographic characteristics are shown in Table II. Fibrinogen levels were associated with the prevalence of CAD (P <0.001) (Fig. 1), and its severity, especially for extremely high levels ([Group III], P < 0.01).

**Table-I**

*Distribution of baseline characteristics among the study group (according to fibrinogen levels)*

| Variables | | Group- I (n=69) | Group-II (n=70) | Group-III (n= 72) | p-value |
|---|---|---|---|---|---|
| Age (Mean ± SD) | | 51 ± 6.93 | 52 ± 6.74 | 53 ± 6.04 | 0.52 (NS) |
| Sex | Male | 62 (89.85%) | 62(89.85%) | 56 (77.77%) | 0.34(NS) |
| | Female | 7 (10.14%) | 8(11.42%) | 16 (22.22%) | <0.001 |
| Smoking | | 28 (40.54%) | 39 (55.71%) | 48 (66.66%) | <0.01 |
| Diabetes | | 17 (24.63%) | 24(34.28%) | 31(43.05%) | <0.01 |
| Hypertension | | 22(31.88%) | 28 (40%) | 36(50%) | <0.01 |
| Dyslipidaemia | | 16(23.18) | 12 (17.14%) | 15 (20.83%) | 0.64(NS) |
| Family history of IHD | | 8(11.59%) | 11(15.71%) | 15 (20.83%) | <0.01 |
| Clinical pattern | CSA | 11(15.94%) | 9(12.85%) | 8(11.11%) | <0.01 |
| | ACS(UA, NSTMI & STMI) | 58(84.05%) | 61 (87.14%) | 64(88.88%) | |

**Table-II**

*Angiographic characteristics among the study group (according to fibrinogen levels)*

| Variables | Group- I | Group-II | Group-III | p-value |
|---|---|---|---|---|
| CAD% | 67% | 72% | 79% | .001 |
| Vessel score | 1.14 ± 0.56 | 2.24 ± 0.58 | 3.00± 0.65 | .001 |
| Stenosis score | 6.00 ± 4.19 | 18.72 ± 4.94 | 32.41± 10.31 | .001 |
| Multivessel Disease% | 35% | 42% | 51% | .001 |
| Complex Lesion(Type B & C)% | 21% | 32% | 39% | .001 |
| LM disease (%) | 9% | 8% | 11% | .72 (NS) |

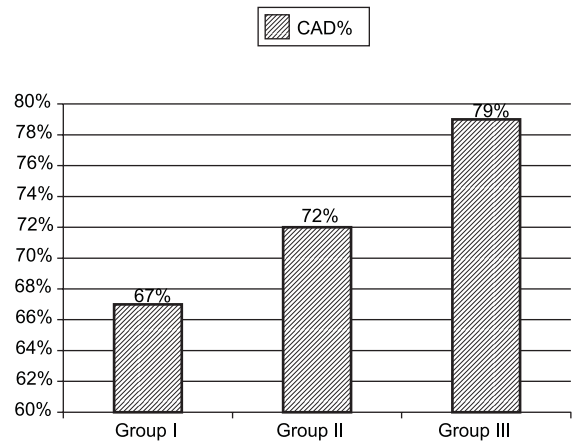


**Fig.-1:** *CAD prevalence in relation to study groups.*

In this study, angiographic severity was assessed by vessel score, stenosis score and lesion morphology (Fig. 2, 3 & 4), and we tried to find out their relationship with angiographic severity and Fibrinogen level. Vessel score in Group I, Group II & Group III were 1.14 ± 0.56, 2.24 ± 0.58, & 3.00 ± 0.65 respectively which was statistically significant ($p < 0.01$). Stenosis score in group- I, group- II & group- III were 6.00 ± 4.19, 18.72 ± 4.94, & 32.41 ± 15.75 respectively which was statistically significant ($p < 0.01$). Regarding morphology of the lesions, complex lesions in group I, group II & group III were 21%, 32% & 39% respectively (statistically significant; $p < 0.01$) but left main involvement was not significant among the groups ( 9%, 8% & 11% respectively in 3 groups, $P< 0.05$).

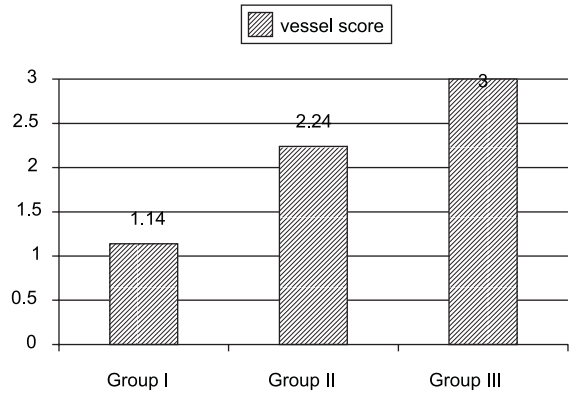


**Fig.2:** *Vessel score in relation to study groups.*

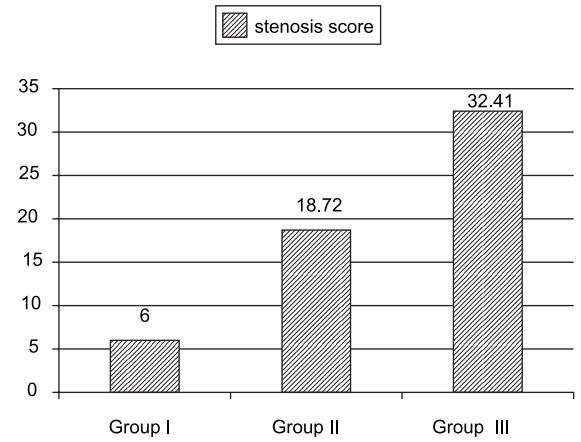


**Fig.-3:** *Stenosis score in relation to study groups.*

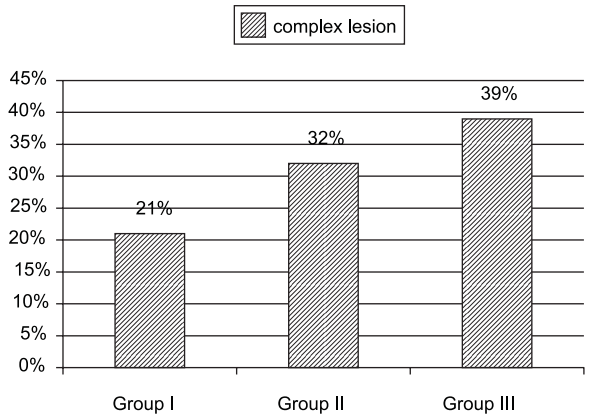


**Fig.-4:** *Morphology of the lesion in relation to study group.*

**Table-IIIa**

*Prediction of vessel score in relation to serum fibrinogen and other risk factors.*

| Variable | Observed power | p value |
|---|---|---|
| Fixed Variable | .89 | .02 |
| serum fibrinogen | | |
| Co-variable | | |
| Smoking | .32 | .13 |
| Diabetes | .25 | .35 |
| Hypertension | .26 | .36 |
| Dyslipidemia | .19 | .38 |
| Family history of IHD | .07 | .63 |

**Table-IIIb**

*Prediction of stenosis score in relation to serum fibrinogen and other risk factors.*

| Variable | Observed power | p value |
|---|---|---|
| Fixed Variable | .99 | .001 |
| serum fibrinogen | | |
| Co-variable | | |
| Smoking | .63 | .02 |
| Diabetes | .67 | .02 |
| Hypertension | .56 | .03 |
| Dyslipidemia | .53 | .03 |
| Family history of IHD | .55 | .03 |

Multivariate analysis for predicting angiographic severity of coronary artery disease was also observed in the study ( Table III) Study observed that high Fibrinogen level, as independent predictors of severe coronary artery disease, were statistically significant (vessel score, $p < 0.5$ & stenosis score, $p < 0.5$) Diabetes mellitus, hypertension, smoking, dyslipidaemia & family history of IHD was found independent predictors of severe stenotic lesion ( $p < 0.5$) but not multivessel disease in this study.

**Discussion:**

This study was conducted to investigate the relationship between fibrinogen levels and CAD as evaluated by coronary angiography. We found that high fibrinogen levels (> 600 mg/dl) are independently associated with the prevalence of CAD. Several studies have focused on fibrinogen, demonstrating a strong association with the presence of CAD. Novel data from the EPIC-Norfolk study [21] showed prospectively that fibrinogen levels were significantly higher in patients presenting with fatal or non-fatal coronary heart disease, than in those remaining free of any cardiovascular disease during follow up, while Acevedo et al [22] reported that fibrinogen was directly associated with the presence of MI and was revealed to be an independent short-term predictor of mortality. Interestingly, increased levels of fibrinogen have been correlated with adverse cardiac events after intracoronary stenting, suggesting a potential role of fibrinogen levels in the outcomes following percutaneous coronary interventions.[23] Despite the data supporting a role of fibrinogen as a marker of CAD and its manifestations, several studies have investigated the role of fibrinogen as a risk factor mediator of CAD. Fibrinogen levels have been found to be independently related to cardiovascular mortality, extent, as well as the severity of disease.[24] Moreover, fibrinogen levels were significantly higher in patients presenting with unstable than in those with stable angina, suggesting a role for fibrinogen in the pathophysiology of acute coronary syndromes.[24]

Repeated meta-analyses and reviews have shown that increased concentrations of fibrinogen are associated with the development or presence of atherothrombotic disease.[25,26] In middle-aged men and women, Bielak et al.[27] noted a significant association between fibrinogen and coronary artery calcification, a marker of subclinical coronary atherosclerosis. Handa et al.[38] observed the relationship between plasma fibrinogen levels and the severity of coronary atherosclerosis in the Department of Internal Medicine, Fukuoka University, School of Medicine, Japan and was examined in 229 patients, aged 25-82 years (162 men and 67 women), undergoing coronary angiography. Severity of coronary atherosclerosis was assessed in terms of the number of vessels with a 75% or greater stenosis and Gensini's severity score.[26] Fibrinogen levels increased progressively with the severity of coronary atherosclerosis, determined by both the number of involved vessels and Gensini's severity score in men, and the relationships were statistically significant. Similar patterns were noted among women, but the trends were not statistically significant. These results provide evidence that plasma fibrinogen levels can serve as an independent predictor of the progression of coronary atherosclerosis.

Our study was conducted to investigate the relationship between fibrinogen levels and CAD as evaluated by coronary angiography. In this study, angiographic severity was assessed by vessel score, stenosis score and lesion morphology and tries to find out their relationship with angiographic severity and Fibrinogen level. Vessel score in Group I, Group II & Group III were $1.14 \pm 0.56$, $2.24 \pm 0.58$, &

3.00 ± 0.65 respectively which was statistically significant ($p < 0.01$). Stenosis score in group- I, group- II & group- III were 6.00 ± 4.19, 18.72 ± 4.94, & 32.41 ± 15.75 respectively which was statistically significant ($p < 0.01$). Regarding morphology of the lesions, complex lesions in group I, group II & group III were 21%, 32% & 39% respectively (statistically significant; $p < 0.01$) but left main involvement was not significant among the groups (9%, 8% & 11% respectively in 3 groups, $P< 0.05$). High fibrinogen levels were associated with the prevalence and extent of CAD that persisted after the correction for baseline confounding factors. At multivariate analysis, after correction for baseline confounding factors, high fibrinogen level (Group- III) was still associated with the prevalence of CAD (OR [95% CI] = 1.24 [1.03–1.76], $P < 0.01$).

Although the results of this study support the hypothesis, there are some facts to be considered which might affect the results:

- Angiography was evaluated by visual estimation so there was chance of inter observer and intra observer variation of interpretation of the severity of stenosis.
- IVUS study was not done to assess coronary lesion. The use of intravascular ultrasound would have certainly improved the results of the current study, as it may provide more accurate information on the amount of coronary atherosclerotic plaque and extent of coronary atherosclerosis, as compared to coronary angiography.

**Conclusion:**

We can conclude from the study that high Fibrinogen level independently and significantly associated with more severe coronary artery disease. The study observed that high Fibrinogen level was significant predictor of multivessel disease and high stenosis score. Serum Fibrinogen is simple, affordable and widely available test which can be used as a new and even simpler tool for risk stratification for the patients with ischemic heart disease. It can be used as a marker to identify those subsets of patients with ischemic heart disease who may need to undergo invasive or conservative strategies.

**Conflict of Interest - None.**

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