Coronary artery disease (CAD) is the leading cause of cardiovascular mortality worldwide, with > 4.5 million deaths occurring in the developing countries. Both CAD mortality and the prevalence of CAD risk factors continue to rise rapidly in developing countries. An epidemiological transition is now occurring in the developing world where the major cause of death is changing from infectious to non-communicable diseases. This epidemiological transition is due, in part, to improved longevity. As life expectancy increase, the period of exposure to CAD risk factors also increases.

In India, perhaps because of the rapid pace of economic development, epidemiological changes have spanned a much shorter time. As a consequence, cardiovascular disease (CVD) has emerged as the leading cause of death all over India, with coronary heart disease (CHD) affecting Indians at least 5-6 years earlier than their western counterparts. Current estimates from disparate cross-sectional studies indicate the prevalence of CHD to be between 7-13 per cent in urban and 2-7 per cent in rural India.

CVD mortality and morbidity are promoted by major traditional risk factors, such as hyperlipidemia, hypertension, and smoking. The sequence of events leading to CVD includes endothelial dysfunction, atherosclerotic plaque formation, and rupture. Inflammation has been implicated in all these stages in the evolution of atherosclerotic plaques. Moreover, oxidative stress is currently considered a key event in CVD development.

Growing evidence demonstrate the action of MPO as central participant linked to both inflammation and oxidative stress in CVD. Myeloperoxidase (MPO) is a hemoprotein that is stored in the azurophilic granules of neutrophils and monocytes, released in a state of inflammation and catalyze the formation of several reactive species, including hypochlorous acid, and thus have a role in host defense against microorganisms.

The significance of MPO in the development of CAD has been demonstrated in studies showing association of systemic MPO level and expression of MPO with the prevalence of CAD or with chronic heart failure. Interestingly, MPO serum and plasma levels are markedly elevated in patients with acute coronary disease, forming
a firm mechanistic link between PMN activation, MPO release, and compromised vascular reactivity.16

Along with several environmental factors, family history also plays an important role in the genetic predisposition of CAD. A functional MPO promoter polymorphism −463G/A, which alters MPO expression levels20, 23 was associated with increased incidence of CAD and severity of atherosclerosis.19, 24 Patients who were deficient in MPO were less susceptible to cardiovascular diseases.18

Several environmental, metabolic and genetic factors had been suggested as the risk factors for CVD. Reports pertaining to their association with CVD and its pathophysiology, however, are not uniform from different parts of world, suggest different milieu of gene-environment– metabolic interactions. Thus we have made an all round effort to investigate whether systemic release of MPO is a characteristic feature in patients suffering from CVD. Also the role of oxidative stress and association of −463G/A genetic polymorphism in Myeloperoxidase in different subgroups of patients (SAP, UAP & AMI) with reference to control subjects was also elucidated.

In the present case - control study, 215 subjects were selected for analyzing the risk factors and genetic polymorphism of MPO in various healthy control (n=54) group and patient subgroups (SAP=52, UAP=53 and AMI=56) respectively. The baseline characteristics in control and patient sub-groups such as age, BMI, Systolic and diastolic blood pressure (expressed as Mean ± SD) and sex, diet, smoking, alcohol consumption and family history (expressed as frequency distribution) were found elevated in SAP, UAP and AMI patient sub-groups than the healthy controls as shown in Table 5.1(a & b).

In present study the Mean ± SD, age in patient sub-groups were found significantly higher (p < 0.001) in comparison to control. Furthermore, non-significant (p > 0.05) correlations were found on comparison within the patient sub-groups. Similar, results were obtained earlier in studies conducted by Zhang et. al, 2001,125 Apple et. al, 2007,152 Ndrepepa et. al, 2008,21. This implies that the occurrence of CVD increases in older age groups as per Table 5.2 (a & b).
Highly significant (p < 0.001) correlation was found in terms of BMI when controls were compared with patient subgroups (Table 5.3 a & b) as supported by studies performed by Meuwese et al, 2007\textsuperscript{17} and Heslop et al, 2010.\textsuperscript{133} Comparison between SAP vs UAP has shown non-significant (p > 0.05) correlation whereas a significant (p < 0.05) correlation was observed between SAP vs. AMI sub-group and a highly significant (p < 0.001) correlation was observed on comparison between UAP and AMI sub-group. Thus, this suggests that increasing BMI must have a significant association with CVD.

Statistical analysis of levels of systolic and diastolic BP between control and patient subgroups showed highly significant correlation in all the three patient subgroups (SAP, UAP, AMI) in comparison to control (Table 5.4 & 5.5). Similar results were obtained in the studies done by Zhang et al, 2001,\textsuperscript{125} Meuwese et al, 2007\textsuperscript{17} and Heslop et al, 2010.\textsuperscript{133} Also according to Van der Zwan et. al, 2010\textsuperscript{134} the relationship between myeloperoxidase and blood pressure was strongest under conditions associated with oxidative stress, like obesity, low high-density lipoprotein cholesterol, metabolic syndrome, and type 2 diabetes. The strength of these associations was only marginally attenuated by adjustment for other cardiovascular risk factors. Thus their data demonstrate that myeloperoxidase is positively and independently associated with blood pressure, and this association is strongest in subjects with (hyperglycemia-induced) oxidative stress. These observations, together with emerging evidence that myeloperoxidase-derived oxidants contribute to the initiation and propagation of cardiovascular disease, identify myeloperoxidase as a promising target for drug development.

The clinical and laboratory characteristics such as Total Cholesterol, LDL-C, VLDL-C, and Triglycerides found highly elevated (p < 0.001) in patient subgroups than in healthy controls. On the contrary HDL-C was higher (p < 0.001) in controls with respect to patient sub-groups. (Table 5.6). Our findings correlates with the studies conducted by Meuwese et al, 2007,\textsuperscript{17} Kubala et al, 2008,\textsuperscript{96} Zhong et al, 2009\textsuperscript{129} and Lobbes et al, 2010.\textsuperscript{132} Furthermore, non-significant (p > 0.05) correlations were observed on comparisons within the patient sub-groups in above mentioned biochemical parameters i.e TC, LDL-C, VLDL-C & TG. Comparison of HDL-C indicates highly significant (p < 0.001) association between SAP vs UAP, moderately significant (p < 0.01) correlation between SAP vs AMI and significant (p
< 0.05) association was found between UAP and AMI as seen in studies performed by Holvoet P et al, 1998\textsuperscript{124} (table 5.7 to 5.11).

According to NCEP guidelines, the optimal level for non-HDL-C should be < 130 mg/dl. In the present study, the biochemical levels of non-HDL-C was found to be significantly elevated ($p < 0.001$) in all the three patient subgroups i.e SAP, UAP & AMI respectively in comparison to the control group as shown in table 5.12(a & b).

Similar findings of the lipid research follow up study, in which a total of 4,462 men and women were followed for 19 years, showed that non-HDL-C emerged as a better predictor of CVD mortality than LDL.\textsuperscript{153} The systolic hypertension in elderly program (SHEP), non-HDL-C was assessed along with serum cholesterol, TG, LDL-C and HDL-C as a predictor of cardiovascular event in 4736 participants. During an average 4.5 years of follow up, non-HDL-C was shown to be a predictor of cardiovascular events in multivariate analysis in the study population.\textsuperscript{154} The diagnostic and prognostic significance of non-HDL cholesterol is limited in different types of CVD subjects having only impaired lipid profile.

Dyslipidemia represents one of the most important risk factors for cardiovascular morbidity and mortality.\textsuperscript{155} An inverse relationship between plasma HDL-cholesterol and atherosclerosis was already described in 1950s\textsuperscript{156}, but the importance of this relationship was only realized in 1975.\textsuperscript{157} Many subsequent studies have emphasized that low HDL-C is associated with increased cardiovascular risk.\textsuperscript{158} Current opinion is that next to high LDL-C and low HDL-C levels, high plasma triglycerides should be regarded as a risk factor for the development of CVD.\textsuperscript{159}

Exner et. al, 2006, studied the progression of stenosis of the internal carotid artery in 1019 asymptomatic CAD patients with a follow-up of 7.5 months. Patients with progressive stenosis had significantly higher baseline MPO concentrations compared to patients with stable disease. Interestingly, the relation between MPO and progression of stenosis was modified by HDL cholesterol level. An MPO concentration above the median was associated with a 2.6- fold increased risk (95% CI, 1.4–4.8) of disease progression, but only in patients with HDL cholesterol concentrations below the median. Thus they concluded that Myeloperoxidase was associated with progression of carotid atherosclerosis in patients with HDL cholesterol levels below 49 mg/dl.\textsuperscript{126}
DISCUSSION

Also in a study conducted by Jerlich A et al. 2000, modification of apolipoproteins of HDL-C and LDL-C in the presence of MPO was monitored by measuring the decrease in tryptophan fluorescence and they found that HDL may have a beneficial effect in retarding LDL modification in inflammatory processes. Suggestive evidence shows that oxidative stress plays a role in the pathophysiology of CVD. MDA and catalase belongs to the group of oxidative stress markers. MDA on one hand is a product of lipid peroxidation involved in the generation of oxidative stress while catalase on the other hand is an enzyme providing protection against the toxic effect of oxidants. In the current study, the Mean ± SD levels of MDA were greatly increased in controls as compared to patient sub-groups whereas levels of Catalase were decreased from control towards patient sub-groups (Table 5.13).

Comparison of control with patient subgroups showed highly significant (p < 0.001) correlation with respect to the levels of MDA and Catalase (Table 5.14 & 5.15). Karajibani et. al, 2009 revealed the differences in the levels of oxidant and antioxidant markers between CVD patients and healthy persons. Significant increase in MDA levels a lipid peroxidation product, and decrease in total antioxidant capacity indicates elevated oxidative stress in CVD patients. Similarly, Serdar A, 2006 observed an increase in MDA level in patients with coronary artery disease (CAD).

According to a study conducted by Kumar et. al, 2012 when the mean values of the serum enzymes were compared, a marked decrease in the levels of SOD and catalase was found, whereas the level of TBARS, indicating lipid peroxidation, was markedly increased. Evaluation of the serum values in various demographic subsets of the population was performed, and the greatest changes were found in smokers, followed by non-vegetarians, suggesting that smoking has an important role in causing oxidant stress. Free radicals, cytokines, nitric oxide (NO), and antioxidants play a major role in both atherosclerosis and myocardial damage and preservation. In their study, it was found that rural people from the Nilgiris admitted with IHD, MI, and UA had increased TBARS levels and reduced SOD, catalase, and ascorbic acid levels. Previous studies have demonstrated the biological relevance of the antioxidant defense system to myocardial infarction. Chandra et. al, 1994 demonstrated that there were elevated superoxide anion, malonyldialdehyde, and glutathione reductase levels and reduced superoxide dismutase and catalase levels in unstable angina and acute myocardial infarction cases. Gupta and Chari 2006 measured the levels of
proxidants and antioxidants in patients with IHD and type II diabetes mellitus. Significantly increased levels of malondialdehyde and decreased levels of superoxide dismutase, glutathione peroxidase, and vitamin C were found in diabetics without complications and nondiabetics with IHD compared with control subjects.166

In our findings, the Mean ± SD levels of oxidized LDL and Plasma MPO were found elevated in patient subgroups (SAP, UAP and AMI) in comparison to controls (Table 5.16). Oxidized LDL (ox-LDL) plays an important role in the pathogenesis of atherosclerosis.167 Several studies have demonstrated that subclinical atherosclerosis168 and clinical coronary heart disease (CHD)94 are associated with higher concentrations of circulating ox-LDL. Recently, they showed, in older adults in the Health, Aging, and Body Composition (Health ABC) cohort, that high CHD risk status (based on Framingham score) before CHD events is associated with high concentrations of circulating ox-LDL169 and that increased ox-LDL predicts future myocardial infarction.170 The latter has been confirmed in middle-aged adults in the MONICA/ KORA Augsburg cohort171 and the FRISC-II (Fragmin and Fast Revascularization in Instability in Coronary Artery Disease Trial) cohort.172

Present study highlights highly significant correlation (p<0.001) with respect to Ox-LDL in all the three patient sub-groups - SAP, UAP and AMI respectively in comparison to control. Furthermore, comparison of UAP with AMI showed highly significant (p<0.001) correlation whereas comparison of SAP with AMI indicates nearly significant (p<0.05) correlation and that of SAP vs UAP showed non-significant association (p>0.05) as shown in Table 5.17 (a & b) and Fig. 5.1. Moreover, observations of the Mean ± SD levels of ox-LDL in all the three patient subgroups indicate larger deviation in the SAP subgroup in comparison to UAP & AMI subgroup. Thus, ox-LDL is used for the diagnosis of CVD but its prognostic value is not reliable.

In agreement to our study, Holvoet P et. al, 1998 investigated the association between plasma levels of oxidized LDL and malondialdehyde (MDA)-modified LDL with acute coronary syndromes and stable CAD and found that plasma levels of oxidized LDL were independent of LDL-C but correlated inversely with HDL-C levels. Thus they concluded that elevated plasma levels of oxidized LDL are associated with CAD. Elevated plasma levels of MDA modified LDL suggests plaque
instability and may be useful for the identification of patients with acute coronary syndromes.\textsuperscript{124}

Numerous lines of evidence implicate role of myeloperoxidase (MPO) in the pathogenesis of atherosclerosis. Enriched within vulnerable plaque, MPO serves as an enzymatic source of eicosanoids and bioactive lipids and generates atherogenic forms of both low- and high density lipoproteins. These factors likely contribute to clinical studies demonstrating that increased systemic levels of MPO and its oxidation products predict increased cardiovascular risk. As a result, interest has focused on the potential to target MPO for the development of new risk markers, imaging, and therapies to prevent cardiovascular events.\textsuperscript{173}

Thus, we were interested to investigate the levels of plasma MPO in different sub-groups of CVD patients and our findings suggests that Plasma MPO levels were significantly elevated in patients with UAP (p < 0.001) and AMI (p < 0.001) compared with controls. There is no significant difference in plasma MPO levels in patients with SAP (p > 0.05) and controls (Table 5.18 a & b) (Fig 5.2). Our findings resembles with the studies conducted by Kubala et al, 2008.\textsuperscript{96} Furthermore, plasma MPO levels were significantly higher in AMI and UAP compared with SAP (p < 0.001), but there is no significant difference between AMI and UAP (p > 0.05) corresponding to the study performed by Lobbes et al, 2010.\textsuperscript{132} Present study confirms MPO to be a good predictive marker of CVD on the basis of ROC curve analysis corresponding to the studies conducted by Esporcatte et al 2007 \textsuperscript{127} and Brevetti et al 2007.\textsuperscript{174}

The first epidemiological report assessing the association between MPO and CVD was a case-control study published by Zhang et. al, 2001.\textsuperscript{125} Using an enzyme assay, they showed that blood and leukocyte MPO activity were higher in patients with CAD than angiographically verified normal controls, and that this increased activity was significantly associated with presence of CAD. Results were independent of the patient’s age, sex, hypertension, smoking, or diabetes status, LDL concentration, leukocyte count, and Framingham global risk score.

In ACS, MPO has been consistently found to be associated with the presence of instability and risk of future events in the studies that have explored these topics. Biasucci et al, 1996 first observed that circulating neutrophils in patients with acute
myocardial infarction (AMI) and unstable angina (UA) have a low MPO content, and therefore high MPO levels in the circulation, as compared with those with chronic stable angina and variant angina. This is indicative of a significant release of MPO from neutrophils related to their activation. The lack of neutrophil activation in patients with variant angina, and after stress test suggests that this phenomenon may occur independently of ischemic episodes. Therefore, MPO is prevalently a marker of instability and not simply a marker of oxidative stress and damage.  

In a multivariate analysis performed by Dominguez et al, 2008, MPO was the strongest independent predictor of CVD outcome. In 38 patients with ST-segment myocardial infarction presenting with cardiogenic shock and treated with percutaneous coronary interventions, baseline MPO was an independent predictor of inhospital mortality, after adjustment for clinical, laboratory, and angiographic variables.  

Mocatta et al, 2007 have investigated the relationship between plasma MPO and clinical outcome after AMI. The study deals with measurement of plasma MPO in AMI patients and found a significant association of MPO with follow-up events. Importantly, MPO was of incremental prognostic value on the top of ejection fraction and BNP, a finding observed also by Khan SQ et al, 2007 in a similar population of patients with STEMI.  

Thus according to existing literature MPO is a risk factor in causing CVD. In our study we found relatively non-significant but elevated levels of MPO in SAP subgroup. Also, levels of MPO were found significantly elevated in UAP and AMI subgroup. Therefore it can be said that the levels of MPO are increasing with increasing severity of the disease. So, it can be used as a prognostic marker to assess the severity of CVD. Further studies are required to establish its role in prevention from the increasing severity of the disease, if its levels should be checked on proper time. Our study therefore suggests that MPO is a mechanism based marker of inflammation and oxidative stress that has been consistently demonstrated to be elevated in patient subgroups and found involved in the progression and severity of the disease.  

Myeloperoxidase (MPO) is a peroxidase enzyme produced by white blood cells (mainly neutrophil granulocytes and mononuclear cells). It represents a class of
hemeproteins belonging to the heme peroxidase family. Several single nucleotide polymorphisms (SNPs) are present at sp1 binding sites in the promoter region of the MPO gene, including variants -463G/A, -129G/A, -V53F, -A332V, -638C/A, I642L, and IVS11-2A/C. To date, several studies have shown that the -463G/A, -129G/A, -V53F, -A332V, and -638C/A SNPs and MPO levels are risk factors in coronary artery disease (CAD)\textsuperscript{95,144}. Therefore it is of public interest to investigate the environmental and genetic factors determining the levels of plasma MPO and its association with MPO genetic polymorphism.

The MPO gene itself and in particular the promoter region with its sequences implicated in the transcriptional control is a prime candidate for such investigation. Mutation in this region could affect transcription rates and thus alters the synthesis of MPO enzyme which could affect the progression and severity of the CVD. Thus we investigated the association of -463 G/A MPO genetic polymorphism frequency distribution along with the levels of plasma MPO in control and patient sub-groups.

The frequencies of GG, GA and AA genotypes of the -463 G/A genetic polymorphism were not significantly different between control and patient sub-groups. But when comparisons were done within the individual sub-groups then the frequency distribution of GG genotype was significantly higher in control and all the three patient sub-groups with respect to GA and AA genotypes. Significant association between these individuals were found at chi-square = 3.15 at p-value =0.789. Further allele frequency distribution of both the alleles (G & A) in control and patient individuals shows significant chi-square association at 4.09 at p-value =0.2515 (Table 5.21) (Figure 5.5 to 5.9).

The distribution of GG genotype (51.85% vs 57.69%; $\chi^2 = 0.3647, \ p = 0.5459$), GA genotype (37.04% vs 32.69%; $\chi^2 = 0.2201, \ p = 0.6390$) and AA genotype (11.11% vs 9.62%; $\chi^2 = 0.063, \ p = 0.800$) were not significantly different in controls and SAP cases. The comparison of Odd ratios of GG, GA and AA genotypes between control and SAP subjects were found to be 0.7897 (95% CI: 0.3669-1.700), 1.211 (95% CI: 0.5438-2.697) and 1.175 (95% CI: 0.3355-4.115) respectively (Table 5.22 a, b & c).

Similarly comparison between control and UAP subjects show non-significant association according to the frequency distribution of GG genotype (51.85% vs
66.04%; $\chi^2 = 2.223$, $p = 0.136$), GA genotype (37.04% vs 28.3%; $\chi^2 = 0.927$, $p = 0.3356$) and AA genotype (11.11% vs 5.66%; $\chi^2 = 1.032$, $p = 0.3098$). The Odd ratios of GG, GA and AA genotypes among comparison between control and UAP were 0.5538 (95% CI: 0.2539-1.208), 1.490 (95% CI: 0.6603-3.363) and 2.083 (95% CI: 0.4927-8.808) respectively (Table 5.22a, b & c).

Likewise the distribution of GG genotype (51.85% vs 64.29%; $\chi^2 = 1.747$, $p = 0.186$), GA genotype (37.04% vs 28.57%; $\chi^2 = 0.8949$, $p = 0.3442$) and AA genotype (11.11% vs 7.14%; $\chi^2 = 0.5238$, $p = 0.4692$) between control and AMI sub-groups indicates non-significant correlation. Comparison between control and AMI cases provides Odd ratios of GG, GA and AA genotypes to be 0.5983 (95% CI: 0.2786-1.285), 1.471 (95% CI: 0.6602-3.276) and 1.625 (95% CI: 0.432-6.113) respectively (Table 5.22a, b & c).

Thus, our findings suggests that the allele A of MPO gene was less frequent in comparison to allele G in different patient sub-groups, corresponding to the study conducted by Nikpoor B et al, 2001 and Zhong et al, 2009. Also according to our study, no significant association was found between the MPO G -463 A polymorphism and cardiovascular disease but indirectly this gene was found to regulate the synthesis of MPO enzyme affecting at transcriptional level signifies its indirect association with CVD.

Overall, the data from our study showed that AA and GA genotypes were significantly associated with reduced risk of CVD whereas individuals with GG genotype were largely suffering from CVD. In a meta-analysis performed by Tang et al, 2013 according to the published data on the association between the myeloperoxidase (MPO) G-463A polymorphism and coronary artery disease (CAD) found strong evidence for an association between the MPO G-463A polymorphism and CAD. Their data also indicates that AA and GA genotypes were significantly associated with reduced risk of CAD (AA vs. GG: OR = 0.37, 95% CI = 0.17–0.78; GA vs. GG: OR = 0.73, 95% CI = 0.57–0.92). In subgroup analyses, statistically significant results were observed in the Chinese population (AA vs. GG: OR = 0.21, 95% CI = 0.10–0.43; GA vs. GG: OR = 0.57, 95% CI = 0.44–0.74) and in hospital-based control studies (AA vs. GG: OR = 0.20, 95% CI = 0.10–0.39; GA vs. GG:
OR = 0.61, 95% CI = 0.48–0.77). This meta-analysis suggests that the MPO -463G/A variant genotypes is associated with decreased risk of CAD.\textsuperscript{136}

Comparison between plasma MPO levels of control and SAP subjects according to the GG, GA and AA genotypes shows that the Mean ± SD levels of plasma MPO in SAP were slightly higher in comparison to control group which were found to be relatively non-significant (p > 0.05) as shown in study conducted by Kubala et. al, 2008\textsuperscript{96} and Li Aihua et al.\textsuperscript{135} Comparisons of control with that of UAP and AMI respectively have shown significant correlation (p < 0.05) between the plasma MPO levels of GG, GA and AA genotypes of both the sub-groups (Table 5.23). We also found that the Mean ± SD levels of Plasma MPO of GG genotype in three patient sub-groups with respect to controls were found to be highly elevated suggesting significant association of MPO genetic polymorphism and its levels with CVD (Table 5.23).

In agreement to our study, Li Aihua et. al, 2010 explored the relationship between myeloperoxidase (MPO) and coronary heart disease to predict the risk of CHD and found that the plasma levels of MPO were obviously higher in ACS groups than that in SAP and control group (P<0.01). The mean levels of plasma MPO in SAP group were not significantly different, compared with that in control group (P>0.05). According to them the risk of CHD in the GA genotype 3.10 times that of AA. The risk of CHD in the GG genotype was 2.70 times that of AA. Thus they concluded that MPO, a maker of the unstability of the plaque in coronary artery, is correlated with coronary heart disease. -463G/A polymorphism of the MPO gene influences the risk of CHD.\textsuperscript{135}

Furthermore, comparison between plasma MPO levels of different patient sub-groups with respect to GG, GA and AA genotypes suggests highly significant (p < 0.001) correlation between SAP & UAP with respect to GG and GA genotype whereas AA genotypes have shown nearly significant (p < 0.05) correlation. Likewise, comparison between SAP and AMI has shown highly significant (p < 0.001) association between plasma MPO levels with respect to all the three genotypes i.e GG, GA and AA respectively. On the other hand, a non-significant (p > 0.05) correlation was observed between UAP and AMI sub-groups (Table 5.23) in ref. to GG, GA and AA genotypes respectively.
In present study comparison between plasma MPO levels in GG, GA and AA genotypes of SAP, UAP and AMI subgroup showed slightly higher, relatively non-significant (p > 0.05) elevation of plasma MPO in AMI subgroup compared to UAP subgroup whereas highly significant elevations (p < 0.001) were found in UAP and AMI subgroups when compared to SAP suggested plasma MPO levels along with -463 G/A genetic polymorphism found associated with the progression and severity of CVD (Table 5.23).

Thus, the present study detected significant indirect association of -463 G/A MPO genetic polymorphism expressed in the form of elevated plasma MPO levels in GG genotype (with respect to AA genotype) with different forms of CVD in all the cases suffered with SAP, UAP and AMI. It is possible that the variation of this genetic polymorphism regulates the synthesis of MPO enzyme that modulates the lipid profile by increasing the oxidative stress thereby contributing to the generation of oxidized LDL and dys-functional HDL leading to the occurrence and progression of CVD. The MPO gene is located in chromosome 17q23-q24, and its expression is regulated by nutrilites. The MPO -463G > A polymorphism, located at the promoter region, was first detected by Austin et. al, 1993 in a study on acute myeloid leukemia patients. More recently, this same gene polymorphism was proven to be a risk of both CAD and cardiovascular events in CAD patients, the A allele being associated with less probability of developing cardiovascular disease.

It has been reported that MPO gene -463G > A polymorphism is related to changes in lipid levels, and is a mechanism that may be involved in the oxidation of low-density lipoprotein, the high levels of MPO increasing the brittleness of artery plaques, thereby converting the plaque from the stable to the unstable state, thus increasing the risk of acute coronary syndrome. The MPO -463A allele could interfere with the binding sites of the sp1 transcription factor, by reducing the level of MPO gene expression in its role in atherosclerotic plaque formation, thus having a definite impact on the risk of CAD. Meanwhile, MPO could promote the oxidation of HDL-C and affect the reverse cholesterol transport, thereby interfering in the development of atherosclerosis. The multivariate logistic regression that we performed showed that TC, diabetes mellitus, smoking and a family history of CAD are independent predictors of premature CAD, thus confirming that these are really traditional cardiovascular risk factors contributing independently to this disease.
Thus, documentary evidence demonstrates that MPO and its reactive oxidant species play a role in the promotion of pathological events involved in all stages of atherosclerotic CVD.\textsuperscript{181} Our observations of associations between systemic MPO levels and cardiovascular risks in humans suggest that MPO testing may play an important role in clinical risk prediction.\textsuperscript{182}