Overview

As we stand here in the first quarter of the 21st century, few can deny the challenge of health concerns and risks that lower the quality of life of people and curtail their longevity. Due to increased stress, rapid pace of living and unhealthy lifestyle, industrialization and urbanization there is a growing burden of non communicable diseases (NCDs). Cardiovascular disease (CVD) currently accounts for nearly half of NCDs. CVD is also the leading global cause of death, accounting for 17.3 million deaths per year, a number that is expected to grow to more than 23.6 million by 2030. Although CVD death rates are declining in most high income countries, trends are increasing in most low and middle income countries. They are known to cause significant morbidity and mortality between the age group of 35-64 years across India, irrespective of urban or rural population. According to available information NCDs in general and CVDs in particular are a big cause of concern in India, it being the largest reason of mortality in all regions of the country.

Further, looking at the world scenario of CAD it is alarming to note that by 2020, 60% of the world’s heart disease is predicted to occur in India. Coronary artery disease (CAD) being the most common type of heart disease has a high rate of morbidity and mortality. India has the highest burden of CAD causing three million deaths per year, accounting for 25% of mortality in India. According to the National Commission on Macroeconomics and Health, there would be around 62 million patients with CAD by 2015 in India, and of these, 23 million would be patients younger than 40 years of age. The risk of CAD in Indian population is 3-4 times higher than white Americans, 6 times higher than Chinese and 20 times higher than Japanese. Thus, India suffers a tremendous loss of productivity due to increased prevalence of CHD. The total years of life lost due to total CVDs among the Indian population is between 35-65 years which has been estimated to be higher than comparable countries such as Brazil and China. These estimates are predicted to increase by 2030.

1.1 The Prevalence

CAD includes a spectrum of disease manifestations ranging from asymptomatic atherosclerotic disease to acute coronary syndrome (ACS). The prevalence of CADs has increased in both urban as well as rural populations of India in the last decade.
CAD rates have halved in the West in the last 30 years, the same has doubled in India. The average age of first myocardial infarction (MI) has decreased by 20 years in India. Among Asian Indian men, about half of all MI occur under the age of 50 and 25% under the age of 40. This excess burden of premature CAD in Asian Indians is due to a genetic susceptibility, mediated through elevated levels of lipoprotein(a) (Lp(a)). Although CAD has high morbidity and mortality rate, it is also highly predictable with the existing knowledge. ACS, which encompass unstable angina pectoris (USAP), acute myocardial infarction (AMI) with non-ST-segment elevation (NSTEMI) and ST-segment elevation (STEMI), are the commonest causes of mortality in patients with CAD. AMI continues to be the leading cause of death in developing countries like India, despite spectacular progress in their detection and treatment over the last three decades. A large number of asymptomatic individuals are at serious risk of developing MI because of their genetic predisposition, smoking behaviour and sedentary lifestyle. Thus, MI remains an important health concern and it deserves continued attention from basic and clinical researchers, epidemiologists as well as physicians.

1.2 The factors of growing concern with regard to CAD risk in Indian populace

A) Hypertension (HTN) is a standard risk factor associated with CAD. Prevalence of HTN is increasing in urban population, as compared to rural population. In metropolitan cities the prevalence is as high as 11%-27%. Data of epidemiological studies shows that HTN is present in 25% urban and 10% rural subjects in India. The relationship between blood pressure (B.P.) and risk of CVD events is continuous, consistent, and independent of other risk factors. The presence of each additional risk factor compounds the risk from HTN. HTN is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India. It is a leading cause of death and disability causing 13.5% of the world’s premature death and 6% of its disability. However the increased risk for cardiovascular disease in this group cannot totally be attributed to conventional risk factors.
B) Obesity, a major risk factor for CAD, has reached pandemic proportions and research shows that around two thirds of the prevalence of HTN is directly attributed to obesity. WHO data also show that, globally, there are more than 1 billion adults overweight and 300 million obese people.\textsuperscript{22,23} There is an increasing prevalence of abdominal obesity, which plays a major role in the pathogenesis of several metabolic and cardiovascular problems. In India over nine crore people are suffering from obesity whereas in Gujarat itself at least 75 lakh people are suffering from the condition. Stressing, the need to avoid heavy consumption of ghee and oil in food which has led the people of Gujarat towards major problem of ‘Obesity’ (DNA- 17 June, 2009).\textsuperscript{24} The intra-abdominal adiposity associated with abdominal obesity increases cardiometabolic risk directly, via altered secretion of adipokines, and indirectly, via promotion insulin resistance, diabetes and the cluster of cardiometabolic risk factors associated with the MS.\textsuperscript{25-30}

C) Dyslipidemias are disorders of lipoprotein metabolism, including lipoprotein overproduction and deficiency. They may manifest as one or more of the following: elevated TC, LDL, and TG levels or as decreased HDL levels with a rise in IR causing MS in obesity. Asian Indians have the highest risk of premature coronary artery disease CAD and diabetes. When compared with Whites, Asian Indians have double the risk of CAD and triple the risk of DM, when adjusted for traditional risk factors for these diseases. The excess burden of CAD among Indians is primarily due to dyslipidemia that is characterized by: (i) High levels of lipoprotein(a); (ii) High levels of Apo B and non-HDL-C; (iii) High levels of triglycerides; (iv) Borderline high levels of LDL-C; (v) Low levels of Apo A-I and HDL-C; and (vi) High ratios of TC/HDL-C, TG/HDL-C, and apo B/Apo A-I.\textsuperscript{31-34} Raised blood cholesterol increases the risk of heart disease and stroke. Globally, one third of ischemic heart disease (IHD) is attributed to high cholesterol. Lowering raised blood cholesterol reduces the risk of heart disease.

D) Metabolic syndrome (MS) also known as the prediabetic state is yet another risk factor for the development of CAD. It is highly prevalent in developed countries, affecting about 22\% of adults in the United States. There is a growing trend towards MS in India. In India, community-based studies have estimated the prevalence to be 36.4\% in males and 46.5\% in females.\textsuperscript{25,35-37} The MS confers at least two-fold increase in risk of CVD and at least a 5-fold increase in risk of for
subsequent development of DM. About 10% of Gujarat’s population is borderline diabetic and many more have MS. This syndrome is a clustering of cardiovascular and metabolic risk factors that includes HTN, diabetes, high basal metabolic index (BMI), and dyslipidemia due to abdominal (central) obesity. A higher prevalence of MS in South Asians is mostly attributed to the higher prevalence of central adiposity and is also known to be strongly associated with the development of diabetes and CVDs. Studies have also shown that increased serum uric acid (UA) levels are often seen in patients with components of the MS and increased UA levels are strongly associated with increased cardiovascular risk like MS. 

E) Diabetes mellitus 2 and CVD show an unprecedented increase in their prevalence according to the WHO report, which shows that India tops the world with the largest number of diabetic subjects. India now has 40.9 million people with diabetes and the projected estimate for the year 2025 was 69.9 million. At present 8.3% population have diabetes in India and is expected to be 10.2% by 2030. Gujarat has the maximum number of people with diabetes in the country (DNA-8August, 2011). According to renowned diabetologist, Dr V Mohan, Gujarat and more importantly Ahmedabad may emerge as the diabetes capital of India (TOI-20 April, 2012). NCDs including diabetes now cause a substantial health burden in the developing world. The major cause of mortality in diabetic patients is CVDs.

1.3 The early and silent onset

Most individuals with CAD show no evidence of disease for decades as the disease progresses before the first onset of symptoms like acute myocardial infarction (AMI). Clinical CAD in Indians occurs at a younger age, which is more severe and extensive and follows a malignant course. Therefore its prevention poses a huge challenge. The most important aspect of prevention of CAD in Indian population is to identify at an early age those who are at a high risk of developing the same. As traditional risk factors like smoking, HTN, diabetes obesity and MS are reported to account for only 50% of prevalence and severity of the disease, it now becomes imperative to identify early markers and risk factors of CAD.
1.4 The hope
Lp(a) is now recognized as an independent risk factor for CAD. It is a genetic risk factor. It is not affected by any level of life-style modifications like changes in diet and exercise. It is ten-times more atherogenic than low density lipoprotein cholesterol (LDL-C). Since it is fully expressed in the first year of life, tracking Lp(a) from childhood may be more helpful than focusing on other dyslipidemias which are not expressed until later in life. \(^{45}\) Lp(a) has been reported to be an independent risk factor for CVDs. \(^{46-48}\) Some Epidemiological studies have however reported conflicting results showing no association at all. \(^{49-51}\) Studies have also reported higher levels of Lp(a) among Asian Indians compared to other ethnic groups. \(^{52-55}\) It has been reported that the concentration of apolipoproteins A1 (Apo A-I) and B (Apo B) are better predictors of CAD in comparison to measurements of total plasma lipids. \(^{56-58}\) Apo B, that represents the number of potentially atherogenic lipoprotein particles and Apo A-I, which reflects anti-atherogenic HDL-C particles, may indicate more accurately CAD risk than LDL-C and other lipids. Lipid tetrad or the deadly quartet, a unique pattern of dyslipidaemia, has also been observed to be as the single best predictor of CAD risks in diverse populations, especially Asian Indians, as it gives a reflection of total lipid burden in a subject measured as comprehensive lipid tetrad index (CLTI). Research has also shown that homocysteine is an independent risk factor of CAD.\(^{59}\) High sensitivity C-reactive protein (hs-CRP), a marker of inflammation is yet another novel CAD risk assessor.\(^{60}\)

1.5 The Contradictions
The European (European Guidelines on Cardiovascular Disease Prevention in Clinical Practice) and Canadian (2012) update of the Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia for the Prevention of Cardiovascular Disease in the adult guidelines, both reviewed and recommended some emerging cardiometabolic risk factors (Lp(a), ApoA1, Apo B, CRP, Fibrinogen and fasting blood glucose) \(^{61}\). These emerging cardiometabolic risk factors have also been identified and reviewed by various researchers. However there is lack of consensus on the use of these as markers\(^{61-64}\). Indians have the highest rate of CAD compared to any ethnic groups studied thus far. Coronary atherosclerosis in this population occurs early and is very severe and extensive with high mortality \(^{65}\). Conventional risk factors, such as high cholesterol, HTN, and cigarette smoking, have
failed to explain the excess risk of CAD fully. Considering the present Indian scenario, it becomes necessary to find out the underlying biochemical defect in the progression of CAD at the earliest in order to take adequate measures for its prevention and better life expectancy.

1.6 The rationale for undertaking this project
Since Lp(a) is fully expressed in the first year of life, tracking it from childhood may be more helpful than depending on other dyslipidemias which are not expressed until later in life. To simplify the risk evaluation new data are accumulating which support apolipoproteins as more informative risk factors than conventional lipids and as targets for lipid-lowering therapy. This is the rationale for using Apo A-I and Apo B along with Lp(a). Besides there is dearth of studies conducted on Indian populations that have reported Lp(a), Apo A-I, Apo B-100 and CLTI levels (multiple markers) in patients of CAD or those having CAD risk factors despite the alarming rise in its incidence. To the best known from of the available information there are hardly any published studies in Gujarati population with Lp(a), Apo A-I, Apo B-100 and CLTI levels. The present study is therefore an attempt in this direction. The current work aimed to gain better understanding of clinical relevance and utility of newer markers across healthy and diseased populations.