CHAPTER I

INTRODUCTION

India is a unique country which is united despite of all its diversities. Conversely the existing diseases in the Indian society are quite awesome and life threatening over the past couple of decades. There is an alarming increase in both communicable and non-communicable diseases and is expected to get upturned in 2025 from its distribution in 1990. India is emerging as the „diabetes capital” of the world with 32 million persons with diabetes and is projected to have 69.8 million in 2025. The count of "hypertensive" individuals is expected to increase from 118 million in 2000 to 214 million in 2025 (Kearney et al., 2005).

Considerably this is to a great extent because of rapid growth in economic and urbanization in India over the past decades, a large number of the population has moved towards unhealthy lifestyles with physical inactivity, increasing stress levels, changes in diet and possible an underlying genetic component. A number of regions in India appear to be in the first phase of transition, while others are in the second or still in the third phase. As reported by the World Health Organization (WHO), 60 percent of the world's cardiac patients will be in India (Leeder et al., 2004).

1.1. Cardiovascular disease

Cardiovascular disease (CVD) is a general term which refers to the class of diseases that involve the heart or blood vessels, also called heart disease. Although the term technically refers to any disease which affects the cardiovascular system, it is frequently used to refer to those related to atherosclerosis (Maton and Anthea, 1993). Atherosclerosis also occurs in other blood vessels that carry blood to the brain which may cause transient ischemic attacks (TIAs) or strokes, or the arteries that provide blood to the legs and it may cause peripheral arterial blood vessel disease.

CVD is more frequent in the common population, which affecting the majority of adults who past the age of 50 years. CVD is more prevalent and so expensive disease to the society than any other life threatening diseases. The occurrence of coronary heart disease (CHD) is approximately one-third to one-half that of total CVD.
CVD is the main cause of mortality, accounting for approximately half of all deaths resulting from non-communicable diseases. Most of the Western countries face high and increasing prevalence of CVD. In America, the death rate of heart disease is higher than cancer. CVD alone caused 30% of all deaths and with other diseases of the cardiovascular system further causing death and disability. Every year, since 1900 excluding 1918, CVD accounted for more deaths than any other major cause of death in the United States (National Center for Health Statistics, Centers for Disease Control and Prevention, 2007).

Similarly, CVDs accounted for approximately one-fourth of all deaths in India in 2008. CVD are projected to be the fastest growing chronic disease between 2005 and 2015, growing at 9.2% annually, and accounting for the second largest number of non-communicable diseases patients after mental disease (Informational page on International Heart Protection Summit, 2011). The most worrying fact is that between 2000 and 2030, in India, about 35 percent of all CVD deaths will occur among those aged 35 to 64, compared with only 12 percent in the United States and 22 percent in China (Leeder et al., 2004) and two out of three cardiac deaths occur without any diagnosis of CVD (Informational page on CVD at Itamar Medical).

1.2. Risk factors

Many more are said to be at risk for developing CVD. The concept of risk factors has developed only over the past 45 years, and new factors are periodically added to the list as our understanding of the disease process grows. Some scientists were convinced that there was a single cause for atherosclerosis—dietary fat and cholesterol—while others were more impressed by the association of high blood pressure or cigarette smoking with heart attacks. Most researchers preferential the theory that there had to be multiple causes for atherosclerosis, although accurately what they were, was questionable.

The first large-scale, extensive study to determine the causes of atherosclerotic heart disease the Framingham Heart Study (FHS), was begun after the second world war. Within a short time, the Framingham researchers recognized that there are, certainly, many factors that influence an individual to the development of
atherosclerosis. The list of these factors, currently called cardiovascular risk factors, continues to grow as the information from Framingham and various other studies becomes available and it explicate more about the promising causes of atherosclerotic disease.

Whereas useful in clinical practice, currently used and recognized risk factors may sometimes be less helpful measures in research. A main reason is the different nature of cardiovascular risk factors. Some are more or less “singular” factors like low-density lipoprotein (LDL) cholesterol or C-reactive protein (CRP), while others represent aggregates of several risk factors like the metabolic syndrome.

Most traditional cardiovascular risk factors such as age, gender, obesity, familial predisposition, diabetes, hypertension, may rather define collections of several pathophysiological pathways and numerous pathogenic agents. The same holds true for risk related with lifestyle with less physical activity and. Dissecting these collections into singular pathways and individual risk factors is not easy as in most cases close associations of several risk factors will not allow definite dissection.

In some of the aggregated risk factors risk may depend on the combination of factors–as long as one is missing the other(s) may not be pathogenic. Addition of the number of different pathophysiological pathways or mechanisms pretentious as well as accounting for the severity by which each pathophysiogical pathway is pretentious rather than simply adding up more and more individual risk factors may help to improve the individual risk assessment (Renke and Rainer, 2003).

1.3. Changing prevalence of risk factors

As suggested by the term “modifiable” risk factors, not all risk factors are essentially constant. This may be significant to notice that clinical impact and thresholds defining elevated risk are likely to vary considerably over time. The intensifying prevalences of obesity and diabetes may serve as examples (Flegal et al., 2002). The extensive use of statins or the countrywide fortification of food with folate in the Unites States (Jacques et al., 2000) (likely to appreciably reduce the cardiovascular risk
associated with homocysteine) may also lead to significant changes in the relative incidence of risk factors.

As there is convincing evidence for the utility of the drug therapy for primary and secondary prevention of CVD (Grundy, 2002; Sever et al., 2003), drug naive patients with cardiovascular risk factors may become increasingly rare. While subsequent implementation of drug treatment is certainly beneficial for the patients it begins to pose very practical problems in clinical research. For example it becomes more and more not easy to acquire LDL cholesterol–related survival data without interference by statin treatment.

Drug treatment may correspond to another major confusing factor, as many drugs affect multiple pathways. In sufficiently treated populations it may be hard to distinguish which effects of a new drug are independent of the presence of co–administered drugs. Additionally, advances in treatment may completely change the risk associated with some risk factors. As a result of successful drug treatment we may have to totally change our views on some well–liked and significant risk factors.

Statin treatment may again serve as an example. Looking at patients with elevated cardiovascular risk, recent data propose that the patients with hypercholesterolemia actually fare better (because they receive statins) than normocholesterolemic patients (Rupprecht et al., 2001). CVD risk factors should not be measured constant; long–term follow–up of today’s populations may lead to unexpected results. In populations where the “old” risk factors have been addressed by therapeutic measures, other risk factors may increase significance.
1.4. General (Aim) and Specific Objectives

Early findings and treatment of hypercholesterolemia, diabetes and hypertension have significantly reduced the incidence of cardiovascular deaths (Kuulasmaa et al., 2000). Even though, the yearly decline in mortality, CVD is the first cause of death (Preventive cardiology, 2002). Therefore it is necessary to improve CVD prevention, in particular by putting into practice the progresses concerning diagnosis of high CVD risk that exposes to increase their probability in the next ten years.

While the measurement of total cholesterol (TC), triglycerides (TG), LDL cholesterol, and high-density lipoprotein (HDL) cholesterol are suggested in most current cardiovascular screening algorithms (Conroy et al., 2003). High sensitivity CRP (hsCRP), fibrinogen, tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) were also studied because half of all patients with CVD were found to have normal plasma lipid levels (Braunwald, 1997; Levine et al., 1990; Luc et al., 2003).

Several investigations have also recommended that superior risk prediction may be attained by alternatively measuring lipoprotein (a) [Lp(a)], apolipoproteins B (apo B) and apolipoproteins A-I (apo A-I) (Akanji et al., 1999; Sniderman et al., 2003; Yusuf et al., 2004) than other lipid or lipoprotein index. At the same time, recent guidelines have highlighted the importance of non-high density lipoprotein (non–HDL) cholesterol as a predictor of cardiovascular risk (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001).

While others have strongly support the use of specific lipid ratios such as TC to HDL cholesterol, LDL cholesterol to HDL cholesterol, TG to HDL cholesterol, apo B to apo A-I, and apo B to HDL cholesterol (Natarajan et al., 2003; Kinosian et al., 1994; Grover et al., 1995; Natarajan et al., 2003). On the basis of available evidence, this study with two broad objectives is aimed to investigate the clinical utility of various biochemical parameters

(i) As a risk marker
(ii) As a target therapy with atorvastatin.
• The first general objective is to describe the role of hsCRP, fibrinogen, TNF-α and IL-6 as a marker of risk for CVD and its role in risk reduction and disease prevention for the primary care provider.

• To directly evaluate the clinical efficacy of TC, TG, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, Lp(a), apo A-I and apo B and the ratios (TC to HDL cholesterol, LDL cholesterol to HDL cholesterol, TG to HDL cholesterol, non-HDL cholesterol to HDL cholesterol, apo B to apo A-I, and apo B to HDL cholesterol) as an individual marker of cardiovascular events.

• To address the implication of uric acid as an independent risk marker of CVD and to investigate whether a positive association exists between uric acid and inflammation.

• To focus on the prognostic significance of inflammatory markers alone and in combination with lipid profile in patients with CVD.

Aggressive reduction of LDL cholesterol in agreement with the National Cholesterol Education Program (NCEP) guidelines is warranted, the approach to primary and secondary prevention of cardiovascular events must includes other risk factors as well. 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins are extensively used as lipid-lowering drugs in patients with CVD. Despite their confirmed efficacy in primary and secondary prevention trials (Scandinavian Simvastatin Survival Study Group, 1994; Shepherd et al., 1995; Downs et al., 1998), these agents remain underutilized in numerous settings.

LDL cholesterol screening alone has not been found efficient in determining statin efficacy. Preferably, with progress of routine screening tools that identify patients at high risk, including those with elevated markers of systemic inflammation, statin therapy can be better integrated into a targeted, gainful approach to primary prevention of cardiovascular events. To date, little consideration has been given to the effect of pharmacotherapy on hsCRP, fibrinogen, TNF-α, IL-6, Lp(a), apo A-I and apo B levels in patients with CVD. NCEP Adult Treatment Panel III (ATP III) guidelines indicate that
inflammatory markers for example, hsCRP, fibrinogen, TNF-α and IL-6 are emerging risk factors and should be considered in combination with standard risk factors when treating patients (Stone et al., 2005).

- Therefore, the secondary general objective is to investigate lipid-independent and anti-inflammatory effects of atorvastatin in patients with cardiovascular

- To find out the possible effect of atorvastatin on the vascular system in addition to those derived from reductions in LDL cholesterol.

- To evaluate the safety and efficacy of atorvastatin.