CHAPTER - I

INTRODUCTION
1.0 INTRODUCTION

Despite major advances in the pharmacological treatment of coronary heart disease (CHD), it remains the leading cause of death (Evans M et al. 2004) and is the chief cause of premature, permanent disability in the workforce (Matthew K et al. 2006). According to World Health Organization (WHO) in 2002 there were 7.22 million deaths from CHD globally (Global burden of coronary heart disease, 2002; and International Cardiovascular Disease Statistics, Cardiovascular Disease (CVD), 2002). Projections suggests that for CHD the mortality for all developing world will increase by 120% for women and 137% for men. The WHO predicts 11.1 million deaths from CHD in 2020 (Yusuf S et al. 2001).

Hypercholesterolemia is a major risk factor for development of CHD. Thus, it is not surprising that cholesterol is the most "decorated" molecule in history, having contributed to as many as 13 Nobel prizes. In the past 20 years, major strides have been made in the understanding and treatment of hypercholesterolemia and other dyslipidemias. Since its inception in 1985, the National Cholesterol Education Program (NCEP) has battled to reduce the prevalence of high blood cholesterol through educational campaigns and science-based practice guidelines. However, cholesterol levels are still undertreated (Matthew K et al. 2006).

Elevated levels of total cholesterol and low density lipoprotein (LDL) cholesterol are well recognized risk factors. Only in populations that maintain very low levels of serum cholesterol, e.g., total cholesterol <150 mg/dL (or LDL cholesterol <100 mg/dL) throughout life do we find a near-absence of clinical CHD. Moreover, the elevated cholesterol level in young adulthood predicts development of CHD later in life. Since LDL-cholesterol levels <100 mg/dL throughout life are associated with a very low risk for CHD in populations, they can be called optimal. Even when LDL-cholesterol concentrations are near optimal (100-129 mg/dL), atherogenesis occurs; hence, such levels must also be called above optimal. At levels that are borderline high (130-159 mg/dL), atherogenesis proceeds at a significant rate, whereas at levels that are high (160-189 mg/dL) and very high (≥190 mg/dL) it is markedly accelerated (Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of
A sustained reduction in blood total cholesterol concentration of 1% is associated with a 2-3% reduction in incidence of CHD (Tang JL et al. 1998). In fact, LDL cholesterol lowering reduces risk even when LDL cholesterol levels are not categorically high (Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report, September 2002). Thus, even a small reduction could be worthwhile (Tang JL et al. 1998).

Adult treatment panel (ATP) III recommendations call for achieving the goals of therapy by the safest and most cost-effective means. (Third Report of the NCEP, ATP III, September 2002). With recent evidence supporting a more aggressive approach using higher potency statins, and a lower threshold for initiating drug therapy for high risk patients has been recommended. Providers and administrators in managed care are charged with finding the most effective and cost-effective means of attaining these goals. Cost-effective care can be defined as the point at which the minimum amount of input (of which cost is one measurement) is used to achieve a given output or result. Thus, in the search for cost-effective statin therapy, achieving a given level of LDL-C reduction at the lowest pharmacy and medical cost (attained via efficacy and safety) achieves high cost efficiency. Therefore, one would seek to achieve optimal utilization of resources by minimizing the cost to achieve the defined goal (LDL-C reduction). Changes in the market, such as newer high-potency statins and statin available at lower cost and expiration of patents on widely accepted brand drugs, have provided practitioners with the ability to reduce LDL-C at lower costs than ever (Killilen and Funk, 2006).

In the drug classes, considerable variability can be seen among different brands of the same drug formulation with respect to cost. This variability poses a challenge to physicians who wish to reduce patient's expenditures by prescribing the least expensive among similarly effective drugs within a drug class (Shrank WH et al, 2004). A variety of mechanisms are used to drive down medication costs, such as discounted pharmacy pricing for "preferred drugs," Generic and therapeutic
an unbranded drug product that is the same chemical entity and meets criteria for bioequivalence. Therapeutic substitution is the dispensing of an alternate chemical entity for the original drug prescribed by the physician from the same general therapeutic class. The American Heart Association and the American College of Cardiology have formally and vigorously opposed therapeutic substitution, arguing that it is the province and responsibility of the physician to integrate the medical history, physical status of the patient, and the disease process. Furthermore, therapeutic substitution may result in the patient’s receiving a drug that may not be effective, produces life-threatening toxicity, and interacts adversely with other drugs the patient is receiving. Therapeutic substitution is also opposed by the American Medical Association, World Medical Association, and American Academy of Family Physicians (Antman EM and Ferguson JJ, 2003).

Cardiovascular drugs comprise the largest therapeutic segment in the global pharmaceutical market. In 2004, sales of cardiovascular drugs exceeded $63.1 billion in the worldwide market, of which $24 billion, or nearly 40%, is represented by statins prescribed to treat dyslipidemia. Statins represent the largest selling drug class in the world and the top two competitors in the industry are atorvastatin (holds a market share of 39%) and simvastatin (holds a market share of 26%). An analysis by the Food & Drug Administration suggests that generic drugs usually fall to 52% of the retail price (Baliga S, 2006). Statins are one of the great success stories of preventive medicine. Extensive evidence, excellent safety, and high efficacy have resulted in an exponential rise in prescriptions for statins, currently increasing at 30% a year in England. Statins represent the largest drug cost to the NHS (£738 million in 2004). Around 85% of all statin prescriptions in England are for atorvastatin (Editorial:BMJ 2006;332:1344–5).

National Institute of Clinical Excellence (NICE) has issued guidance on the use of statins (Technology Appraisal 94) in January 2006 (TA94 Cardiovascular disease, 2006). This guidance recommends that ‘when a decision has been made to prescribe a statin, the therapy should usually be initiated with a drug with a low acquisition cost (taking into account the daily required dose and product price per dose).
The pharmaceutical sector in India comprises about 350 large and medium size firms and about 20,000 small scale establishments, (the largest number in the world) with little or no GMP compliance. Nearly forty five formulations are available in the market, the ratio of the costliest brand to the cheapest generic formulation is 2.5. There is no available data to show that the cheaper formulations are bioequivalent to the costliest brand formulations and are hence safely switch able. This information is vital for the prescribing physician to do cost effective prescribing.

The purpose of the present study therefore was:
1. To study and compare the lipid lowering effects of three different marketed formulation of atorvastatin in normal human subjects.
2. To determine if these brands of atorvastatin can be safely substituted in general practice.