CHAPTER V

DISCUSSION
5.0 DISCUSSION

Elevation of serum cholesterol levels is widely recognized as a major risk factor for the development of CHD. Asian Indians have the highest rates of CHD of any ethnic group studied, despite the fact that nearly half of these groups are life-long vegetarians. Although the incidence of classic risk factors is low, high triglyceride and low high-density lipoprotein cholesterol levels, high lipoprotein(a) levels, hyperinsulinemia, and apple-type obesity all show a substantial prevalence in this population. Aggressive modification of lifestyle beginning before adolescence seems justified in view of the malignant nature of CHD in this population. Pharmacologic intervention similar to that of secondary prevention of CHD seems justified as primary prevention in high-risk Asian Indians (Enas EA and Mehta J, 1995).

The risk of CHD in Indians is 3-4 times higher than White Americans, 6-times higher than Chinese, and 20-times higher than Japanese. Indians are prone as a community to CHD at much younger age. CHD is affecting Indians 5-10 years earlier than other communities. In the Western population, incidence of CHD in the young is up to 5% as compared to 12-16% in Indians. In some studies from India, the percentage of patients below the age of 45 years suffering from acute myocardial infarction is reported as high as 25-40%. In Singapore, mortality from CHD below 30 years of age is 10 times higher in Indian than Chinese population of the same age group. Angiographically, Indians have 15 times higher rate of CHD than Chinese and 10 times higher rate than local Malays below the age of 40 years (Rissam HS et al, 2001).

The Indian Council of Medical Research surveillance project reported a prevalence of dyslipidaemia of 37.5 per cent among adults aged 15-64 year, with an even higher prevalence of dyslipidaemia (62%) among young male industrial workers (Abhinav Goyal and Salim Yusuf, 2006). By the year 2015, cardiovascular diseases could be the most important cause of mortality in India. The prevalence of coronary artery disease increased from 1% in 1960 to 9-6% in 1995 in urban populations, and in rural areas it has almost doubled in the last decade (Singh RB et al, 1997). Indians worldwide demonstrate a triad of high triglycerides with high LDL levels and low HDL levels (Rissam HS et al, 2001).
A survey revealed that 25% or more of the adult US population have cholesterol levels above the desirable range (200 mg/dL). In Britain about 40% of adults have serum cholesterol concentration in the moderate to high risk category and are therefore considered to need clinical care. Therefore serum cholesterol reduction is an important global health priority for a large segment of population [Davidson MH et al (1991) and Ramsay LE et al (1991)].

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. 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 (Killilea T and Funk L, 2006).

Prescribing physicians who manage patients must be familiar with the variability in their patients' formulary incentives to help patients choose therapy wisely. However, the degree of formulary variability among and within health plans over time is unclear. 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
substitution of drugs. Generic substitution is the act of dispensing a different brand or 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 for Clinical Excellence issued guidance on the use of statins (Technology Appraisal 94) in January 2006. This guidance recommends that ‘when a decision has been made to prescribe a statins that 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). In India, several pharmaceutical companies are marketing atorvastatin. The price differential in the lowest and the highest priced product is
about 2.5 fold. However, whether or not the low price product is therapeutically
equivalent to high price product is not known. Also, atorvastatin dosage rather than
systemic drug concentration correlates better with LDL-C reduction (US Prescribing
information LIPITOR®, Pfizer, July 2004).

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 45 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 switchable. 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 switched in general
practice.

The study was conducted as an open-label, balanced, randomized parallel trial. The
study was carried out in accordance with the Basic Principles defined in the ICH
'Guidance for Good Clinical Practice' and the principles enunciated in the Declaration
of Helsinki. The protocol and the corresponding informed consent form (ICF) used to
obtain informed consent of study subjects were reviewed by the Jamia Hamdard
Institutional Review Board and the study subjects were not be dosed until the Board
has approved the protocol and the ICF. The purpose of the study, the procedures to be
carried out and the potential hazards that may be encountered during the conduct of
the study were described to the subjects in non-technical terms. All subjects provided
formal written informed consent after attending an oral presentation and after
thoroughly reading the Informed Consent Form (ICF) were admitted to the Ranbaxy
Clinical Pharmacology Unit. The standard SOP's of the Ranbaxy clinical
pharmacology unit were adhered to while conducting the study, analysis and statistics.
A total of 36 subjects were enrolled for the study and were randomized in three treatment groups. Randomization schedule was generated by SAS software. Each subject received the medication for 4 weeks. All the subjects were cooperative throughout the conduct of the study and showed good compliance to the medication. Of the 36 subjects, 35 showed 100% compliance and remaining one subject missed only one dose.

**Total Cholesterol**

Only in populations that maintain very low levels of serum cholesterol, e.g., total cholesterol <150 mg/dL throughout life do we find a near-absence of clinical CHD. Moreover, the cholesterol level in young adulthood predicts development of CHD later in life. In three prospective studies with long-term follow up, detection of elevated serum cholesterol in early adulthood predicted an increased incidence of CHD in middle-age. Earlier clinical trials found that a 1 percent reduction in serum total cholesterol level reduces risk for CHD by about 2 percent. Epidemiological studies suggest that beginning cholesterol-lowering therapy at an earlier age will lead to a greater risk reduction than starting later in life. Law et al. found that a 10 percent reduction in serum cholesterol level attained at age 40 yields a reduction in relative risk for CHD of 50 percent at age 40, whereas a 10 percent cholesterol reduction gives only a 20% reduction in risk if begun at age 70. This finding implies that the greatest long-term benefit is attained by early intervention. (National Cholesterol Education Program (NCEP) Guidelines, September 2002).

Zivast, Lipicor and Atocor 20 mg/day administered for 4 weeks produced statistically significant and clinically important changes in total cholesterol levels measured in this study. Mean percent decrease in total cholesterol at the end of week 4 was 35.14% in group receiving Zivast; 32.06% in group receiving Lipicor and 36.14% in group receiving Atocor, respectively. In the present study, 12 out of 36 (33.33%) subjects had total cholesterol levels above 150 mg/dL. After 4 weeks of treatment with atorvastatin all the subjects had total cholesterol levels < 150 mg/dL i.e. the therapeutic goal was achieved. There was no difference among the three formulations used. A marked response was seen within 1 week, and the maximum therapeutic response occurred within 4 weeks. On intergroup comparison, there was no significant difference between any of the three groups at 4 weeks of treatment. The percent
changes in total cholesterol levels reported here in are very similar to those reported in earlier studies of healthy volunteers and patients. Atorvastatin is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol (US Prescribing information LIPITOR®, Pfizer, July 2004). Total cholesterol reduction of 33.4% was produced by atorvastatin at dose of 20mg in twenty four subjects with elevated LDL-cholesterol (Stern RH et al, 2000). Overall, mean reductions of 34% in total cholesterol were produced in 16 normolipidemic subjects after administration of atorvastatin 40 mg daily for 15 days (Cilia DD Jr et al, 1996). In healthy normolipidemic, elderly and young subjects, 40 mg atorvastatin decreased the serum total cholesterol level with a mean of 38 and 28%, respectively (Weverling-Rijnsburger AW et al, 2004).

Overall, in the present study, 13 out of 36 subjects (36.1 %) had Tc levels above 130 mg/dl (the optimal level) at baseline. After four weeks of treatment, all the 36 subjects had Tc levels of < 130 mg/dl i.e. the goal of treatment was achieved.

The AFCAPS/TexCAPS results indicate that cholesterol reduction for men and women with average total cholesterol and LDL levels could potentially improve quality of life by extending CHD event-free survival and conserving invasive treatments (Downs JR et al, 1998).

Low Density Lipoprotein Cholesterol
LDL cholesterol as low as 25–60 mg/dL is physiologically sufficient (Brown MS and Goldstein JL, 1986). Epidemiological investigations of human populations incriminate high levels of LDL cholesterol as being atherogenic. The Framingham Heart Study (Wilson PWF et al., 1998), the Multiple Risk Factor Intervention Trial (MRFTI) (Stamler J et al., 1986), and the Lipid Research Clinics (LRC) trial (Lipid Research Clinics Program, 1984) found a direct relationship between levels of LDL cholesterol and the rate of new-onset CHD in men and women who were initially free of CHD. Any LDL cholesterol level above 100 mg/dL appears to be atherogenic. Only in populations that maintain very low levels of serum cholesterol, e.g., LDL cholesterol <100 mg/dL throughout life do we find a near-absence of clinical CHD (National Cholesterol Education Program (NCEP) Guidelines, September 2002). Even
when LDL-cholesterol concentrations are near optimal (100–129 mg/dL), atherogenesis occurs. 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.

LDL lowering has been shown to produce marked benefit regardless of gender, age, and the presence of diabetes, smoking, and hypertension. Furthermore, in CHD patients, LDL lowering decreases stroke rates, improves angina and myocardial perfusion and decreases the need for subsequent revascularization. ATP III, identified the LDL-cholesterol goal for secondary prevention to be a level ≤100 mg/dL. Epidemiological data strongly suggest that the prevalence of CHD is lowest when the LDL-cholesterol level is <100 mg/dL. Large studies and metaanalyses have revealed that CHD rates decrease with declining cholesterol levels down to a total cholesterol of 150 mg/dL, corresponding to an LDL cholesterol of about 100 mg/dL (National Cholesterol Education Program (NCEP) Guidelines, September 2002).

Zivast, Lipicor and Atocor 20 mg/day administered for 4 weeks produced statistically significant and clinically important changes in LDL cholesterol levels estimated in this study. Mean decreases in LDL cholesterol at the end of week 4 was 53.31% in group receiving Zivast; 46.27% in group receiving Lipicor and 45.13% in group receiving Atocor, respectively. Though, there was non-significant difference between three group, the difference of 7.04% between Zivast and Lipicor; and the difference of 8.18% between Zivast and Atocor can be clinically significant, as 1% reduction in LDL is associated with 2% decrease in incidence of CHD.

Overall in the present study 6 out of 36 (16.66%) of subjects had elevated LDL levels (> 100 mg/dL) at baseline. After 4 weeks of treatment with atorvastatin all the subjects had LDL levels < 100 mg/dL i.e. the goal of treatment was achieved.

The steady-state LDL-cholesterol reductions observed in this study are similar to those reported previously; doses of 5, 20 and 80 mg produced adjusted mean percent changes in LDL-C from a baseline of −29.0, −44.3, and −61.0, respectively (Nawrocki JW et al, 1995). In another study, twenty-four subjects with elevated LDL-cholesterol were treated with escalating daily doses of 5, 20, and 80 mg atorvastatin for 6 weeks.
each. LDL cholesterol reductions of 34%, 43%, and 57% were produced by atorvastatin doses of 5, 20, and 80 mg, respectively (Stern RH et al, 2000). Overall, mean reductions of 48% in low-density lipoprotein (LDL) cholesterol were observed in 16 normolipidemic subjects after administration of atorvastatin 40 mg daily for 15 days (Cilia DD Jr et al, 1996). Atorvastatin consistently reduces serum total and LDL-cholesterol levels in a nonlinear dose-dependent manner, with atorvastatin 10, 20, 40 and 80 mg/day producing reductions in serum LDL-cholesterol levels of 35 to 42%, 42 to 44%, 50% and 59 to 61%, respectively, in placebo-controlled and noncomparative studies (Malhotra HS and Goa KL, 2001). The fall in serum LDL-cholesterol levels with atorvastatin occurs rapidly, with 90% of the maximum observed reduction in serum LDL-cholesterol levels produced by atorvastatin 80 mg/day observed by the end of 2 weeks (Nawrocki JW et al, 1995). Serum LDL-cholesterol levels declined by 28% as early as 1 week after starting atorvastatin 10 mg/day in a placebo controlled study (Schrott HG et al, 2000).

In the present study, the goal of treatment i.e. total cholesterol levels < 150 mg/dL and LDL levels < 100 mg/dL was achieved in all the 36 subjects and there was no difference between the three formulations of atorvastatin. Thus, switching from a costlier brand of atorvastatin to a cheaper generic version of atorvastatin, would result in no loss whatsoever in therapeutic efficacy.

The mechanism of the LDL-lowering effect of statin may involve both reduction of VLDL concentration, and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL. Apolipoprotein B also falls substantially during treatment with lovastatin. Since each LDL particle contains one molecule of apolipoprotein B, and since little apolipoprotein B is found in other lipoproteins, this strongly suggests that lovastatin does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles (US Prescribing information MEVACOR®, Merck & Co., November 2004).

High Density Lipoprotein Cholesterol
HDL cholesterol normally makes up 20–30% of the total serum cholesterol. HDL-cholesterol levels are inversely correlated with risk for CHD. Some evidence indicates that HDL protects against the development of atherosclerosis, although a low HDL
level often reflects the presence of other atherogenic factors (National Cholesterol Education Program (NCEP) Guidelines, September 2002). At any level of cholesterol low HDL increases the rate of CHD. The NCEP ATP III guidelines clearly defines a level < 40 mg/dL as an independent risk factor for CHD. Raising HDL is not a target for either primary or secondary prevention at this time, however its importance as a tertiary target is rapidly emerging. Michael Miller has stated: "Low HDL is the most common lipoprotein abnormality in patients with CHD and is predictive of CHD events, even when total cholesterol levels are normal" (Hayden M and Tyagi SC, 2005). Over the past two decades, modifying LDL has been the major target for preventing atherosclerotic cardiovascular disease (ASCVD). However, an increasing number of trials, both observational and interventional, have shown the association of low levels of HDL and ASCVD, and the benefits of raising low levels of HDL in reducing the risk of ASCVD. This has led to the recognition of low levels of HDL as an important major cardiovascular risk factor, and led to HDL levels being included as a target of treatment of dyslipidaemia, especially in high-risk patients, such as those with diabetes mellitus. Approximately one-quarter to one-third of patients with pre-existing coronary disease and desirable total cholesterol [less than 5.2 mmol/L] have low levels of HDL (less than 1.0 mmol/L) as the primary abnormality. Regardless of LDL levels, it has been estimated that each mg/dL increase in HDL reduces the risk of cardiac events by 2% in men and by 3% in women (Tavintharan S et al, 2005). The Framingham Study showed that the incidence rate for initial CHD events in men and women with total cholesterol <200mg/dL was about 4% for patients with HDL of 40 mg/dL or greater and 12% in those patients with the HDL <40 mg/dL. (Castelli WP et al, 1986). Epidemiological data taken as a whole signify that a 1% decrease in HDL cholesterol is associated with a 2–3% increase in CHD risk. Moreover, a low HDL level can be a sign of insulin resistance and its associated metabolic risk factors (National Cholesterol Education Program (NCEP) Guidelines, September 2002).

Lipitor and Atorv 20 mg/day administered for 4 weeks produced statistically non-significant but clinically important increase in HDL cholesterol levels of 6.662% and 1.69%, respectively by the end of week 4. Whereas, Zivast on the other hand produced a non-significant decrease of 1.56% at the end of week 4. Previous studies have shown that effects on HDL may differ among statins. HDL cholesterol was
increased by 2.1% with atorvastatin at dose of 20 mg in twenty four subjects with elevated LDL-cholesterol (Stern RH et al, 2000). Atorvastatin increased HDL-cholesterol levels by about 5 to 9% in most studies (Malhotra HS and Gou KL, 2001).

The effect on HDL-cholesterol is not dose related; higher doses of atorvastatin (40 and 80 mg/day) do not produce a greater increase in serum HDL cholesterol levels than those achieved with a dosage of 20 mg/day [Kastelein JJP et al (2000) and Crouse III JR et al (1999)]. Combined data from 25 clinical trials showed increases in HDL-cholesterol levels of 6.7, 8.2, 8.6 and 7.0% with atorvastatin 10, 20, 40 and 80 mg/day, respectively (Nawrocki JW et al, 1999). A variable increase in HDL (approximately 3-10%) results with statins but the mechanism underlying this is unclear, although there are reports to indicate that statins increase HDL by decreasing the activity of cholesterol ester transfer protein (Tavintharan S et al, 2005).

Three clinical trials viz Veterans Affairs HDL-Cholesterol Intervention Trial [VA-HIT], Bezafibrate Infarction Prevention [BIP] trial & the AFCAPS/TexCAPS have focused on the benefits of lipid-regulating therapy in populations with normocholesterolaemia and low HDL. The AFCAPS/TexCAPS demonstrated that a statin could decrease acute coronary events in patients with isolated low HDL-cholesterol in a primary prevention setting. The absolute risk reduction in coronary events in the VA-HIT study compares favourably with those reported from the statin-based Cholesterol and Recurrent Events (CARE) and Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trials. The absolute risk reduction in AFCAPS-TexCAPS is similar to that in West of Scotland Coronary Pravastatin Study (WOSCOPS). The VA-HIT results suggest that when LDL cholesterol levels are optimal, or near optimal, increasing HDL-cholesterol with reduction in triglyceride-rich lipoproteins may be a cost-effective approach to decreasing the incidence of coronary events in secondary prevention (Watts GF, 2001).

**Total cholesterol/ High Density Lipoprotein cholesterol ratio**
Many studies show that the total cholesterol/HDL cholesterol ratio is a powerful predictor of CHD risk. It is proposed that this “cholesterol ratio” is a simple approach for lipid risk assessment. This ratio reflects two powerful components of risk. A high total cholesterol is a marker for atherogenic lipoproteins, whereas a low HDL
cholesterol correlates with the multiple risk factors of the metabolic syndrome and probably imparts some independent risk. ATP III does not define the total cholesterol/HDL cholesterol ratio as a specified lipid target of therapy. Instead, LDL cholesterol is retained as the primary target of lipid-lowering therapy. Nor is the total cholesterol/HDL cholesterol ratio recommended as a secondary target of therapy (National Cholesterol Education Program (NCEP) Guidelines, September 2002). The excess risk of CHD in Indians appears to be greater at younger age. Indians have low levels of HDL resulting in a high total cholesterol/HDL ratio.

Zivast, Lipitor and Atocor 20 mg/day administered for 4 weeks produced statistically significant and clinically important changes in TC/HDL ratio measured in this study. Mean percent decreases in TC/HDL ratio was 38.38% in group receiving Zivast; 33.33% in group receiving Lipitor and 35.94% in group receiving Atocor, respectively.

**Low Density Lipoprotein cholesterol to High Density Lipoprotein cholesterol ratio**

Results of prospective studies have suggested that a high LDL/HDL ratio combined with hypertriglyceridemia is associated with highest CHD risk. Thus, algorithms have been produced showing that an elevated LDL/HDL ratio combined with elevated triglyceride is associated with high CHD risk. This dyslipidemic state (lipid triad) has been described as atherogenic dyslipidemia. Reduction of total cholesterol/HDL and of the LDL/HDL ratio in patients initially free of IHD who were treated with a lipid-lowering drug (lovastatin) was found to predict a decreased risk of a first IHD event (Isabelle Lemieux et al. 2001).

Zivast, Lipitor and Atocor 20 mg/day administered for 4 weeks produced statistically significant decrease in LDL/HDL ratio in this study. Mean percent decreases in LDL/HDL ratio was 52.34% in group receiving Zivast; 48.74% in group receiving Lipitor and 45.33% in group receiving Atocor, respectively. In patients aged 40-80 years with established cardiovascular disease and HDL-C < 40 mg/dL, after 6 weeks of treatment with atorvastatin 20 mg, mean percentage change from baseline in LDL-C/HDL-C ratio was -41.9%. After 12 and 18 weeks of treatment, change from baseline was -47.9% and -49.6%, respectively (Jukema JW et al, 2005).
A high LDL/HDL cholesterol ratio is strongly associated with an increased risk of ischemic heart disease. The LDL/HDL cholesterol ratio provides information about the relative proportion of cholesterol transported in the undesirable vs. desirable lipoprotein fraction. However, some authors advise against using this ratio because some individuals may have similar ratios yet show large differences in the concentration on plasma total cholesterol, LDL and HDL (Kris-Etherton PM et al, 1988) and similar trend was observed in the present study.

Triglyceride
The acceptable “normal” level of triglycerides was decreased from <200 mg/dL in the ATP II report to <150 mg/dL in the ATP III classification. In the United States, 43% of Asian Indian males and 24% of Asian Indian females have levels that exceed 150 mg/dL. The CHD risk among Asian Indians is at least 2-fold higher than other populations, even when adjusted for all conventional risk factors and the various components of the metabolic syndrome (Enas EA, 2002).

In the present study, Zivast, Lipicor and Atocor 20 mg/day administered for 4 weeks produced statistically significant decrease in triglycerides. Mean percent decreases in triglycerides was 48.70% in group receiving Zivast; 31.69% in group receiving Lipicor and 49.05% in group receiving Atocor, respectively. In the present study, 11 out of 36 (30.6%) of subjects had elevated triglyceride levels of above 150 mg/dL. Atorvastatin treatment decrease triglycerides levels in all the subjects and at the end of 4 weeks only 3 out of 36 (8.33%) subjects had triglyceride levels above 150 mg/dL. Overall, mean reductions of 25% in triglycerides were observed in 16 normolipidemic subjects after administration of atorvastatin 40 mg daily for 15 days (Cilla DD Jr et al, 1996). Atorvastatin 10 to 80 mg/day reduced triglyceride levels by 17 to 45% (Malhotra HS and Goa KL, 2001). In another study, 14 patients experienced 39% reductions in triglyceride levels after 6 months of atorvastatin 10 to 20 mg/day (Malhotra HS and Goa KL, 2001).

Overall, in this study, 13 out of 36 subjects (36.1%) had TG levels above the optimal 150 mg/dl at baseline. After 4 weeks of treatment with atorvastatin, only 2 out of 36 subjects (5.6%) had TG levels above 150 mg/dl.
A significant fall in plasma triglyceride concentrations, produced by statin can be an indirect support for its inhibitory effect on LDL. Statins exert triglyceride lowering effects via several different mechanisms: (i) by increasing expression of LDL receptor; (ii) increasing the clearance of triglyceride containing lipoproteins, and (iii) inducing activation of PPARα, which may decrease hepatic transcription of apolipoprotein C-III, thus altering the composition of triglyceride containing lipoproteins such that their catabolism is enhanced (Evans M et al, 2004).

Adverse Events
The study treatments were well tolerated by study subjects and there were no adverse events during the study.

Clinical Context
Statins have been shown to be effective in reducing morbidity and mortality from coronary heart disease. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines now are applicable to a wide group of patients with more aggressive LDL control. In conclusion, brand switching may lead to harm to patients if clinically inferior treatments are erroneously deemed equivalent to a standard approach, or if potentially superior therapies are discarded as merely “equivalent.” With the increasing development and use of generic drugs, and the pressure to control medical costs by substituting less expensive therapies (or to deny therapies regarded as not cost effective), the claim that one drug, intervention, or therapy is “equivalent” to another requires close scrutiny. Attention to proper methods for conducting studies of equivalence will help avoid false claims, inconsistencies, and the inappropriate use of suboptimal therapies. Our findings may have implications for clinical practice.

Further, statin therapy has been advocated in normolipidemic patients with multiple risk factors. The results obtained in the present study, confirm that atorvastatin significantly decreases TC, LDL and TG levels, both in normolipidemic and hyperlipidemic normal subjects.
Limitations of the present study

A major limitation of the present study was the small sample size. A sample size of 12 subjects per treatment group was chosen as a preliminary investigation. A truly powered study with a larger sample size would have required a longer time to complete which was in itself a limitation.