LDL-CHOLESTROL LOWERING EFFECT OF DIFFERENT GENERIC PRODUCTS OF SIMVASTATIN COMPARED TO SIMVASTATIN IN PAKISTANI HYPERCHOLESTEROLEMIC SUBJECTS - A RANDOMIZED STUDY

A THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

By

NAZIR AHMED SOLANGI
M. Phil

Department of pharmacology
Faculty of pharmacy
University of Karachi
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<table>
<thead>
<tr>
<th>S. No.</th>
<th>Title</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>List of Tables</td>
<td>I</td>
</tr>
<tr>
<td>2.</td>
<td>List of Figures</td>
<td>II</td>
</tr>
<tr>
<td>3.</td>
<td>List of Abbreviations</td>
<td>III</td>
</tr>
<tr>
<td>4.</td>
<td>Acknowledgements</td>
<td>IV–VI</td>
</tr>
<tr>
<td>5.</td>
<td>Summary</td>
<td>VII–IX</td>
</tr>
<tr>
<td>6.</td>
<td>Khulasa</td>
<td>X–XI</td>
</tr>
<tr>
<td>7.</td>
<td>Introduction</td>
<td>1–67</td>
</tr>
<tr>
<td>8.</td>
<td>Purpose of Study</td>
<td>68–69</td>
</tr>
<tr>
<td>9.</td>
<td>Materials &amp; Methods</td>
<td>70–82</td>
</tr>
<tr>
<td>10.</td>
<td>Observations and Results</td>
<td>83–113</td>
</tr>
<tr>
<td>11.</td>
<td>Discussion</td>
<td>114–139</td>
</tr>
<tr>
<td>12.</td>
<td>Conclusion</td>
<td>140</td>
</tr>
<tr>
<td>13.</td>
<td>References</td>
<td>141–160</td>
</tr>
<tr>
<td>14.</td>
<td>Appendix -1</td>
<td>161–162</td>
</tr>
<tr>
<td>S.No.</td>
<td>LIST OF TABLES</td>
<td>Pg.Nos.</td>
</tr>
<tr>
<td>------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>1.</td>
<td>Division of Patients Included In the Study According To Gender, Suffering from Hyperlipidemia</td>
<td>84</td>
</tr>
<tr>
<td>2.</td>
<td>Therapeutic Effectiveness of Zocor 20 mg OD in Hyperlipidemia in All Parameters on Day-0, Day-45, and Day-90</td>
<td>88</td>
</tr>
<tr>
<td>3.</td>
<td>Therapeutic Effectiveness of Atcol 20 mg OD in Hyperlipidemia in All Parameters on Day-0, Day-45, and Day-90</td>
<td>92</td>
</tr>
<tr>
<td>4.</td>
<td>Therapeutic Effectiveness of Limitrol 20 mg OD in Hyperlipidemia in All Parameters on Day-0, Day-45, and Day-90</td>
<td>96</td>
</tr>
<tr>
<td>5.</td>
<td>Parameter-wise Observations of All Groups on Day-0 and Day-90 SERUM CHOLESTEROL (mg/dl)</td>
<td>99</td>
</tr>
<tr>
<td>6.</td>
<td>Parameter-wise Observations of All Groups on Day-0 and Day-90 SERUM TRIGLYCERIDES (mg/dl)</td>
<td>103</td>
</tr>
<tr>
<td>7.</td>
<td>Parameter-wise Observations of All Groups on Day-0 and Day-90 SERUM LDL-C (mg/dl)</td>
<td>107</td>
</tr>
<tr>
<td>8.</td>
<td>Parameter-wise Observations of All Groups on Day-0 and Day-90 SERUM HDL-C (mg/dl)</td>
<td>110</td>
</tr>
<tr>
<td>S.No.</td>
<td>LIST OF FIGURES</td>
<td>Pg.Nos:</td>
</tr>
<tr>
<td>-------</td>
<td>---------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>1.</td>
<td>Division of Patients Included In the Study According To Gender, Suffering from Hyperlipidemia</td>
<td>85</td>
</tr>
<tr>
<td>2.</td>
<td>Therapeutic Effectiveness of Zocor 20 mg OD in Hyperlipidemia in All Parameters on Day-0, Day-45, and Day-90</td>
<td>89</td>
</tr>
<tr>
<td>3.</td>
<td>Therapeutic Effectiveness of Atcol 20 mg OD in Hyperlipidemia in All Parameters on Day-0, Day-45, and Day-90</td>
<td>93</td>
</tr>
<tr>
<td>4.</td>
<td>Therapeutic Effectiveness of Limitrol 20 mg OD in Hyperlipidemia in All Parameters on Day-0, Day-45, and Day-90</td>
<td>97</td>
</tr>
<tr>
<td>5.</td>
<td>Parameter-wise Observations of All Groups on Day-0 and Day-90 SERUM CHOLESTEROL (mg/dl)</td>
<td>101</td>
</tr>
<tr>
<td>6.</td>
<td>Parameter-wise Observations of All Groups on Day-0 and Day-90 SERUM TRIGLYCERIDES (mg/dl)</td>
<td>105</td>
</tr>
<tr>
<td>7.</td>
<td>Parameter-wise Observations of All Groups on Day-0 and Day-90 SERUM LDL-C (mg/dl)</td>
<td>109</td>
</tr>
<tr>
<td>8.</td>
<td>Parameter-wise Observations of All Groups on Day-0 and Day-90 SERUM HDL-C (mg/dl)</td>
<td>113</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary Artery Disease</td>
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<tr>
<td>CETP</td>
<td>Cholesterol-Ester Transport Protein</td>
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</tr>
<tr>
<td>CHD</td>
<td>Coronary Heart Disease</td>
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<td>CPK</td>
<td>Creatine Phospho Kinase</td>
<td></td>
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<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
<td></td>
</tr>
<tr>
<td>ELAMS</td>
<td>Endothelial-Leukoeyte Adhesion Molecules</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>High Density Lipoproteins</td>
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<td>HDL-C</td>
<td>High Density Lipoprotein Cholesterol</td>
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<tr>
<td>LCAT</td>
<td>Lecithin Cholesterol Acyl Transferase</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>Low Density Lipoproteins</td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>Low Density Lipoprotein Cholesterol</td>
<td></td>
</tr>
<tr>
<td>LRP</td>
<td>LDL-Receptor Related Protein</td>
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<td>LFTs</td>
<td>Liver Function Tests</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
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</tr>
<tr>
<td>Ox-LDL</td>
<td>Oxidized Low-Density Lipoproteins</td>
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<tr>
<td>SD</td>
<td>Standard Division</td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>Standard Error of Mean</td>
<td></td>
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<tr>
<td>VLDL</td>
<td>Very Low Density Lipoproteins</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
<td></td>
</tr>
</tbody>
</table>
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The present study reports the LDL-Cholesterol lowering effects of Simvastatin. The LDL-Cholesterol lowering effects of generic products of Simvastatin have been compared to the original brand of Simvastatin i.e. Zocor in hypercholesterolemic subjects. The generic drugs used were of Atco Laboratories and that of Pharm evo Laboratories.

All the drugs used in the present study significantly reduced the total cholesterol; the serum triglycerides and the Low density lipoproteins cholesterol (LDL-C). High density lipoprotein (HDL); however increased significantly in all the three groups.

The group A i.e. Zocor treated individuals after 90 days of drug administration showed a decrease in cholesterol from 242.18±42.15 to 166.20±31.24. The triglycerides reduced from 289.18±149.14 to 213.36±103.12. LDL-C reduced from 192.92±29.65 to 125.00±17.33; however the HDL increased from 30.83 to 36.33 after 90 days of treatment which has increased significantly.

In group B i.e. Atcol treated group after 90 days of treatment total cholesterol decreased from 242.77±46.92 on day 0 to 167.61±35.78 on
day 90. The mean serum triglycerides level decreased significantly from $291.56 \pm 148.44$ to $221.88 \pm 106.61$ on day 90. Highly significant decrease in serum low density lipoprotein cholesterol (LDL-C) was observed which decreased from $185.52 \pm 19.59$ on day 0 to $123.00 \pm 12.87$ on day 90. However serum high density cholesterol (HDL-C) increased from $31.80 \pm 4.98$ on day 0 to $37.01 \pm 5.61$ on day 90.

In Limitrol treated group i.e. group C; a significant decrease in cholesterol was observed from $238.37 \pm 48.35$ to $160.14 \pm 21.83$ on day 90. The triglycerides reduced from $243.00 \pm 41.19$ to $175.37 \pm 31.30$ on day 90; similarly LDL-C reduced from $186.31 \pm 10.35$ to $124.00 \pm 9.94$ on day 90. However HDL-C increased from $31.14 \pm 5.44$ on day 0 to $37.00 \pm 4.87$ on day 90.

Subsequently, safety of statin therapy was also observed in this study. As far as the safety is concerned; the results in our study show that, Zocor, Atcol; as well as Limitrol caused no serious adverse effects. In all 7 patients from group A; 9 patients from group B; and 11 patients from group C showed the side effects. The side effects were not severe to discontinue the treatment. Reassurance and symptomatic treatment was sufficient to continue the therapy.
Out of 264 patients in this study; 8 patients from group A were lost during the study period and similarly other 08 patients were lost from group B and further 07 patients were lost during the study period from group C. In all 23 patients were dropped from the study.
KHULASA
خلاصة

بسم الله الرحمن الرحيم

الاستعدادات:
- تقييم مرضى سمنون
- دراسة تأثير مواجهة الأمراض والصحة العقلية
- تقييم مرضى السمن

 результатات:
1. تأثير المضادات الحيوية على مساحة الحفر
2. تأثير المضادات الحيوية على عدد الخلايا
3. تأثير المضادات الحيوية على نسب التهاب

ناتج:
- المضادات الحيوية تزيد من مساحة الحفر
- المضادات الحيوية تزيد عدد الخلايا
- المضادات الحيوية تزيد نسبة التهاب

ملاحظات:
- النتائج تؤكد على ضرورة التحكم في المضادات الحيوية
- الهلالسون (متمثلة في الكلي) يلعب دوراً في التحكم في المضادات الحيوية
- المراعاة للحالة الصحية العقلية للمرضى

الاستنتاج:
- التحكم في المضادات الحيوية يساهم في تقليل التهابات الأسنان
- تغيير النمط الغذائي يمكن أن يبطئ نمو الحفر
- تحسين مستوى المضادات الحيوية يمكن أن يساهم في تقليل التهابات الأسنان

المراجع:
- د. محمد مصطفى
- د. علي محمد
- د. محمد أحمد

ال炤_ALI

زمینه مقاله می‌تواند از میزان تأثیر ار امکانپذیر باشد که مشاهده کی گیا. این مقاله کا مقصودن از امکانپذیری کی تأثیر ار حفاظت‌کا مشاهده این میزان بر گرکنندا چن کی خون می‌چربی کی مقدار ب‌هی‌هولی پایای گی. جهان تک تحقیقات كا ذکر هی، اس تحقیق می‌تواند اینکول اور لیمیت‌کردن می‌تواند به شدید منجر اثرات مرتب نهی کی اور صرف گرو. الف کی سات میزان گروه ب کی ۹ میزان اور گروه. ج. کی گیاهی میزان میزان اثرات پایای گی. و هم‌مرض اثرات انتی‌شاداین که تهیه‌که‌که دوا کی به‌کنندا چن گرکنندا چن صرف اطمینانات دانگر اور علاجی علاج کی بعد دوای‌یون کو جاری گیا. گیا.

دوران علاج جمله ۲۴ میزان می‌دانند گروه. الف کی ۸ میزان گروه. ب کی ۸ میزان اور گروه. ج. کی ۷ میزان علاج جاری گر کی سکس اگر چی ۲۳ میزان کو ارج تحقیق کی نتایج که اعداد و شمار می‌بیش شامل نهی گیا گیا.
INTRODUCTION
The rise in cardiovascular diseases (CVD) reflects a significant change in diet habits, physical activity levels, and tobacco consumption worldwide as a result of industrialization, urbanization, economic and food market globalization. People are consuming a more energy-dense, nutrient-poor diet and are less physically active. Imbalanced nutrition, reduced physical activity and increased tobacco consumption are the key lifestyle factors. High blood pressure, high cholesterol, overweight and obesity – and chronic disease of type II diabetes – are among the major biological risk factors for CVD. Unhealthy dietary practices include the high consumption of saturated fats, salt and refined carbohydrates, as well as low consumption of fruit and vegetables. The risk factors tend to cluster (WHO Global strategy on diet, physical activity & health, 2004).

Heart disease has no geographic, gender, or socioeconomic boundaries. An estimated 16.7 million – or 29.2% of total global deaths – result from the various forms of cardiovascular disease (CVD), many of which are preventable by action on the major primary risk factors; unhealthy diet, physical inactivity, and smoking. More than 50% of the deaths and disability from heart disease and strokes, which together kill more than 12 million people
each year, can be cut by a combination of simple, cost-effective national efforts and individual actions to reduce major risk factors such as high blood pressure, high cholesterol, obesity and smoking. At least 20 million people survive heart attacks and strokes every year; many require continuing costly clinical care.

The major CVDs include:

- Coronary (or ischemic) heart disease (heart attack)
- cerebrovascular disease (stroke)
- hypertension (high blood pressure)
- heart failure
- rheumatic heart disease

Compelling evidence indicates that at least three dietary strategies are effective in preventing CVD, and in helping manage the disease:

- substitute nonhydrogenated unsaturated fats (especially polyunsaturated fat) for trans-fats
- increase consumption of omega-3 fatty acids from fish oil or plant sources
- consume a diet high in fruits, vegetables, nuts and whole grains, and low in refined grains
- avoid excessively salty or sugary foods
- At least 30 minutes of regular physical activity daily
Avoid smoking

- Maintain a healthy weight (Scott M et al, 1997)

**LIPIDS, LIPOPROTEINS AND APOLIPOPROTEINS:**

Lipids have an important role virtually in all aspects of life – serving as hormones or hormone precursors, aiding in digestion, providing energy storage and metabolic fuels, acting as functional and structural components in cell membranes and forming insulation to allow nerve conduction or to prevent heat loss. However only a limited number of the numerous different lipids known to exist in humans are usually of clinical importance. (Rifai N et al, 1999)

**Table**

**Classification of Clinically important Lipids:**

<table>
<thead>
<tr>
<th>Sterol Derivatives</th>
<th>Glycerol Esters</th>
</tr>
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<tbody>
<tr>
<td>Cholesterol and cholesteryl esters</td>
<td>Tri-di-and monoglycerides</td>
</tr>
<tr>
<td>Steroid hormones</td>
<td>(acylglycerols)</td>
</tr>
<tr>
<td>Biles acids</td>
<td>Phosphoglycerides</td>
</tr>
<tr>
<td>Vitamin D</td>
<td><strong>Sphingosine Derivatives</strong></td>
</tr>
<tr>
<td></td>
<td>Sphingomyelin</td>
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<tr>
<td>Fatty Acids</td>
<td>Glycosphingolipids</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Short chain (2-4 carbon atoms)</td>
<td></td>
</tr>
<tr>
<td>Medium chain (6-10 carbon atoms)</td>
<td></td>
</tr>
<tr>
<td>Long chain (12-26 carbon toms)</td>
<td></td>
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<tr>
<td>Prostaglandins</td>
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</tbody>
</table>

In the past three decades, much attention has been on certain lipids and the lipoproteins that transport them in the circulation, mainly because of their strong association with coronary heart disease (CHD). Therefore the use of the term lipids in clinical chemistry has become virtually synonymous with lipoprotein metabolism and atherosclerosis, a cause of CHD. Lipids can be broadly subdivided into five groups based on their chemical structure.

**PLASMA LIPOPROTEINS:**

Plasma lipoproteins are classified in to four major groups according to their density; which can be determined by the process of ultracentrifugation (Khan AS and Tayyab M, 2004).

These are:
1. Chylomicrons – mainly composed of triglycerides – These lipoproteins transport triglycerides from the gut.

2. VLDL (very low density lipoproteins) – their main constituent is also triglycerides. They transport triglycerides from the liver to peripheral tissues.

3. LDL (low density lipoproteins) – These are mainly composed of cholesterol esters. They are end products of VLDL metabolism. Their function is to transport cholesterol to tissues.

4. HDL (high density lipoproteins) – They are also mainly cholesterol esters. They are scavengers of cholesterol. Their function is to transport cholesterol from the tissues to the liver.

About 60% of plasma cholesterol is normally found in LDL fraction, 25% in the HDL fraction while the rest of cholesterol is present in VLDL variety. In the fasting state chylomicrons are absent from plasma, and in that situation 50-80% of plasma triglycerides is found in the VLDL fraction.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Defect</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong> (familial LPL deficiency, familial hyperchylomicronemia)</td>
<td>(a) deficiency of LPL&lt;br&gt;(b) production of abnormal LPL&lt;br&gt;(c) apoC-II deficiency</td>
<td>Slow chylomicron clearance, reduced LDL and HDL levels; treated by low fat/complex carbohydrate diet; no increased risk of coronary artery disease</td>
</tr>
<tr>
<td><strong>Type II</strong> (familial hypercholesterolemia, FH)</td>
<td>4 classes of LDL receptor defect</td>
<td>Reduced LDL clearance leads to hypercholesterolemia, resulting in atherosclerosis &amp; coronary artery disease</td>
</tr>
<tr>
<td><strong>Type III</strong> (familial dysbeta lipoproteinemia, remnant removal disease, Broad beta disease, apolipoprotein E deficiency)</td>
<td>hepatic remnant clearance impaired due to apoE abnormality; patients only express the apoE₂ isoform that interacts poorly with the apoE receptor</td>
<td>Causes xanthomas, hypercholesterolemia and atherosclerosis in peripheral and coronary arteries due to elevated levels of chylomicrons and VLDLs</td>
</tr>
<tr>
<td>Type IV (familial hypertriacylglycerolemia)</td>
<td>elevated production of VLDL associated with glucose intolerance and hyperinsulinemia</td>
<td></td>
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<td>------------------------------------------</td>
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</tr>
<tr>
<td><strong>Type V familial</strong></td>
<td>elevated chylomicrons and VLDLs due to unknown cause</td>
<td></td>
</tr>
<tr>
<td>Hypertriacylglycerolemia and hypercholesteolemia with decreased LDLs and HDLs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial hyperalphalipoproteinemia</td>
<td>increased level of HDLs</td>
<td></td>
</tr>
<tr>
<td>a rare condition that is beneficial for health and longevity</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type II Familial hyperbetalipoproteinemia</strong></td>
<td>increased LDL production and delayed clearance of triacylglycerols and fatty acids</td>
<td></td>
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<tr>
<td>strongly associated with increased risk of coronary artery disease</td>
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</tbody>
</table>

Continued..
<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Pathological Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial ligand-defective apoB</td>
<td>2 different mutations: Gln for Arg (amino acid 3500) or Cys for Arg (amino acid 3531); both lead to reduced affinity of LDL for LDL receptor</td>
<td>dramatic increase in LDL levels; no effect on HDL, VLDL or plasma triglyceride levels; significant cause of hypercholesterolemia and premature coronary artery disease</td>
</tr>
<tr>
<td>Familial LCAT deficiency</td>
<td>absence of LCAT leads to inability of HDLs to take up cholesterol (reverse cholesterol transport)</td>
<td>decreased levels of plasma cholesteryl esters &amp; lysolecithin; abnormal LDLs (Lp-X) &amp; VLDLs symptoms also found associated with cholestasis</td>
</tr>
<tr>
<td>Wolman's disease (cholesteryl ester storage disease)</td>
<td>defect in lysosomal cholesteryl ester hydrolase; affects metabolism of LDLs</td>
<td>Reduced LDL clearance leads to hypercholesterolemia resulting in athero-sclerosis and coronary artery disease</td>
</tr>
<tr>
<td>Heparin-releasable hepatic triglyceride lipase deficiency</td>
<td>Deficiency of the lipase leads to accumulation of triacylglycerol-rich HDLs and VLDL remnants (IDLs)</td>
<td>causes xanthomas and coronary artery disease</td>
</tr>
</tbody>
</table>

(King M. W. 2005).
CHOLESTEROL:

Although every living organism has been found to contain sterols, cholesterol is found almost exclusively in animals, in which it is also the main sterol. Virtually all cells and body fluids contain some Cholesterol. Like other sterols, cholesterol is a solid alcohol of high molecular weight and possesses the tetracyclic perhydrocyclopentano-phenenthrene skeleton. The molecule contains 27 carbon atoms. Knowledge of this sterane skeleton and numbering system is important not only to clinical laboratories but to practising physicians because cholesterol is the initial starting point in many metabolic pathways. These include vitamin D synthesis, steroid hormone synthesis and bile acid metabolism. As the enzymes modifying the sterane ring or its radicals in metabolic pathway are known by both their site and type of reaction (e.g. 21-hydroxylase in cortisol synthesis), the diagnosis of many disease states consequently depends on isolating the site of enzyme dysfunction (e.g. 21-hydroxylase deficiency in adrenogenital syndrome) (Rifai, N 1999).
**Cholesterol Absorption:**

Cholesterol is presented to the intestinal wall from three sources:

i. The diet.

ii. Bile and intestinal secretions and cells.

iii. Animal products especially meat, egg yolk, seafood, and whole-fat dairy products, provide the bulk of dietary cholesterol.

Practically all cholesterol in the intestine is present in the unesterified (free) form; esterified cholesterol in the diet is rapidly hydrolyzed in the intestine to free cholesterol and free fatty acids by cholesterol esterases secreted from the pancreas and small intestine.

**Cholesterol synthesis:**

Of the total cholesterol synthesized daily, about 300 to 1000 mg is derived from dietary intake. Cholesterol can also be synthesized endogenously by liver and other tissues from simple molecules, particularly acetate. Knowledge of endogenous cholesterol synthetic pathway has assumed great significance in the past decade as agents have been sought to suppress or decrease endogenous cholesterol synthesis. The need for clinical medicine to understand the fundamental biochemistry of this pathway was underscored by the triparanol disaster of 1960. Triparanol is a drug
Figure showing cholesterol synthesis

HMG-CoA formation and conversion to mevalonate
Conversion of mevalonate to isoprenoid precursors
Synthesis of squalene and its conversion to lanosterol
Conversion of lanosterol to cholesterol
Regulation of cholesterol synthesis and pharmaceutical intervention
mevalonate, then decarboxylated to five carbon isoprene units.

**Cholesterol Requirement:**

The body requires some cholesterol to function, but increased levels of cholesterol can lead to cholesterol deposits within the walls of the arteries that eventually form "atherosclerotic plaques." These plaques grow over time and can break open into the artery and trigger the formation of a blood clot. The sudden blockage of an artery by the blood clot prevents oxygen from arriving at the heart muscle or brain, causing heart attacks or strokes, respectively. People with elevated levels of LDL, which accounts for the majority of the total cholesterol measurement, are more likely to suffer heart attacks or die prematurely. For every 10-milligram (mg) increase in LDL per deciliter (dL) of blood, the risk of a heart attack increases by almost 20%. Conversely, people with higher levels of the "good" HDL cholesterol have a lower risk of cardiac events.
CHOLESTEROL INTAKE AND UTILIZATION:

The body derives cholesterol from two sources:

1. Diet (0.2-2.0 G/day)
2. De novo synthesis (endogenous).

The liver synthesizes daily about 900 mg cholesterol. Approximately the same amount is lost from the body in the form of:

1. Bile acids (250 mg)
2. Free cholesterol in the bile (550 mg)
3. Through skin 100 mg (cell loss).

Both the endogenous and exogenous cholesterol enter into one of the three pathways:

1. Incorporation into VLDL
2. Conversion to bile acids
3. Excretion as free cholesterol in the bile.

The VLDL after secretion by the liver is acted upon by the enzyme lipoprotein lipase and is converted into LDL. The LDL contains apolipoproteins B which can bind to specific receptors on the surface of extra hepatic and hepatic cells. The LDL is then internalized (taken up) into these cells. The lipoproteins are
hydrolyzed by lysosomal enzymes and the cholesterol liberated is either esterified and stored or used for the production of steroids or cell membranes synthesis. Thus VLDL and LDL are responsible for the transport of cholesterol from liver to the peripheral tissues.

Cholesterol in the tissue membranes is in free form; it is in equilibrium with free cholesterol of plasma. This cholesterol can be removed and esterified by HDL and LCAT enzyme. The HDL is finally degraded in liver, releasing cholesterol into the liver pool. Cholesterol is partly converted to bile salts and these are excreted into the bile with unchanged cholesterol. This scavenging property of HDL may explain the observation that HDL is a negative risk factor for coronary artery disease (increased HDL, decreased risk).

The HDL is divided into three sub-fractions i.e. HDL1, HDL2 and HDL3 according to their Ultra centrifugal behavior. HDL1 is the least dense, it is a minor component. HDL is released from the liver HDL3, conversion into HDL2 is accompanied by increase in cholesterol ester content.

This is due to the action of enzyme LCAT (Lecithin-cholesterol acyltransferase). Generally speaking it has been accepted that:
1. High plasma levels of LDL and possibly VLDL are associated with increased risk of premature atherosclerosis and coronary artery disease.

2. Plasma HDL cholesterol concentration is a negative risk factor, so that high levels appear to protect against CAD and low levels are associated with increased risk of CAD (coronary artery disease); (Khan A,S and Tayyab, M; 2004).

Clinical Significance – Association with Coronary Heart Disease:

Increased cholesterol is a causative factor in the etiology of atherosclerotic diseases. As early as 1910, Windaus described cholesterol in the lesions of diseased arteries. Subsequently many studies have confirmed that free and esterified cholesterol accumulate in the aorta, coronary arteries and cerebral vessels and that the rate of accumulation varies among individuals.

The association between serum cholesterol and atherosclerosis in humans was first suggested in 1938, when Thanhanser and Muller each demonstrated familial aggregation of hypercholesterolemia and CHD. Further studies showed that when the total cholesterol
concentration is high, the incidence and prevalence of CHD are also high.

Many epidemiological and clinical studies have shown that both increased LDL-cholesterol and decreased HDL-cholesterol are associated with increased risk of CHD. Some studies showed that a reduction in LDL cholesterol is correlated with regression in atherosclerotic lesion (Rifai, N; 1999).

The normal function of lipoproteins is to distribute and recycle cholesterol. Cholesterol is absorbed from the intestine and transported to the liver by chylomicron remnants, which are taken up by the low-density lipoprotein (LDL)-receptor related protein (LRP). Cholesterol is then transported to peripheral tissues where, for example, it is converted to steroid hormones or used to form cell walls and membranes. Hepatic cholesterol enters the circulation as very low density lipoprotein (VLDL) and is metabolised to remnant lipoproteins after lipoprotein lipase removes triglyceride. The remnant lipoproteins are removed by the liver through apolipoprotein E-receptors or LDL-receptors (LDL-R) or further metabolized to LDL and then removed by peripheral tissues or the liver by LDL-R (Rifai, N 1999). The quantity of cholesterol transported from the liver to peripheral tissues greatly exceeds its
catabolism there and mechanisms exist to return cholesterol to the liver. Through this reverse transport cholesterol is carried by high-density lipoprotein (HDL) from peripheral cells to the liver where it is taken up by a process involving hepatic lipase. Cholesterol in the plasma is also recycled to LDL and VLDL by cholesterol-ester transport protein (CETP).

Cholesterol in liver is reassembled into lipoproteins or secreted in bile then recycled by absorption at the terminal ileum or excreted in faeces.

**ANATOMY AND PHYSIOLOGY OF HEART:**

The heart is a hollow muscular organ that is somewhat pyramidal in shape and lies within the pericardium in the mediastinum. The walls of the heart are composed of cardiac muscles, the myocardium, covered externally with serous pericardium, called the epicardium, and lined internally with a layer of endothelium, the endocardium.
**Arterial Supply of Heart:**

The arterial supply of heart is provided by the right and left coronary arteries, which arise from the ascending aorta immediately above the aortic valve. The coronary arteries and their major branches are distributed over the surface of heart, lying within subepicardial connective tissue.

**Right Coronary Artery:**

The right coronary artery arises from the anterior aortic sinus of the ascending aorta and runs forward between the pulmonary trunk and the right auricle. It descends almost vertically in the right atrioventricular groove, and at the inferior border of heart it continues posteriorly along the atrioventricular groove to anastomose with the left coronary artery in the posterior interventricular groove. The following branches from the right coronary artery supply the right atrium and right ventricle and parts of the left atrium and left ventricle and the atrioventricular septum (Snell R S 2000)
Branches:

- The right coronary artery supplies the anterior surface of the pulmonary conus (infundibulum of the right ventricle) and the upper part of the anterior wall of the right ventricle.

- The anterior ventricular branches are two or three in number, and supply the anterior surface of the right ventricle. The marginal branch is the largest and runs along the lower margin of the coastal surface to reach the apex.

- The posterior ventricular branches are usually two in number and supply the diaphragmatic surface of the right ventricle.

- The posterior interventricular (descending) artery runs towards the apex in the posterior interventricular groove. It gives off branches to the right and left ventricles, including the inferior wall. It supplies branches to the posterior part of the ventricular septum but not to the apical part, which receives its supply from the anterior interventricular branch of the left coronary artery. A large septal branch supplies the atrioventricular node. In 10% of individuals the posterior interventricular artery is replaced by a branch from the left coronary artery.
The arterial branches supply the anterior and lateral surfaces of the right atrium. One branch supplies the posterior surface of both right and left atria. The artery of sinoatrial node supplies the node and the right and left atria in 35% of individuals it arises from the left coronary artery.

**Left coronary artery:**

The left coronary artery, which is usually larger than the right coronary artery, supplies the major part of heart, including the greater part of the left atrium, left ventricle, and ventricular septum. It arises from left posterior aortic sinus of the ascending aorta and passes forward between the pulmonary trunk and the left auricle. It then enters the atrioventricular groove and divides into an anterior interventricular branch and a circumflex branch.

**Branches:**

- The anterior interventricular (descending) branch runs downward in the anterior interventricular groove to the apex of heart. In most individual it then passes around the apex of heart to enter the posterior interventricular groove and anastomoses with the terminal branches of the right coronary artery. In one third of individuals it ends at the apex of the
heart. The anterior interventricular branch supplies the right and left ventricles with numerous branches that also supply the anterior part of the ventricular septum. One of these ventricular branches (left diagonal artery) may arise directly from the trunk of the left coronary artery. A small left conus artery supplies the pulmonary conus.

- The circumflex artery is the same size as the anterior interventricular artery. It winds around the left margin of the heart in the atrioventricular groove. A left marginal artery is a large branch that supplies the left margin of the left ventricle down to the apex. Anterior ventricular and posterior ventricular branches supply the left ventricle. Atrial branches supply the left atrium (Snell R.S, 2000).

**PATHOLOGICAL CONSEQUENCES:**

1. **ATHEROSCLEROSIS**
2. **PREMATURE CORONARY DISEASE**
3. **MYOCARDIAL INFARCTION**
From Fatty Streaks to Strokes:

In a healthy person, blood flows freely from the heart to all parts of the body through miles of arteries. But disease sometimes damages the arteries, slowing the flow of blood or even stopping it. When that happens, the result can be extremely dangerous, resulting in a stroke or heart attack. The most important artery-damaging disease is atherosclerosis (‘athero' means fatty 'sclerosis' means scarring or hardening).

Atherosclerosis clogs the blood's pathways with an outgrowth called fibrous plaque, which narrows the arteries, developing gradually over years and even decades.

Fibrous plaque begins as changes in the structure of the artery or fatty streaks. These streaks, one of the first signs of atherosclerosis, are composed of fat-laden blood cells and other material that build up in the artery wall. As atherosclerosis progresses, the streaks gradually change, becoming larger and more complex, turning into intermediate lesions. These lesions, in turn, evolve into fibrous plaque the still larger, more complicated and more dangerous advanced form of atherosclerosis. Fibrous plaque can be a serious health problem, not only because it can narrow the arteries, but also because it can be a source of thrombosis (blood clots.) When a
fibrous plaque becomes unstable and breaks or tears, thrombi can form on the surface of the plaque. If these clots are large enough, they can block the artery that has already been narrowed by the fibrous plaque. If such a clot forms in an artery leading to the heart, the blockage that results can cause a heart attack. When a clot cuts off blood to the brain, the result is a stroke.
Microscopic image of an advanced lesion from a coronary artery

(Russell Ross, 1976)
What Causes the Disease?

Scientists have been searching for the causes of atherosclerosis for a long time. They have known for more than a century that people who eat diets high in animal fat tend to have high levels of cholesterol in their bloodstream. And it has been well established that elevated cholesterol in the bloodstream is very likely to lead to atherosclerosis and the health dangers that come with it. But only in the last two decades have scientists begun to unravel exactly how the cholesterol traveling around in the blood leads to the development of a fibrous plaque and blood clots that block the artery (Falk et al 1995).

What causes a silent atherosclerotic lesion to rupture? Activate macrophages, T cells and most cells at sites of plaque rupture produce several types of molecular inflammatory cytokines, proteases, coagulation factors, radicals, and vasoactive molecules that can destabilize lesions. They inhibit the formation of stable fibrous caps, attack collagen in the cap, and initiate thrombus formation. All these reactions can conceivably induce the activation and rupture of plaque, thrombosis and ischemia. (Hansson G.K 2005)
ROLE OF THE ENDOTHELIUM:

Cholesterol in the Blood:

Blood consists of a liquid (plasma) and several kinds of blood cells, including red cells, white cells, and platelets. Blood plasma also carries a huge variety of different substances from one part of the body to another. One key substance is cholesterol, one of the many lipids found in plasma. Scientists have discovered that when people digest fat it goes into the bloodstream, but does not just float around freely. Cholesterol is carried in the blood from place to place on special particles called lipoproteins. One kind of lipoprotein particle, low-density lipoprotein or LDL, carries cholesterol to different parts of the body, including the walls of arteries, and can lead to problems when it carries more cholesterol than cells require to function normally. Another kind, high-density lipoprotein or HDL, carries cholesterol away from the artery walls and eventually out of the body. There is a direct link between elevated levels of LDL and atherosclerosis and decreased levels of HDL, which are protective.
Two Breakthroughs:

Two major, closely related breakthroughs in research have helped scientists understand how the risk of developing atherosclerosis is linked to LDL. The first was the discovery that a part of the artery called the endothelium plays a major role. Arteries consist of three distinct layers. The innermost layer is called the intima. The endothelium, which is only a single cell thick, comprises the lining of that innermost layer and acts as an interface between blood and arterial wall.

The second breakthrough was that atherosclerosis appears to be a healing response by the body that goes haywire. When any part of the body is damaged whether by infection with bacteria, sports injury, a burn, etc. the body increases the flow of blood to the injured area and puts white blood cells to work there. White blood cells surround the bacteria or the damaged tissue. Then, together with other cells in the damaged tissue, the white blood cells neutralize and remove whatever is causing the injury and repair the damage. Researchers now believe that a similar process occurs in atherosclerosis. But the process of inflammation and healing the injury may be slow and excessive, and the result can be increased risk of stroke and heart attack.
Endothelial Activation: From LDL to Oxidized LDL to Adhesion Molecules:

Until about 10 years ago, scientists thought that the endothelium was just a kind of sieve: When people had high levels of cholesterol in their blood, LDL particles would leak into the artery wall and become trapped there. Now it appears that the endothelium does much more.

When high levels of LDL are in the blood, a small amount of the LDL that builds up in the artery wall becomes oxidized. This occurs through chemical reactions in the endothelium that change the LDL by adding extra oxygen atoms to it. This change is important because oxidized LDL is one of the triggers that can set off a chain reaction.

(Hackman, D.G and Anand SS, 2003)

It appears that the more LDL there is in the blood, the more oxidized LDL will be produced. Oxidized LDL injures the endothelium and causes the surface of the endothelium to express a special kind of molecular 'glue' called ELAMS (endothelial-leukocyte adhesion molecules). These cause certain kinds of white blood cells (monocytes and T-lymphocytes), which are floating by in the bloodstream, to adhere to the endothelium.
A Healing Process Gone Haywire:

Scientists now believe that this phase of atherosclerosis (oxidized LDL leading to adhesion molecules, which attract certain white blood cells to the endothelium) is a form of the body's normal healing process. What the endothelium does during atherosclerosis is what all injured tissue does up to a point.

As mentioned above, when any part of the body is hurt, white blood cells help neutralize bacteria or other agents that are causing injury and thus help in the process of repairing damaged tissue. It turns out that most injured tissue uses adhesion molecules to make white blood cells adhere to the spots where they are needed. The problem in atherosclerosis is that after the white blood cells (the monocytes and T lymphocytes) stick to the endothelium, what should be a healing process goes off track.

Specifically, the white cells move between and below the endothelium and start to do real damage in two major ways. In a complex chemical reaction, the white cells cause some of the muscle cells in the artery wall to grow. The white cells also incorporate the particles into the artery wall, consuming oxidized LDL particles.
The result is a fatty streak, which can progress to become a fibrous plaque. These intricate processes occur in the tissues beneath the endothelium and are enhanced by molecules secreted by the blood platelets, macrophages, and smooth muscle cells. Some of these molecules are called cytokines others are called growth factors. The effects of these and other growth-regulatory cell products are now being studied and analyzed by medical researchers worldwide.

**Future Implications:**

Medical research has, however, identified risk factors for atherosclerosis. These include:

- cholesterol levels total serum cholesterol higher than 200 mg (mg=milligrams dL=100 millimeters, 100 milliliters is about 1.6 fluid ounces) per dL, with HDL cholesterol lower than 35 mg per dL
- age men 45+, women 55+
- diabetes mellitus
- family history myocardial infarction or sudden death before age 55 in male first-degree relative or before age 65 in female first degree relative
hypertension blood pressure greater than 140/90 mm Hg, or the taking of medicine for hypertension

Smoking smokers are at higher risk.

In the future, it may be possible to devise new diagnostic tools. For example: current research may well lead to sophisticated blood tests that will detect the molecules such as adhesion molecules that are produced at each stage of the disease. Such tests could be an even more effective early warning system for atherosclerosis. Meanwhile, several therapies are being used to treat atherosclerosis. One of them is having the patient make lifestyle changes. Although scientists have not identified the direct physiological link between smoking and atherosclerosis, stopping smoking lowers the risk of the disease dramatically. For at-risk patients with moderately high levels of serum cholesterol, dietary intervention and increased exercise also have proved effective.

When lifestyle changes alone are insufficient to bring about change, the most effective drugs now available are those that lower the amount of lipids in a patient's blood. Surgical approaches include angioplasty, in which a clogged section of the artery is stretched by introducing a balloon into the artery bypass grafting, in which a
section of healthy vein or artery is used to bypass a clogged artery and endarterectomy, in which the inner part of the affected artery and the blood clot are surgically removed.

In the future, doctors may acquire more weapons against the disease, thanks to ongoing research on the endothelium's role in atherosclerosis. It may be possible to develop new drugs that will target each stage of the disease, preventing atherosclerosis from occurring, or even reversing the growth of fatty.

**CLASSIFICATION OF CHOLESTEROL LEVELS:**

**Total serum cholesterol:**

Desirable: <200 mg per dL (5.20 mmol per L)

Borderline high: 200 to 239 mg per dL (5.20 to 6.20 mmol per L)

High risk: >240 mg per dL (6.20 mmol per L)

**Low-density lipoprotein cholesterol:**

Desirable: <130 mg per dL (3.35 mmol per L)

Borderline high: 130 to 159 mg per dL (3.35 to 4.10 mmol per L)

High risk: >160 mg per dL (4.15 mmol per L)

**High-density lipoprotein cholesterol:**

High risk: <35 mg per dL (0.90 mmol per L)
Desirable: 35 to 59 mg per dL (0.90 to 1.55 mmol per L)
Low risk: >60 mg per dL (1.55 mmol per L) (NCEP Adult Treatment Panel II, 1993).

The relation between an elevated serum cholesterol level and atherosclerosis was first noted in the 1930s in independent studies by Muller and by Thannhauser and Magendantz. Both studies found an excessive prevalence of premature coronary artery disease and myocardial infarction among patients with hereditary xanthomatosis. Kannel and coworkers confirmed these observations in 1971 and reported a strong direct correlation between the total cholesterol level and the development of ischemic heart disease in more than 5000 subjects followed for 14 years in the Framingham Heart Study. As we age, cholesterol builds up in the arteries of the heart and neck, placing us at risk for heart attacks, strokes, and premature death. Treatment that lowers cholesterol in the blood has therefore become the cornerstone of prevention of future heart attack, stroke, and death, both in persons who definitely have heart disease and in those who are at risk of developing it in the future. Evidence suggests that millions of people who could benefit from cholesterol-lowering medicines are currently untreated. According to the American Heart
Association, nearly 38 million patients in the United States would benefit from the combination of diet and drug therapy, and an additional 30 million should follow diet and exercise programs to reduce cholesterol levels. (Scirica, B.M and Cannon C. P 2005)

The importance of coronary thrombosis in acute myocardial infarction was recognized by Herrick early in this century. More recently, Falk, Fuster et al (1995) and others have developed the concept of lesion "activation," a process by which a quiescent atherosclerotic plaque becomes susceptible to and subsequently undergoes rupture and thrombosis, precipitating myocardial infarction or unstable angina. In this context, one consequence of cholesterol reduction may be a decrease in the incidence of lesion activation. (Gylling H and Meittinen, TA, 2002)

Cholesterol-modifying therapy may not only decrease the formation and progression of lipid-laden plaques but also reduce the cholesterol content in cholesterol-rich lesions that have already been formed. The events involved in the reduction of the lipid content of plaques have not been precisely identified, but they appear to involve a process known as "reverse cholesterol transport," in which HDL particles transport cholesterol to the liver for disposal. (Schweitzer M et al, 2002) Although there is no direct evidence of
this process from studies in humans, the administration of HDL cholesterol in animals results in a significant decrease in the formation of atherosclerotic, lipid-laden lesions and a reduction in the size of pre-existing lesions. (D.A.I.S.I, 2001)

Thus, lipid-modification therapy has the potential to reduce the incidence of lesion activation and subsequent plaque rupture. The available evidence suggests that this effect may be a consequence of a decrease in the accumulation of cholesterol in the atheromatous plaque, a reduction in the cholesterol content of the preexisting plaque, or both. Data that provide direct support for such a contention, however, are not yet available.

People with elevated levels of LDL, which accounts for the majority of the total cholesterol measurement, are more likely to suffer heart attacks or die prematurely. For every 10-milligram (mg) increase in LDL per deciliter (dL) of blood, the risk of a heart attack increases by almost 20%. Conversely, people with higher levels of the "good" HDL cholesterol have a lower risk of cardiac events.

The National Cholesterol Education Program calls for intensive cholesterol-lowering therapy in patients with any form of clinical atherosclerotic disease, specifically, acute myocardial infarction or
angina pectoris, coronary artery angioplasty, peripheral arterial
disease, abdominal aortic aneurysm, symptomatic carotid artery
disease, or a history of coronary artery bypass graft. These patients
carry a fivefold to sevenfold elevated risk for developing new or
recurrent CHD and thus need intensive risk reduction.

According to current guidelines, the goal of therapy in patients with
clinical atherosclerotic disease, including CHD, is to decrease LDL
cholesterol to 100 mg/dL. This level is considered optimal for
patients with CHD by the NCEP Expert Panel (1994), the American
Heart Association Secondary Prevention Panel, and the American
College of Cardiology. The consensus opinion on the optimal target
goal for LDL cholesterol in patients with atherosclerotic disease is
supported on both theoretical and experimental grounds, including
clinical trials. (4S Study, 1994).

Immediate institution of non pharmaceutical therapy is warranted in
all patients with CHD and LDL cholesterol levels >100 mg/dL.

If the baseline LDL cholesterol level in patients with CHD is >130
mg/dL, cholesterol-lowering drug therapy is often needed in addition
to maximal non pharmaceutical therapy to achieve the target LDL
cholesterol level of 100 mg/dL. Withholding drug therapy in an
effort to reach target LDL level with the non pharmaceutical approach is not necessary. The major drugs used for LDL reduction are statins, bile acid sequestrants, and nicotinic acid. Large clinical trials have documented that these agents are safe in the vast majority of patients. The choice and dose of drug depends on the baseline LDL cholesterol level as well as lipoprotein patterns. If LDL cholesterol is only slightly above 130 mg/dL, low doses of drug combined with dietary change may be sufficient to reach the target LDL level. Greater LDL elevations will require more aggressive drug therapy. In patients with definite hypercholesterolemia, combined drug therapy, e.g. statin plus sequestrant, may be needed to achieve the LDL level of 100 mg/dL. If the LDL cholesterol concentration declines to 100 to 129 mg/dL on single-drug therapy, the physician must consider efficiency, cost, and side effects before prescribing a second drug to obtain an LDL level 100 mg/dL. If the baseline LDL cholesterol level in patients with CHD ranges from 100 to 129 mg/dL, maximal dietary therapy alone can be tried for 6 weeks. If LDL does not decrease to <100 mg/dL with diet alone, clinical judgment will be needed to determine whether to initiate drug therapy. Many patients with CHD and a baseline LDL cholesterol level ranging from 100 to 129 mg/dL have a low HDL
cholesterol level (<35 mg/dL). In such patients, nicotinic acid can be considered for first-line therapy because of its potential for increasing HDL. Alternatively, a statin can be used to reduce LDL cholesterol levels to well below 100 mg/dL. The aim is to produce an extra low LDL cholesterol level to offset the increased risk associated with low HDL.

**MANAGEMENT OF HYPERLIPIDAEMIAS:**

All patients should receive advice on:

i. life style
ii. diet
iii. weight control

These are important components of overall macrovascular risk prevention. Dietary treatment of hypercholesterolemia has a modest effect at best but diet and weight reduction are more effective for hypertriglyceridaemia. Total fat especially saturated fat should be reduced (and partially replaced with mono- and polyunsaturated fats).

The decision to use the lipid-lowering drugs is made on the basis of the overall absolute CHD risk e.g. evidence of existing CHD,
hypertension, diabetes mellitus, positive family history. The justification is easiest in two cases. Firstly, as primary prevention in the relatively small number of patients who are asymptomatic but have significant abnormalities of their lipid profiles, patients with FH and remnant lipaemia are at high risk. The decision to treat is made on patient’s absolute risk as well as the degree of lipid abnormality. Secondly, as secondary prevention in patients who have evidence of CHD (previous myocardial infarction, angina pectoris), cerebro-vascular or peripheral vascular disease or diabetes mellitus (Bennett MJ and Brown MJ; 2003)

Management may proceed as follows:

1. Any medical disorder that may be causing hyperlipidemia, e.g. diabetes, hypothyroidism, should be treated first.

2. Dietary adjustment.

Those who are overweight should reduce their total caloric intake, ideally until they have returned to weight that is appropriate for their height (i.e. body mass index) but realistically with an initial aim of reducing body weight by 10%. Those who fail to achieve adequate weight reduction or who are already at their ideal weight should reduce their total fat intake poly- and monounsaturated fats or oils may be taken partially to substitute for the reduction in animal fats.
Reduction in dietary cholesterol is much less important element of the diet, but excess egg yolks should be avoided. Benecol or flora proactive should be added.

Specific types of hyperlipidaemia are treated:

- Familial hypertriglyceridaemia responds best to dietary modification and weight reduction with a fibrate nicotinic acid may be added.
- Familial combined hyperlipidemia should be treated with dietary modification and weight reduction together with a statin nicotinic acid and/or fibrate may be added in resistant cases.
- Remnant removal disease (remnant lipaemia) responds to dietary modification and weight reduction and a fibrate nicotinic acid and/or a statin may be added where there is failure to respond.
- Familial or polygenic hypercholesterolemia is treated by dietary modification and a statin an anion-exchange resin and/or a fibrate and/or nicotinic acid may be added.
- Familial hypoalphalipoproteinaemia may respond to exercise, weight loss and nicotinic acid a fibrate and/or a statin may be
added for a small HDL-raising effect but primarily to lower triglycerides and LDL.

**HISTORY OF STATINS:**

Statins were isolated from a mold, penicillium citrinium, and identified as inhibitors of cholesterol biosynthesis in 1976 by Endo and colleagues (Endo et al., 1976). Subsequently Brown et al. (1978) established that stains act by inhibiting HMG-CoA reductase. The first stain studied in human beings was compactin, renamed mevastains, which demonstrated the therapeutic potential of this class of drugs (Yasamoto et al., 1984). However, Alberts and colleagues at Merck developed the first stain (lovastain, formally known as mevinolin) that was approved for use in human beings, which was isolated from Aspergillus terreus (Alberts et al, 1980, Bilheimer et al 1983). Since the approval of lovastatin by the United States Food and Drug Administration (FDA) in 1987, five other statins have been approved. Two of these, pravastatin and simvastatin, are chemically modified derivatives of lovastatin.
such as fibrates and nicotinic acid. Simvastatin is combined with other antihyperlipidemic
drugs (occur more rarely, but is more frequent in
reduction of liver function tests in some 1% of patients
commonly adverse effects being transient and usually
metabolized in the liver. They are well absorbed orally, and
such drugs are well absorbed after administration orally, and

Effect one month after commencing therapy.

Cholesterol and LDL cholesterol fall to nearly a maximum
increase clearance of LDL from the circulation, plasma
synthesis of LDL receptors (up regulation) in the liver
reductase (HMG-CoA) reductase. This results in increased
endogenous cholesterol synthesis, hypercholesterolemia.

I. Statins: These agents block the rate limiting enzyme

HYPERLIPIDEMIA

DRUGS USED IN THE TREATMENT OF
2. **Fibric acid derivatives (Fibrates):** This class includes gemfibrozil, benzasfibrate, ciprofibrate and fenofibrate, the original fbrate, clofibrate is obsolete. The drugs partly resemble short chain fatty acids and increase the oxidation of these acids in both liver and in muscle. In the liver, secretion of triglyceride-rich lipoproteins falls and in muscle the activity of lipoprotein lipase and fatty acid uptake from plasma are both increased. Fibrates act through a nuclear transcription factor (PPAR α) which up regulates expression of LDL-Cholesterol and apolipoprotein C 11 gene. Fibric acid derivatives are well absorbed from the gastrointestinal tract, extremely bound to plasma proteins and excreted mainly by the kidney as unchanged drug or metabolites.

3. **Nicotinic acid and derivatives:** Nicotinic acid acts as an antilipolytic agent in adipose tissue, reducing the supply of free fatty acids and hence the availability of substrate for hepatic triglyceride synthesis and the secretion of VLDL. Nicotinic acid lowers plasma triglyceride and cholesterol concentrations, and raises HDL-cholesterol. Flushing of the skin (preventable by low dose of aspirin) and gastrointestinal upset commonly occur the unpleasantness may be diminished
by gradually building up the oral dose over 6 weeks and in
time tolerance develops. Rarely there is major disturbance of
liver function. Acipimox is better tolerated than nicotinic acid,
has longer duration of action but is less effective.

4. Anion Exchange Resins (Bile Acid Sequestrants):
Colestyramine is an oral anion-exchange resin, which binds
bile acids in the intestine. Bile acids formed from cholesterol
in the liver pass into the gut in the bile and are largely
reabsorbed at the terminal ileum. The total bile acid pool is
only 3-5g but, because such enterohepatic recycling takes
place 5-10 times a day, on average 20-30 g of bile acid are
delivered into the intestine every 24 hours. Bile acids bound
to colestyramine are lost in the faeces and the depletion of the
bile acid pool stimulates conversion of cholesterol to bile
acid: the result is a fall in intracellular cholesterol in
hepatocytes, and an increase (upregulation) in both LDL-
receptors and cholesterol synthesis. The former has the
predominant influence on plasma LDL-cholesterol, which
falls by 20-25%. About half the patients who take
colestyramine experience constipation and some complain of
anorexia, abdominal fullness and occasionally of diarrhea
these effects are dose related but may limit or prevent its use. Because the drug binds anions, drugs such as warfarin, digoxin, thiazide diuretics, phenobarbitone, and thyroid hormones should be taken 1 h before or 4 h after colestyramine to avoid impairment of their absorption. (Bennet PN and Brown MJ 2003).

**Hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins):**

Statins are the drugs of first choice for patients with high or less than optimal LDL-C levels. They inhibit the rate-limiting step of cholesterol synthesis, create a transient decrease in intracellular cholesterol, increase the synthesis of the cell surface LDL receptor, and accelerate removal of LDL-C and triglyceride-rich lipoprotein. The latter accounts for the associated modest reduction in triglyceride levels that is observed with the use of these drugs, although more potent statins also inhibit VLDL synthesis. A mild increase in HDL-C also occurs. Statins are the most potent, most effective, and best tolerated drugs for reducing LDL-C. In fact, availability of this class of drugs made it possible to achieve LDL-C
reductions that reduced CV and all cause mortality and provide confirmation for the lipid hypothesis.

Five statins are currently approved by the FDA for cholesterol lowering. Only three, (lovastatin, pravastatin, and simvastatin) are also approved for prevention of clinical CV events. Although it is likely that all drugs of this class will prevent coronary events, only these three have at this date been shown to do so in RCTs.

The cardioprotective property of these drugs is primarily due to reduction of LDL-C. It is also clear that these drugs have other effects, referred to as pleiotropic properties that may also be important (Gotto Jr and Farmer, 2001). These pleiotropic properties importantly influence the biology of atherosclerosis by modulating immunoregulation, inflammation, coagulation, and vasomotor responsiveness and appear to do so independently of changes in LDL-C. Whether all drugs of this class have similar or identical pleiotropic properties has not been systematically investigated. A recent study of 40 mg/d pravastatin vs. placebo in high CHD risk patients raises serious questions about the cardioprotective pleiotropic properties because LDL-C reduction was modest and there was no decrease in CHD events (Pasternak, 2002). Several recent studies have demonstrated cardioprotective benefits of statins
in persons with low or near optimum LDL-C, suggesting that statins may be antiatherogenic agents. The decision to use a statin is still based on the need for LDL-C reduction and not on putative pleiotropic properties.

Despite their efficacy in large primary and secondary prevention trials, statins have been associated with a maximum CHD risk reduction of 35% (Brown et al, 1993). It is quite likely that the residual risk for CHD events is partly related to suboptimal lipid modification untreated or inadequately treated traditional CHD risk factors such as diabetes, hypertension, cigarette smoking, and dyslipidemia and or to emerging risk factors such as Lp (a), small LDL particles, homocysteine, and insulin resistance whose role has not been clearly defined.

The statins vary in potency, physicochemical characteristics, and routes of metabolism. They are among the safest drugs developed, and most patients tolerate them without serious adverse effects. A few patients may develop serious complications. In many large clinical studies, the risk of hepatic toxicity or myopathy is no greater than that observed in patients receiving placebo. The American Heart Association, American College of Cardiology, and the NCEP have recently reviewed these issues and concluded that statins are
safe for the vast majority of patients who take those (Pasternak et al, 2002). Why a few patients develop serious complications is unclear. However, concomitant use of drugs that are metabolized by the same drug pathway is clearly one important cause for toxicity. In addition, the presence of other serious complex medical conditions, the use of excessive doses of statins in patients on numerous other medications, or the aggressive use of statins in patients with renal or hepatic disease may explain some of the toxicity (Knopp RH, 1999). Also, there are probably pharmacogenetic reasons for susceptibility to drug toxicity. It is also clear, that patients included in clinical trials are fundamentally healthier, and the low toxicity in trials may not accurately reflect the risks of many of the patients that are seen in everyday practice. The issue of myopathy is complicated by the fact that patients treated with statins can have increases in creatine kinase (CK) without myalgia, have myalgia with no increase in CK, or have myalgia with an increase in CK. Recently, a small group of patients with muscle symptoms and normal CK were demonstrated to have histological evidence of myopathy (Phillips PS et al, 2002). Many of us have encountered patients with myopathic symptoms and normal CK whose symptoms disappeared when the drug was stopped and reappeared when it was restarted. In addition, some patients have
symptoms when they are switched to other statins, whereas others experience symptom relief. The significance of all of this is unclear. Selection of a statin should be based on the extent of LDL-C reduction that is desired, cost, and whether the selected statin has been shown to reduce clinical CHD events. The concept that lower is better (Grundy, 2002), although likely, has not been proven, yet it has been endorsed by most physicians because atorvastatin accounts for at least 60% of the statin market (Simons, 2003). Although it is probable that atorvastatin will be cardioprotective, no large RCT has yet been published demonstrating its efficacy in reducing CHD events. It is also curious that most physicians choose atorvastatin because of its potency but never titrate the dose to take advantage of this property, and many also erroneously believe that atorvastatin is a good first drug for patients with hypertriglyceridemia. All statins are capable of reducing triglyceride, but triglyceride reduction parallels LDL-C reduction (Stein et al, 1998). The greater the reduction in LDL-C, the greater the reduction in triglyceride. Patients with hypertriglyceridemia often have modest hypercholesterolemia, which can be due to cholesterol in VLDL or LDL. LDL-C cannot be calculated when the triglyceride is more than 400 mg/dl. For patients with increased LDL-C and triglycerides
of 200–400 mg/dl, atorvastatin or simvastatin are the drugs of choice. Maximum triglyceride reduction in this setting is approximately 30% with atorvastatin and approximately 20% with simvastatin. Modest increases in HDL-C occur with statins, but the effect is attenuated or abolished when large doses of atorvastatin are used (Wierzbicki and Mikhailidis DP 2002, Asztalos et al, 2002).

Statins, except atorvastatin, are usually dosed at night because of higher nocturnal cholesterol synthesis. Studies suggest slightly greater efficacy. Statin tablets can be cut when attempting to curtail expense, but only one tablet at a time should be cut so that the unused half can be taken the next day. This is particularly important in the elderly where drug costs are a vexing problem, but this may be less of an issue for products where there is level pricing. Statins have also been used on alternate days with a small reduction in efficacy. Alternate day dosing is not desirable because it is difficult for many patients to remember to take their medication.

The efficacy of a selected dose of statin can be observed within 3–4 weeks so that titration of the dose can be accomplished rapidly. It is also true that the effect is rapidly lost when the statin is stopped (Dujovne et al, 2002). The expected LDL-C reduction with any given statin dose represents an average of patients taking that dose.
Because some patients are sensitive and others are resistant, it is impossible to know how an individual patient will respond. For reasons that are not well understood, some patients will be resistant and experience a reduction of less than 10%. The efficacy or lack of efficacy may in part be related to the efficiency of intestinal cholesterol absorption. Those whose hypercholesterolemia is primarily exogenous due to efficient cholesterol absorption will be less responsive, whereas those with endogenous hypercholesterolemia will be sensitive (Gylling and Miettinen, 2002). This lack of responsiveness appears to extend to all statins and cannot be circumvented by use of a different statin. A gradual loss of efficacy (tachyphylaxis) has also been described for some patients (Cromwell and Ziajka, 2002). A short drug holiday and then reinitiation of therapy has been associated with restoration of the expected response.

Hypercholesterolemia (increased LDL-C):

Statins are the drugs of choice for this disorder. Although each individual will have a unique response, drug selection should be based on the magnitude of the reduction desired to reach specific goals. Doses should be titrated at 3- to 4-wk intervals, recognizing that doubling the dose further reduces LDL-C by only 6%. At some
point, it becomes more cost-effective and perhaps safer to add a second drug then to increase the statin dose. Statins should be started immediately in all patients with symptomatic CHD (ACS, angina) and simultaneously with lifestyle modification in patients with established CHD (Sacks 2001, Wright et al 2002). In fact, studies suggest benefit in patients with or at high risk of CHD even when LDL-C is less than 100 mg/dl. This suggests that statins have antiatherosclerotic properties and should be used in patients with atherosclerosis regardless of LDL-C levels. Modest further reductions in LDL-C on the order of 10% can be achieved by adding plant stanol/sterol margarine, 15% by adding bile acid sequestrants, and approximately 20% by adding ezetimibe. Lower is probably better, but efficacy and safety have not yet been prospectively proven in RCT designed to address this question. There is no proven adverse effect(s) of LDL-C below 70 mg/dl, and newborns are healthy with LDL-C levels of 30–50 mg/dl. Because further lowering of LDL-C may be of diminishing returns, treatment of coexistent lipid disturbances, such as increasing the HDL-C concentration (Sacks, 2002) or aggressively modifying other risk factors, may be more effective (Yusuf, 2002).
Achievement of optimum LDL-C targets takes precedent in this group of patients with multiple lipid/lipoprotein disturbances. Consequently, therapy should be initiated with a statin. Potent statins, such as atorvastatin, simvastatin, and rosuvastatin (when approved by the FDA) make the most sense because substantial triglyceride reduction can also be expected, but probably not exceeding 35% with current products. When pretreatment triglyceride is below 400 mg/dl, it is possible to calculate the LDL-C concentration. When the triglyceride is above 400 mg/dl, the LDL-C cannot be calculated. Although LDL-C can be directly measured in such patients, this is seldom done. Therapy can be initiated with a fibrate or niacin, although their effects on the lipoprotein profile differ. Gemfibrozil is better than niacin for reducing the triglyceride level but less effective than niacin for increasing HDL-C, niacin also reduces LDL-C, whereas gemfibrozil does not (Sprecher, 2000). When the triglyceride decreases to less than 400 mg/dl, calculation of the LDL-C permits a decision regarding subsequent statin therapy. After achievement of the LDL-C target, the non-HDL-C should determine further additional therapeutic decisions. Statin-fibrate and statin-niacin combinations are more effective than statins alone in correcting lipid abnormalities in combined hyperlipidemia
(Athyros et al 2002, Athyros et al 1997). The use of statins in combination with fibrates or niacin increases the risk of adverse events; consequently, the benefits of such therapy should clearly outweigh the risks. Because you cannot prevent what is not happening, the use of these combinations in persons with low short-term risk is not warranted. Adverse events from drug combinations occur equally across all risk strata, whereas benefits occur only in those most likely to have events.

**Hypertriglyceridemia:**

Patients in this group are heterogeneous with regard to underlying mechanisms and the accumulation of triglyceride-rich lipoproteins that account for the hypertriglyceridemia. A variety of drugs and estrogen-containing preparations can cause or accentuate other genetic and acquired factors that may exist in these patients. Assuming that secondary causes can be identified and eliminated and that patients with increased chylomicrons can be identified, patients in this category have either familial hypertriglyceridemia or combined hyperlipidemia, where the increase in LDL-C has not yet been expressed. Patients with combined hyperlipidemia classically have multiple lipid phenotypes within their family and within
themselves from time to time depending on other metabolic and dietary factors (McNeely et al, 2001). Both groups have reduced levels of HDL-C and small LDL particles, but may be differentiated by increased apolipoprotein B and decreased apolipoprotein A-I levels in combined hyperlipidemia. Because triglyceride levels are often above 400 mg/dl, it may not be possible to immediately differentiate these disorders unless family data showing multiple lipid phenotypes are available. The concept that patients with familial hypertriglyceridemia are not at increased CHD risk no longer appears to be reliable (Austin et al, 2000).

Therapy in persons with hypertriglyceridemia should include extensive lifestyle changes, elimination of secondary factors, and the initiation of therapy with a fibrate. Insulin sensitivity is improved by weight loss and physical activity. In our experience, this seldom reduces triglyceride to optimum levels unless the initial level was only modestly increased and adjunctive measures may be required or desired. Obviously, the imperative to be more aggressive should be based on projected CHD risk, a persisting undesirable non-HDL-C level or other evidence, such as LDL size, that justifies intensified therapy. Omega-3 fatty acids can be used to reduce triglyceride levels, but their efficacy is dose related, and large doses create
problems related to dosing and adverse effects that most patients will not tolerate, at least not for long, and convenience.

**Isolated low HDL-C:**

Many patients with or at risk of CHD have low HDL-C as an identifiable CHD risk factor (Sacks FM, 2002). Some patients with low HDL-C have hypertriglyceridemia and therefore are not isolated, whereas others do not. The relationship between CHD risk and HDL-C is the mirror image of that which exists with LDL-C. Consequently, increasing the HDL-C a small amount may be far more effective in reducing CHD than decreasing the LDL-C by a comparable amount when LDL-C is near or at goal. The only drug currently available that substantially increases HDL-C in patients without hypertriglyceridemia is niacin (Knopp, 2000). The antiatherosclerotic properties of HDL-C are commonly attributed to reverse cholesterol transport, but it is very clear that HDL has other important cardioprotective properties (Assmann and Nofer, 2003). There must be a better understanding of these other properties of HDL to determine when or whether low HDL-C is a CHD risk factor and whether all drugs that increase HDL-C will be cardioprotective. Niacin is known to be cardioprotective (Guyton, 1998) and to
increase HDL-C and apolipoprotein A-I by selectively enhancing hepatic removal of the cholesterol ester from HDL by hepatic sterol receptor-B1 while not removing the HDL particle from the circulation (Tavintharan and Kashyap, 2001). The ATP III does not provide specific goals for low HDL-C, but every milligram per deciliter helps. It is not unreasonable to attempt to increase HDL-C to more than 45 mg/dl (Sacks, 2002), although this may be beyond reach for many patients with current medications.

Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are a breakthrough in the treatment of high serum cholesterol. Several recent clinical trials (4s study 1994) demonstrate that statins can substantially reduce both morbidity and mortality from CHD. They are becoming a mainstay in management of patients with established CHD (secondary prevention), and they hold promise for high-risk patients without evident CHD (primary prevention). Recent statin trials provide a wealth of data documenting the benefit of cholesterol-lowering therapy in both primary and secondary prevention. A major fact has been established: cholesterol lowering with statins is both safe and effective in high-risk patients. Recent statin trials amply underpin the NCEP's promotion of efforts for decreasing coronary morbidity or mortality.
The 4S, a secondary prevention trial, used simvastatin to treat hypercholesterolemic patients. Simvastatin therapy, on average, reduced LDL cholesterol levels by 35%, from a mean of 188 to 122 mg/dL; this change decreased major coronary events by 34%. Although the goal of therapy in 4S was to lower total cholesterol to at least <200 mg/dL (LDL cholesterol <130 mg/dL), many patients experienced even greater reductions in serum cholesterol levels.

A different result is reported from subgroup analysis of the CARE trial. CARE was a secondary prevention trial using pravastatin to treat coronary patients with relatively normal cholesterol levels. In the full CARE trial, the mean LDL cholesterol at baseline was 139 mg/dL. Pravastatin therapy lowered LDL cholesterol to an average level of 98 mg/dL, with this response; major coronary events were decreased by 24%. The positive clinical outcome of CARE and the average level of LDL reached on therapy might be taken to mean that the overall results support current NCEP goals for secondary prevention, i.e., an LDL cholesterol level of ≤100 mg/dL.

The third trial, WOSCOPS, was a primary prevention trial in high-risk patients. According to NCEP guidelines, the LDL cholesterol goal in high-risk primary prevention is a serum concentration of <130 mg/dL. WOSCOPS patients generally had
hypercholesterolemia, and on the basis of risk factor status, most enrollees fell into the high-risk category. Baseline LDL cholesterol levels for all patients averaged 197 mg/dL, and on pravastatin therapy, an average concentration of 142 mg/dL was achieved. This LDL reduction was accompanied by a 31% decrease in major coronary events.

On the basis of these analyses, a few solid conclusions can be drawn, and other tentative conclusions are suggested. First, statin therapy is highly effective for reducing CHD risk in secondary prevention. Clear evidence of benefit is seen when baseline LDL cholesterol levels are >130 mg/dL at baseline. Therefore, most CHD patients whose LDL cholesterol concentrations exceed 130 mg/dL should receive cholesterol-lowering drugs (Carlson et al, 1995). A delay in drug treatment for a trial of dietary therapy in such patients is not necessary or warranted. Unfortunately, a great many CHD patients are not receiving the life-saving benefits of statin therapy, and extension of this therapy to untreated patients is urgently needed.

Saturated Vs Unsaturated fat: Fat has a lot of bad press and for many people; just a mention of the word can evoke misery. You can try to loose it, try to hide it, try to avoid it, but your body still needs it! Did you know that fat helps to insulate our nerve cells, keeps us warm,
balances our hormones, keeps skin and arteries supple, lubricates joints and is a component in every cell?

The key issue here is recognizing which type fat your body needs, how much your body requires and which type is your enemy. Armed with right information, you can focus on getting more of the good fats and less of the bad fats into your daily diet.

There are two types of fat to be aware of. Saturated fats – lets call them “the enemy” and unsaturated fats–“the good guys”! It is easy to tell the difference because saturated fats are hard at room temperature. Saturated fats are not essential to your health. They come from animals and are found in meat, eggs, and cheese. They are harder to digest and full of cholesterol.

Unsaturated fats are liquid at room temperature and have been divided into two groups. Monounsaturated fats such as olive oil, and polyunsaturated fats such as sunflower oil. Polyunsaturated fats are split into Omega 3 fatty acids and Omega 6 fatty acids. Monounsaturated fat (Omega 9) although not essential, is not harmful in moderation – a good quality (extra virgin first cold pressed) olive oil is a healthier alternative to the usual vegetable oil.
Good sources of Omega 6 are safflower oil, sunflower oil, evening primose oil, walnut oil, pumpkin oil, and sesame oil. (Beardmore 2006)

Good sources of Omega 3 are mackerel, herring, salmon, pilchards, sardines, tuna and flax seed oil.

Here are some important facts about fat in our diet.

1. Fat is the ‘energy reserve’ of animals, plants, and humans

2. The ideal body-fat ratio should be approximately 19%-26% of a woman’s body weight, and 12-18% of a man’s body weight

3. There are two different types of fat- brown and yellow. Brown fat is situated inside the body and is ‘active’ containing mitochondria that produce heat (thermogenesis) and as a result burn energy. Yellow fat is found nearer the surface, is less active and more likely to accumulate. Women tend to have higher ratio of yellow fat than men.

4. Women need higher levels of fat because it is essential for reproduction and so the body stores it ‘Just in case’.

5. An average healthy intake of good fats in the diet should be approximately 30-40 grams a day. The fat content of diets in affluent populations can be nearly four times this amount!
6. Most foods containing fat combine saturated, monounsaturated, and polyunsaturated fat in varying quantities. For instance, butters fat content is almost 100%, of which 60% is saturated, 30% monounsaturated and 10% polyunsaturated, compared with sunflower seeds fat content of 73%, of which just 12% is saturated and 21% monounsaturated and 67% is polyunsaturated.

7. Heat, light, and oxygen destroy essential fatty acids, which is why it is best to keep oils in dark containers.

8. Essential fats must come from diet because your body cannot produce them. The essential healthy fats are omega 3 and omega 6 (known as essential fatty acids)

9. Weight for weight, fat provides more than twice the amount of usable energy than carbohydrates or protein (you will find 9 calories in every gram of fat).

10. Fat contributes to the palatability, texture and the smell of many foods; it also slows down the process of digestion providing an extended period of satiation after meal (Beardmore Kim. 2006).
Drug treatment to lower plasma lipoproteins and/or cholesterol is primarily aimed at reducing the risk of atherosclerosis and subsequent coronary artery disease that exists in patients with elevated circulating lipids. Drug therapy usually is considered as an option only if non-pharmacologic interventions (altered diet and exercise) have failed to lower plasma lipids (Scott, M et al 1997). As with all things truly evil, the very essence of plaque vulnerability the modern plague that claims the lives of millions- continues to elude us. However, on the basis of many reported sightings, the composite sketch of the serial killer is slowly coming up in to focus (Zorina S. Ghalis 2004)

**RANDOMIZATION:**

Drug therapy affords an expanding opportunity for prevention and treating disease and for alleviating symptoms. Pharmacologic agents also expose patients to risk. Basic principles of drug therapy provide a conceptual frame work for developing drugs with maximal efficacy, which maximizing the risk of adverse effects. Optimal therapeutic discussions are based on an evaluation of the individual patient in concert with assessment of the evidence for efficacy and safety of the treatment under consideration.
Initial determination of the effectiveness and safety of days is based predominantly on evaluation of experimental interventions in clinical trials. Well designed and effectively executed clinical trials provide the scientific evidence that informs most therapeutic discussions. Evidence from clinical trials may be supplemented by observational studies, particularly in assessing adverse effects that elude detection in clinical trials designed to determine efficacy and that don't occur frequently or rapidly enough.

**Clinical trials and Randomization:**

Similarity of the control group with the group receiving the intervention in the key to obtaining valid information in all experimental Science. In clinical trials this similarly is best advised by random assignment of patients or volunteers to the control group or the group receiving the experimental therapy. Such randomization in the optimal method for distributing between the treatment and control group the known and unknown variables that could affect outcomes. Recognizing that a randomized clinical trials it nonetheless may be impossible to use this design to study all disorders, for patients who cannot by regulation, ethics or both be studied with thus design (e.g. children) fetuses or some patients with
psychiatric) disease or for disorders with a typically fetal outcome (e.g. rabies), it may be historical controls (Oates J.A 2006). A second important element of study design is concealment of outcome of randomization from the study participants and investigators. Concealing whether participants are designated to the control group or the treatment group is referred to as blinding or masking the study. In therapeutic investigators, participants in the control group will receive an inactive replica of the drug e.g., a tablet or capsule containing inert agent. This inert replica of the drug is designated as a placebo. When only the study participants are blinded to treatment assignment but investigators know whether the active agent is being given thus is designated as a single blind study. In a double blind study, neither the study participants nor the investigators bias in interpreting the outcomes and in decisions regarding management of the patient but also eliminates selectively in the enthusiasm for therapy typically conveyed by clinicians. By eliminating participant and observe bias, the randomized, trial blind, placebo-controlled trial provides the highest likelihood or revealing the truth about the effects of a drug (Temple 1997). The double blind placebo controlled design permits evaluation of subjective and points such as pain that is powerfully influenced by
the administration of placebo. Striking instances in which placebo effects are observed include pain in labor when a placebo produces approximately 40% of relief provided by the opioid analgesic meperidine with a remarkable similar time course, and angina pectoris where as much as a 60% improvement in symptoms is achieved with placebo.

**Observational Studies:**

Important but infrequently adverse effects may escape detection in the randomized, controlled trials that demonstrate efficacy in controlled trials that form the basis for approved of drugs for marketing, the numbers of patient’s years of exposure to a drug is small relation to exposure after it is marketing. Also same adverse effects may have a long latency or may affect patients excluded from the controlled trials. Therefore, non experimental or observational studies are used to examine those adverse effects that only become apparent wit widespread, prolonged use of the drug in the practice of medicine. For example such observational studies serious adverse effects of aspirin.
The quality of inflammation derived from observational studies varies would the design and depends highly on the selection of controls and the accuracy of the inflammation on medication use (Ray, 2004; Sackett, 1991).
PURPOSE OF STUDY
In view of rise in cardiovascular diseases due to variety of reasons including the diet and lifestyle changes, it seems to be leading cause of death and disability not only in developed nations but in the developing world as well. It was therefore considered necessary to find out various causes to workout for the strategies that could combat the rise in cardiovascular diseases. In present study in addition to causes and remedies, it was considered essential to have a strategy to reduce the LDL. As low density lipoproteins has accepted as an emerging cause of cardiovascular risk factor by the National cholesterol Education Program Adult treatment Panel III.

The purpose of this study was to help alleviate the rising cost of imported drugs. In view of the rising cost of drugs, one strategy of the National Drug Policy is to promote the usage of locally made generic products. Simvastatin is the drug of which the local production and utilization are strongly encouraged, provided it can give equal safety and efficacy to that of the original product.

In the present study here we report the outcome of the first randomized study conducted in Pakistan on the LDL- cholesterol lowering effect of locally manufactured generic Simvastatin products in comparison with the innovators product Zocor.
To cope with the problems of increasing demand for medicines and help reduce the cost of imported finished pharmaceutical products, a number of developing countries including Pakistan have setup various strategies, one of which is to promote the local manufacture and usage of quality generic drugs.

The purpose of this study was to find out the comparative efficacy and safety of two generic brands of simvastatin i.e. Atcol and Limitrol with that of the original brand of simvastatin i.e. Zocor.
MATERIALS AND METHODS
This study was conducted at the department of cardiology Dow University of Health Sciences, Karachi. 264 patients were included in this study. The patients were selected from out-patient department (OPD) of Cardiology Dow University of Health Sciences.

**STUDY DESIGN AND PROTOCOL:**

The population under study is representative of Pakistani population with hypercholesterolemia (blood LDL cholesterol >160 mg/dL). All the tabs in this study had the same Pharmaceutical properties i.e. equal of active ingredient, similar in vitro release and dissolution profiles.

**Screening visit:**

After giving a written informed consent, each volunteer received physical examination and laboratory screening test (complete blood count, fasting blood sugar, glucose, BUN, creatinine, electrolyte, liver function test, CPK, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride).

**SELECTION CRITERIA:**

All the patients enrolled in this study were selected according to the following criteria:
INCLUSION CRITERIA:

The inclusion criteria of the subjects were:

- Age between 28-68 years old.
- Fasting plasma LDL-cholesterol > 160 mg/dL.
- No previous history of using any antilipedemic drugs
- No pregnancy (urine pregnancy test) must be negative.
- Voluntary participation by signing a consent form.

EXCLUSION CRITERIA:

The exclusion criteria were:

- History of allergy to HMG-COA reductase inhibitors
- Pregnancy or lactation
- Perimenopause or menopause
- Having illnesses such as diabetes mellitus, liver diseases, thyroid diseases, ischemic heart disease or epilepsy.
- Past and present use of cyclosporine, digoxin, erythromycin, gemfibrozil, niacin, vitamin B3, warfarin, immunosuppressive
agents or other drugs having reported interaction with simvastatin.

- Heavy drinking habit of tea or coffee (>1000ml/day)
- Heavy smoking (>20 cigarettes/day)
- Serum aminotransferase more than three times normal
- Serum CPK more than three times normal
STUDY VISITS:

After the subjects who had passed the screening laboratory tests and met inclusion criteria were included in the study. They were randomly allocated in to three groups for participation in a randomized study.

The first group received drug A for 12 weeks. The second group took drug B for 12 weeks. The third group was administered drug C for 12 weeks.

During the 12 weeks of drug intake the individual subjects were followed up at 2 week interval. At each visit they were interviewed and physically examined for any possible side effects. The subjects were excluded from the study in case of development of serious side effects and in case of poor compliance (taking 20% less tab. than normal or refusal to continue drug intake). The primary outcome to be focused in this study was blood LDL-cholesterol.

Group A: Eighty eight hyperlipedemic patients with above criteria were administered original brand of simvastatin (Zocor) 20 mg along with diet control and exercise. Patient were put on low fat i.e step I diet which consisted of fat 30% of total calories, carbohydrates 55 % of total calories and cholesterol less than 300 mg /day. All patients were also advised exercise of 30-40 minutes daily (Brisk Walk) This regimen was followed-up for 12 weeks.
**Group B:** Eighty eight hyperlipidaemic patients with same criteria were administered simvastatin (Atcol) 20 mg. along with diet control and exercise. This regimen was followed for 12 weeks.

**Group C:** Eighty eight hyperlipidemic patients observing same criteria were administered simvastatin (Limitrol) 20 mg along with diet control and exercise. This regimen was followed for 12 weeks.

At each fortnightly visit all patients were fully enquired about drug compliance and side effects of the drugs. Patients were also motivated to keep their nutritional habits, physical activity, and general life style as constant as possible throughout the study period. The patients were forbidden to take any other medication during the study period.

**Collection and Storage of Samples:**

Blood samples were drawn from each patient on the morning of day 0; day-45; and day-90 after an overnight fast of 12-14 hours. Ten ml. of blood was drawn by vein puncture with the help of a plastic disposable syringe in sitting position within one minute after application of tourniquet, considering all aseptic measures. For lipid profile the blood in disposable syringe was transferred in cleaned, previously acid rinsed, washed, oven dried test tubes, then kept at
37°C in water bath and allowed to clot. The serum was separated after centrifuging. Any sample showing haemolysis was discarded (Dreon et al, 1999).

**Materials:**

1. Zocor (simvastatin) 20 mg. tabs.
2. Atcol (simvastatin) 20 mg. tabs.
3. Limitrol (simvastatin) 20 mg. tabs.
4. kits
5. Analyzers
6. Other requirements
   a) sphygmomanometer
   b) disposable syringes
   c) weighing machine

The first group was administered original product tabs. Zocor 20 mg / tablet.

Batch no.H 151 A, Merek Sharp & Dohme.

Mfg: date 02-2005

Exp: date 02-2007

The second group was given a locally manufactured generic product Atcol 20 mg / tablet.
Mfg date 04-2004
Exp. Date 04-2007
Batch no. 04D.023
Ateco laboratories (pvt) Ltd.

Where as the third group was a locally manufactured generic product, Limitrol 20 mg / tablet.

Mfg. feb.2004
Exp.feb. 2006
B.no. 4 B 106.
Pharmevo (pvt) Ltd.

**DETERMINATION OF SERUM TOTAL CHOLESTEROL:**

Serum cholesterol was estimated by the enzymatic calorimetric method using.

Total lipids cat log no. KC 144 lot no. 52800 Italy.

HDL fraction cat log no. KC 133 lot no. A10854 Italy.

SGM Italia kit cholesterol LR- 30081 Rev.o of 2002-12.
**Principle:**

Cholesterol content of the serum forms a colored complex by means of coupled reactions described below, which was measured by spectro-photometer (Siddiqui, 2001).

\[
\text{Cholesterol ester} + \text{H}_2\text{O} \xrightarrow{\text{cholesterol Esterase}} \text{cholesterol} + \text{fatty acids}
\]

\[
\text{Cholesterol ester} + \text{O}_2 \xrightarrow{\text{cholesterol esterase}} 4 \text{cholesteren-3-one} + \text{H}_2\text{O}_2
\]

\[
2 \text{H}_2\text{O}_2 + \text{phenol} + \text{Peroxidase} \rightarrow \text{Redquinone} + 4 \text{H}_2\text{O}.
\]

**DETERMINATION OF SERUM TRIGLYCERIDES:**

Triglycerides were estimated by the enzymatic calorimetric method.

**Principle:**

The triglycerides are enzymatically hydrolyzed to glycerol and free fatty acids. The glycerol liberated reacts with glycerol kinase and glycerol 3-phosphate oxidase yielding \(\text{H}_2\text{O}_2\).
DETERMINATION OF SERUM HDL-CHOLESTEROL:

Principle:

Chylomicrons, low density lipoprotein (LDL) and very low density lipoprotein (VLDL) are specifically precipitated with phosphotungstic acid and magnesium ions and can then be removed by centrifugation, while high density lipoprotein (HDL) remain in the supernatant. Cholesterol included in this phase is measured by an enzymatic method (Qizilbash et al, 1991).

CALCULATION OF LDL-CHOLESTEROL:

LDL- cholesterol was calculated according to Friedwald formula described by Delong et al (1986) and Beaumont et al (1970).

\[ \text{LDL} = \text{TC} - (\frac{\text{TG}}{5} + \text{HDL} - \text{C}) \]

Where:

\( \text{TC} \) = Total cholesterol
\( \text{TG} \) = Plasma triglyceride
\( \text{HDL-C} \) = HDL cholesterol
STATISTICAL ANALYSIS:

The Scale measurement of Cholesterol, Triglycerides LDL-C and HDL were described by their mean ±SD values. For each variable, the comparison among independent groups for their mean values at three stages (day 0, day 45, and day 90) was done by ANOVA and tested by ratio. Results are taken as significant for P<0.05, else it was non-significant. The changes within group during follow up duration from baseline to day 90 were compared by paired t-test and their percentage changes from day 0 to day 90 for all the parameters are also computed using mean values.

The various statistical formulae applied to the data are as follows:

**Mean:**

The mean was calculated by adding up the observed values and dividing by the total number of observations. This is expressed by following formula.

\[
\bar{x} = \frac{\Sigma x}{n}
\]
Where,
\[ x = \text{Mean} \]
\[ x = \text{Individual Observation} \]
\[ n = \text{Number of observations.} \]
\[ \Sigma = \text{The Greek capital Sigma denotes “sum of”}. \]

**Standard Deviation:**

Standard deviation was calculated by the following formula.

\[ SD = \sqrt{\frac{\Sigma (x - \bar{x})^2}{n - 1}} \]

Where,
\[ x = \text{Individual observation.} \]
\[ \bar{x} = \text{Mean.} \]
\[ n = \text{Number of values in series.} \]
\[ \Sigma = \text{Sum of} \]

**Standard Error of Mean:**

Standard error of Mean (SEM) was calculated by dividing Standard Deviation by the square root of number of observations.

\[ \text{SEM} = \frac{SD}{\sqrt{N}} \]

where,
SD = Standard deviation.
N = Number of observations.

**t-test:**
The statistical significance of difference between the mean values of the two groups was evaluated by “student’s t-test”. The value of “t” was calculated by the following formula:
\[
x_1 - x_2 \\
t = \frac{1}{\sqrt{(S.E.1)^2 + (S.E.2)^2}}
\]

where,

\(\bar{x}_1 > \bar{x}_2\)

\(\bar{x}_1\) = Mean of one group of observations
\(\bar{x}_2\) = Mean of other group of observations.

S.E.1 = Standard error of \(\bar{x}_1\)
S.E.2 = Standard error of \(\bar{x}_2\)

**Df (degree of freedom):**

It was calculated by the formula:

\[DF = (n_1 + n_2)\]

n₁ = Number of observations of one group
n₂ = Number of observations in other group.

**Paired “t” Test:**

When comparing the effects of two alternative treatments or experiments, it is sometimes possible to make comparison in pairs.

The value of “paired (t)” was calculated by following formulas:

\[t = \frac{\bar{D}}{SEM}\]

\(\bar{D}\) signifies the mean of differences between members of each pair

SEM is the standard error of mean difference.
**P-value:**

The degree of probability was computed by comparing the calculated value of “t” with tabulated values in the table of “t” distribution against the degree of freedom (Df). The difference in the mean values of the two groups was regarded statistically significant if the p-value was equal to or less than 0.05, and non-significant (NS) if the P-value was more than 0.05. It was highly significant if the p-value was less than 0.001.
OBSERVATIONS AND RESULTS
In this study, a total number of 264 patients of both sexes were enrolled. They were divided in three groups of 88 patients in each group; designated as A, B, and C groups respectively.

All patients ranged in age between 28-68 years. Patients’ evaluation record was noted on prescribed forms specially designed for the study, while written consent to join the study was obtained from all patients before enrollment for the present study. The observations of all treatment groups were recorded on day-0, day-45, and day-90.

The final analysis applied to 241 patients who completed the study protocol. 23 patients were unable to complete the study and were lost to follow up, as shown in table 1 and figure 1.

Results are shown in tables 1-8, and their graphic representation in corresponding figures.
**TABLE - 1**

Division of Patients Included in the Study

According to Gender, Suffering from

Hyperlipidemia

<table>
<thead>
<tr>
<th>Group</th>
<th>Total No.</th>
<th>Males</th>
<th>Females</th>
<th>Dropouts</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>88</td>
<td>54</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>B</td>
<td>88</td>
<td>52</td>
<td>28</td>
<td>8</td>
</tr>
<tr>
<td>C</td>
<td>88</td>
<td>56</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>264</td>
<td>162</td>
<td>79</td>
<td>23</td>
</tr>
</tbody>
</table>
FIGURE-1

Division of Patients Included In the Study
According To Gender, Suffering from
Hyperlipidemia

TOTAL NUMBER OF PATIENTS

264

MALES
61%

FEMALES
30%

DROP OUTS
9%

MALES  FEMALES  DROP OUTS
GROUP A:

88 patients were treated with Zocor. 8 patients were lost to follow up in this group and 80 patients completed the study.

The mean ±SD values in all parameters are shown on day-0, the initial day of therapy, followed by day-45, and day-90 at the completion of the study. P-value is calculated for the time periods between day-0 and day-45, as well as day-45 and day-90, as shown in table 2 and figure 2.

Statistically significant improvement is obtained in this group from day-0 to day-45 and day-45 to day-90 as illustrated in table 2 and figure 2.

Mean Serum Total Cholesterol was calculated to be 242.18 ±42.15 on day-0, which decreased to 196.17±37.15 on day-45 and reduced further to 166.20 ±31.24 on day-90. This decrement in Total Cholesterol is found to be highly significant (p<0.001) in both of these time periods.

The mean Serum Triglyceride level is reduced non-significantly (p>0.05) from 289.18±16.67 to 256.87±14.94 in the treatment period of day-0 to day-45. It still decreased to 213.36±11.53 from
day-45 to day-90, which is calculated to be significant statistically (p<0.05).

Highly significant result (p<0.001) is also seen in Serum Low Density Lipoprotein Cholesterol (LDL-C) which diminished by the treatment with Zocor from 192.92±29.65 on day-0 to 159.53±25.03 on day-45, and 125.00±17.33 on day-90. Moderately significant improvement (p<0.01) is observed in Serum High Density Lipoprotein Cholesterol (HDL-C), which increased from 30.83±5.07 to 33.17±5.37 in treatment period of day-0 to day-45. Its further increase to 36.33±5.68 on day-90 is observed to be highly significant (p<0.001).

Eight patients were found to be non-compliant, and 7 patients reported adverse effects. Abdominal pain and nausea/vomiting were muscular pain and giddiness were reported. The side effects were mild, which compelled no patient to quit study treatment. Reassurance and/or symptomatic treatment were sufficient to get going.
TABLE-2

Therapeutic Effectiveness of Zocor 20 mg OD in Hyperlipidemia in All Parameters

On Day-0, Day-45, and Day-90

(Group A) = Zocor Treated Group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Observations</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 45</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>242.18 ±42.15</td>
<td>196.17 ±37.16</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>289.18 ±149.14</td>
<td>256.87 ±133.62</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>192.92 ±29.65</td>
<td>159.53 ±25.03</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>30.83 ±5.07</td>
<td>33.17 ±5.37</td>
</tr>
</tbody>
</table>

Values are expressed in Mean ±SD

S = Significant  
HS = Highly Significant  
MS = Moderately Significant  
NS = Not Significant  

Negative (-) sign indicates reduction in symptoms
FIGURE-2

Therapeutic Effectiveness of Zocor 20 mg OD in Hyperlipidemia in All Parameters
On Day-0, Day-45, and Day-90

(Group A)
GROUP B:

(Tab. Atcol 20 mg OD)

This group included 88 patients. 8 patients could not continue the study due to non-compliance, and 80 patients completed the study in this group.

The mean ±S.D values in all parameters are shown on day-0, day-45, and finally day-90. Statistical significance is shown by improvement in all the symptoms (p<0.05) for the time periods of day-0 to day-45, and day-45 to day-90; as shown in table 3 and figure 3.

Significant p-values are obtained for the period from day-0 to day-45, and day-45 to day-90 in this group, which decreased significantly, as depicted in table 3 and figure 3.

Mean Serum Total Cholesterol was observed to be 242.77 ±46.92 on day-0, which decreased to 198.17±39.39 on day-45 and it reduced further to 167.61 ±35.78 on day-90. This reduction in Total Cholesterol is statistically highly significant (p<0.001) in both of these time periods.
The mean Serum Triglyceride level decreased significantly (p<0.05) from 291.56±148.47 to 262.63±131.43 in the treatment period of day-0 to day-45. It further reduced significantly (p<0.05) to 221.88±106.61 from day-45 to day-90.

High significance (p<0.001) is also observed in Serum Low Density Lipoprotein Cholesterol (LDL-C) during the treatment period which diminished by taking Atcol from 185.52±19.59 on day-0 to 152.43 ±16.78 on day-45, followed by 123.00±12.87 on day-90.

Serum High Density Lipoprotein Cholesterol (HDL-C) increased from 31.80±4.98 to 34.09±5.33 in the treatment period of day-0 to day-45. This improvement is moderately significant statistically (p<0.01). It further increased to 37.01±5.61 on day-90, which is highly significant statistically (p<0.001).

Eight patients were dropped due to non-compliance, and 9 patients complained of side effects. Abdominal pain, dyspepsia, diarrhea, and nausea/vomiting and headache were reported. The side effects were mild, which compelled no patient to quit study treatment. Reassurance and/or symptomatic treatment were sufficient to get going.
TABLE 3

Therapeutic Effectiveness of Atcol 20 mg OD in Hyperlipidemia in All Parameters

On Day-0, Day-45, and Day-90

(Group B) = Atcol treated group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Observations</th>
<th></th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 45</td>
<td>Day 90</td>
<td>Day 0-45</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>242.77 ±46.92</td>
<td>198.18 ±39.39</td>
<td>167.61 ±35.78</td>
<td>&lt;0.001 HS</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>291.56 ±148.47</td>
<td>262.63 ±131.43</td>
<td>221.88 ±106.61</td>
<td>&lt;.002 S</td>
</tr>
<tr>
<td>LDL - C (mg/dl)</td>
<td>185.52 ±19.59</td>
<td>152.43 ±16.78</td>
<td>123.00 ±12.87</td>
<td>&lt;0.001 HS</td>
</tr>
<tr>
<td>HDL - C (mg/dl)</td>
<td>31.80 ±4.98</td>
<td>34.09 ±5.33</td>
<td>37.01 ±5.61</td>
<td>P&gt;.05 NS</td>
</tr>
</tbody>
</table>

Values are expressed in Mean ±SD

S = Significant,  HS = Highly Significant
MS = Moderately Significant,  NS = Not Significant
Negative (-) sign indicates reduction in symptoms
FIGURE 3

Therapeutic Effectiveness of Atcol 20 mg OD in Hyperlipidemia in All Parameters

On Day-0, Day-45, and Day-90

(Group B)
GROUP C:

(Tab. Limitrol 20 mg OD)

This group comprised of 88 patients, they were administered drugs and were followed-up for 90 days. 7 patients were lost to follow up in this group. 81 patients completed the study in this group.

The mean ±S D values in all parameters are shown for data recorded on day-0, followed by day-45, and day-90. P-value is calculated for the time periods between day-0 and day-45, and day-45 and day-90, as depicted in table 4 and figure 4.

Statistically significant treatment effect with Limitrol is obtained in this group for the study period from day-0 to day-45, and from day-45 to day-90 in all parameters is found to be highly significant (p<0.001) in this group, as illustrated in table 4 and figure 4.

Mean Serum Total Cholesterol was noted to be 238.37±48.35 on day-0, which decreased to 192.32±25.46 on day-45 and was further controlled to 160.14 ±21.83 on day-90.

The mean Serum Triglyceride level is observed to decrease from 243.00±41.19 to 212.96±37.30 in the treatment period of day-0 to day-45. Moreover it reduced to 175.37±31.30 from day-45 to day-90.
Serum Low Density Lipoprotein Cholesterol (LDL-C) diminished with Limitrol use from 186.31±10.35 on day-0 to 153.30±9.60 on day-45. It further reduced to 124.00±9.94 on day-90.

Mean Serum High Density Lipoprotein Cholesterol (HDL-C) improved from 31.14±5.44 on day-0 to 33.73±4.80 on day-45 of the treatment. This benefit is markedly significant (p<0.002). It further increased to 37.90 ±4.87 on day-90, which is highly significant statistically (p<0.001).

7 patients of this group could not complete the study, which were lost to follow up and 11 patients showed side effects, abdominal pain, dyspepsia, nausea/vomiting. The reported side effects were mild and relieved with the symptomatic treatment and reassurance.
# TABLE-4

Therapeutic Effectiveness of Limitrol 20 mg OD in Hyperlipidemia in All Parameters
On Day-0, Day-45, and Day-90

(Group C) = Limitrol Treated Group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Observations</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 45</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>238.37 ±48.35</td>
<td>192.32 ±25.46</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>243.00 ±41.19</td>
<td>212.96 ±37.14</td>
</tr>
<tr>
<td>LDL - C (mg/dl)</td>
<td>186.31 ±10.35</td>
<td>153.30 ±9.60</td>
</tr>
<tr>
<td>HDL - C (mg/dl)</td>
<td>31.14 ±5.44</td>
<td>33.73 ±4.80</td>
</tr>
</tbody>
</table>

Values are expressed in Mean ±SD
S = Significant, HS = Highly Significant
MS = Moderately Significant. NS = Not Significant
Negative (-) sign indicates reduction in symptoms
FIGURE 4

Therapeutic Effectiveness of Limitrol 20 mg OD in Hyperlipidemia in All Parameters

On Day-0, Day-45, and Day-90

(Group C)
PARAMETER-WISE OBSERVATIONS

FROM DAY-0 TO DAY-90:

Serum Total Cholesterol:

Mean Serum Total Cholesterol is observed to decrease highly significantly (p<0.001) in all three groups at the completion of 90-days study period. In group A, it was calculated to be 242.18 ±42.15 on day-0, which reduced to 166.20 ±31.24 on day-90. In group B, it was found to be 242.77 ±46.92 on day-0, which decreased to 167.61 ±35.78 on day-90. Simultaneously in group C, mean Serum Total Cholesterol was noted to be 238.37±48.35 on day-0, which reduced to 160.14 ±21.83 on day-90 as illustrated in table 5 and figure 5.
TABLE 5
Parameter-wise Observations of All Groups On Day-0 and Day-90

SERUM CHOLESTEROL (mg/dl)

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>DAY 0</th>
<th>DAY 90</th>
<th>% CHANGE</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 0–Day 90</td>
<td></td>
</tr>
<tr>
<td>GROUP A</td>
<td>242.18</td>
<td>166.20</td>
<td>-31.37</td>
<td>&lt;0.001 HS</td>
</tr>
<tr>
<td>(n=80)</td>
<td>±42.15</td>
<td>±31.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GROUP B</td>
<td>242.77</td>
<td>167.61</td>
<td>-30.96</td>
<td>&lt;0.001 HS</td>
</tr>
<tr>
<td>(n=80)</td>
<td>±46.35</td>
<td>±35.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GROUP C</td>
<td>238.37</td>
<td>160.14</td>
<td>-32.82</td>
<td>&lt;0.001 HS</td>
</tr>
<tr>
<td>(n=81)</td>
<td>±48.35</td>
<td>±21.83</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Values are expressed in Mean ±SD

Group A = Group of patients treated with Zocor

Group B = Group of patients treated with Atcol

Group C = Group of patients treated with Limitrol

n = no. of patients who completed the study

HS = Highly Significant
FIGURE - 5

Parameter-wise Observations of All Groups
On Day-0 and Day-90

SERUM CHOLESTEROL (mg/dl)

DAY- 0

242.18 242.77 238.37

DAY- 90

167.61 166.2 160.14

Group A  Group B  Group C
Serum Triglycerides:

Mean Serum Triglycerides is observed to decrease highly significantly \((p<0.001)\) in all three groups at the completion of 90-days study period. In group A, it was calculated to be \(242.18 \pm 4.71\) on day-0, which reduced to \(166.20 \pm 3.49\) on day-90. In group B, it was found to be \(242.77 \pm 5.24\) on day-0, which decreased to \(167.61 \pm 4.00\) on day-90. Simultaneously in group C, mean Serum Total Cholesterol was noted to be \(238.37 \pm 5.37\) on day-0, which reduced to \(160.14 \pm 2.42\) on day-90 as depicted in table 6 and figure 6.

Percentage change for the study period from day-0 to day-90 calculated for Group A, treated with Zocor, has shown the percentage reduction of \(30.96\%\) in mean Serum Triglycerides. Group B, the Atcol receiving group, has resulted in a decrease of \(31.37\%\), and Group A, taking Zocor, has produced \(32.82\%\) fall in Triglyceride level in 90 days of the study as shown in table 6 and figure 6.
**TABLE - 6**

Parameter-wise Observations of All Groups On Day-0 and Day-90

**SERUM TRIGLYCERIDES (mg/dl)**

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>DAY 0</th>
<th>DAY 90</th>
<th>% CHANGE</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Day 0–Day 90</td>
</tr>
<tr>
<td><strong>GROUP A</strong></td>
<td>289.18</td>
<td>213.36</td>
<td>-26.22</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>(n=80)</td>
<td>±149.14</td>
<td>±103.12</td>
<td></td>
<td>HS</td>
</tr>
<tr>
<td><strong>GROUP B</strong></td>
<td>291.56</td>
<td>221.88</td>
<td>-23.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n=80)</td>
<td>±148.47</td>
<td>±106.61</td>
<td></td>
<td>HS</td>
</tr>
<tr>
<td><strong>GROUP C</strong></td>
<td>243.00</td>
<td>175.37</td>
<td>-27.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n=81)</td>
<td>±41.19</td>
<td>±31.30</td>
<td></td>
<td>HS</td>
</tr>
</tbody>
</table>
Values are expressed in Mean ±SD

Group A = Group of patients treated with Zocor

Group B = Group of patients treated with Atcol

Group C = Group of patients treated with Limitrol

n = no. of patients who completed the study

HS = Highly Significant
FIGURE - 6

Parameter-wise Observations of All Groups
On Day-0 and Day-90

SERUM TRIGLYCERIDES (mg/dl)

DAY- 0

DAY- 90

289.18 291.56

213.36 221.88

243

175.37

Group A   Group B   Group C
Serum LDL-Cholesterol:

Mean serum LDL-cholesterol is noted to reduce highly significantly (p<0.001) in all three groups at the completion of 90-days study period. In group A, it was observed to be 192.92±29.59 on day-0, which decreased to 125.00±17.33 on day-90. In group B, it was calculated to be 185.52±19.59 on day-0, which decreased to 123.00±12.87 on day-90. Meanwhile in group C, mean serum LDL-Cholesterol was noted to be 186.31±10.35 on day-0, which reduced to 124.00±9.94 on day-90: as illustrated in table 7 and fig 7.

Percentage change for the study period from day-0 to day-90 calculated for group A, treated with Zocor, has shown the decrease of 35.21% in mean serum LDL-C. In group B, taking Atcol, LDL-C has resulted in reduction of 33.7%, and group C, receiving limitrol, has shown 33.44% fall in LDL-C in 90 days of the study, as shown table 7 and fig 7.
### TABLE-7
Parameter-wise Observations of All Groups On Day-0 and Day-90

**SERUM LDL-C (mg/dl)**

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>DAY 0</th>
<th>DAY 90</th>
<th>% CHANGE Day 0–Day 90</th>
<th>P-VALUE Day 0–Day 90</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GROUP A</strong> (n=80)</td>
<td>192.92 ±29.59</td>
<td>125.00 ±17.33</td>
<td>-34.8</td>
<td>&lt;0.001 HS</td>
</tr>
<tr>
<td><strong>GROUP B</strong> (n=80)</td>
<td>185.52 ±19.59</td>
<td>123.00 ±12.87</td>
<td>-33.51</td>
<td>&lt;0.001 HS</td>
</tr>
<tr>
<td><strong>GROUP C</strong> (n=81)</td>
<td>186.31 ±10.35</td>
<td>124.00 ±9.94</td>
<td>-33.3</td>
<td>&lt;0.001 HS</td>
</tr>
</tbody>
</table>
Values are expressed in Mean ±SD

Group A = Group of patients treated with Zocor

Group B = Group of patients treated with Atcol

Group C = Group of patients treated with Limitrol

n = no. of patients who completed the study

HS = Highly Significant
FIGURE 7

Parameter-wise Observations of All Groups
On Day-0 and Day-90

SERUM LDL-C (mg/dl)
Serum HDL-Cholesterol:

Mean serum HDL-Cholesterol is observed to decrease highly significantly (p<0.001) in all three groups at the completion of 90-days study period. In group A, it was observed to be 30.83±5.07 on day-0, which increased to 36.33±5.68 on day 90. In group B, it was noted to be 31.80±4.98 on day-0 which improved to 37.01±5.61 on day-90. Which in group C, mean serum HDL-C was noted to be 31.14±5.44 on day-0, which rose to 37.00±4.87 on day-90, as shown in table 8 and fig 8.

Percentage change for the study period from day-90 calculated for group A, treated with Zocor, has shown a rise of 17.84% in mean serum HDL-C. group B, the atcol treated group, has resulted in an improvement in mean serum HDL-C level of 16.38%, and group C, taking limitrol, has shown 18.82% increase in HDL-C level in 90 days of the study: as shown table 8 and fig 8.
### TABLE - 8

Parameter-wise Observations of All Groups

On Day-0 and Day-90

**SERUM HDL-C (mg/dl)**

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>DAY 0</th>
<th>DAY 90</th>
<th>% CHANGE</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 0–Day 90</td>
<td>Day0–Day90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36.33</td>
<td>+17.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>30.83</td>
<td>36.33</td>
<td>+17.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>±5.07</td>
<td>±5.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GROUP A</td>
<td>31.80</td>
<td>37.01</td>
<td>+16.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n=80)</td>
<td>±4.98</td>
<td>±5.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GROUP B</td>
<td>31.14</td>
<td>37.00</td>
<td>+18.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n=81)</td>
<td>±5.44</td>
<td>±4.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GROUP C</td>
<td>31.80</td>
<td>37.01</td>
<td>+16.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n=80)</td>
<td>±4.98</td>
<td>±5.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31.14</td>
<td>37.00</td>
<td>+18.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>±5.44</td>
<td>±4.87</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Values are expressed in Mean ±SD

Group A = Group of patients treated with Zocor

Group B = Group of patients treated with Atcol

Group C = Group of patients treated with Limitrol

n = no. of patients who completed the study

HS = Highly Significant
FIGURE-8

Parameter-wise Observations of All Groups

On Day-0 and Day-90

SERUM HDL-C (mg/dl)

DAY-0

30.83 31.8 31.14

DAY-90

36.33 37.01 37

Group A  Group B  Group C
DISCUSSION
A predominance of small, dense low-density lipoproteins (LDL) has been accepted as an emerging cardiovascular risk factor by the National Cholesterol Education Program Adult Panel Treatment III. LDL size seems to be an important predictor of cardiovascular events and progression of coronary heart disease and evidences suggests that both quality (particularly small, dense LDL) and quantity may increase cardiovascular risk (Rizzo, M and Bernies K 2006). “Statins are among our best drugs for treating individuals who have elevated cholesterol, “said Robert Eckel, M.D president of the American Heart Association. “Overwhelmingly, the majority of individuals tolerate statins very well, and the absolute risk of side effects is low”.

Decreasing age in incidence for sudden cardiac death is a worrisome cause and should be addressed with Public health awareness regarding life style and dietary modifications (Mushtaq, S et al 2006).

We need energy for our bodies functioning and growth. We consume food for this energy. Every constituent of food has some amount of energy. We have all heard of the word “caloric”. Caloric is actually a measure of energy that a particular food can provide us with. A healthy or balanced diet is one which provides us just
enough calories required by our bodies. Different people having different lifestyles, require different number of calories to stay healthy. Excessive food i.e. excessive calories remain in the blood as blood glucose, or get deposited in various parts of the body in the shape of fat, thus increasing body weight. Every person has, what is called a desired weight. Desired weight is that weight which reflects that a person is taking just enough calories his or her body is burning up i.e. there is no extra food that is being stored in the form of fat. Excessive weight is that weight which is over and above desired weight and has been suggested to be responsible for diabetes, high blood pressure, cardiac problems, stroke, joint diseases, lung diseases etc (Memon Mohammad Saleh, 2006). There is overwhelming evidence that stopping smoking reduces the risk of cardiovascular disease, lung disease, cancer and stroke. As diabetes increases the risk for heart disease and stroke, it follows that stopping smoking will reduce the risk of complications from diabetes and heart disease.

Cardiovascular disease (CVD) is a leading cause of death among individuals with type 2 diabetes (Abdul Ahrah et al; 2006). Low density lipoproteins (LDLs) and their oxidized derivatives initiate and promote the atherosclerotic process, leading to the
development of coronary artery disease (Berliner et al, 1995). Increased plasma levels of LDL Cholesterol are significant predictors of the developments of coronary artery disease (CAD) (Castelli, et al, 1986 and Casteli et al, 1992). Several cholesterol-lowering interventions have reduced coronary heart disease (CHD) events in clinical trials, drug therapy for hypercholesterolemia has not been as widely used as the US and European guidelines recommend, mainly because until recently there was insufficient clinical trial evidence for improved survival. The Scandinavian simvastatin survival study (4S) is the first trial of lipid lowering therapy to demonstrate an unequivocal reduction in total mortality. Largely as a result of this study, there is now little disagreement on the necessity to reduce low density lipoprotein (LDL) Cholesterol effectively in hypercholesterolaemic patients with (CHD), (Pedersen and Tobert 1996).

Studies of the efficacy of cholesterol lowering began in the 1960s. However, it was not until the advent of powerful cholesterol-reducing drugs known as statins that clear-cut evidence of the benefit of cholesterol lowering became available (Illingworth and Durrington, 1999). Several important trials in the 1970s and 1980s showed that average cholesterol reductions of 10% resulted in 20%
reductions in non fatal CHD events, but these trials were not large enough to detect an effect on mortality (Lipids research clinics Program, 1984a, committee of Principals investigators 1984, Frick et al 1987, Durrington and Illingworth 1998). In fact increases in non cardiac mortality in these trials raised concerns about the safety of cholesterol-lowering therapy (Wysowski and Gross, 1990).

In 1994, the Scandinavian Simvastatin Survival Study (4S), a secondary prevention trial, proved to for the first time that lowering cholesterol levels with simvastatin reduced total mortality among CHD patients with normal HDL levels and high mean baseline LDL-C levels (188 mg/dl). Simvastatin therapy reduced LDL-cholesterol levels by an average 35%, CHD mortality by 42%, non fatal CHD events by 40%, and total mortality by 30%. Simvastatin therapy did not increase non cardiac mortality from any cause (Scandinavian simvastatin survival study Group, 1994).

Subsequently, the efficacy and safety of statin therapy in patients with established CHD at base line was evaluated in the cholesterol and recurrent events (CARE) trial and the long-Term intervention with Pravastatin in Ischaemic disease (LIPID) study (Sacks et al 1996).
There also have been clinical trials of lipid lowering in patients who had no evidence of vascular disease at base line (primary prevention trials). The West of Scotland Coronary prevention Study demonstrated a benefit of pravastatin therapy in male patients with baseline LDL-C > 155mg/dl. The average LDL-C in WOSCOPS was high (192 mg/dl) and the mean HDL-C level was 44mg/dl. The average on-treatment LDL-C WAS142 mg/dl, a 26% decrease from baseline, and this resulted in a 31% reduction in CHD death and nonfatal myocardial infarction.

Another statin trial in patients without vascular disease was the Airforce /Texas Coronary Atherosclerosis Prevention study (AFCAPS/ Tex CAPS) (Down et al, 1998). These trials provided convincing evidence that supported the 2001 revision of the National Cholesterol Education Program (NCEP) guidelines for the management of dyslipidemic patients.

National Cholesterol Education Program Guidelines for Treatment: Managing patients with dyslipidemia. The current NCEP guidelines for management of patients with lipid disorders are of two types. One is population based approach, which is intended to lower blood cholesterol by dietary recommendations: Reduce total calories from fat to less than 30% and from saturated fat to less than 10% consume
less than 300 mg of cholesterol per day and maintain desirable body weight (National Cholesterol Education Program, 1990). The second is the patient based approach described in 2001 report of the NCEP Adult treatment panel III, which continues to focus on lowering LDL-C levels as the primary goal of therapy (National cholesterol education program Expert Panel 2001). The 2001 Adult Treatment Panel III guidelines for the management of adults 20 years and older recommend a complete lipoprotein profile (total cholesterol, LDL-C, HDL-C, and triglycerides) rather than screening for total cholesterol and HDL-C alone. Fasting for 12 hours is required to accurately measure the triglyceride and LDL-C levels \[LDL-C = \text{total cholesterol} - (\text{triglyceride} - 5) - \text{HDL-C}\].

More effective lipid-lowering agents and a better understanding of atherogenesis have helped to prove that aggressive lipid-lowering therapy has many beneficial effects over and above those obtained by simply decreasing lipid deposition in the arterial wall. Arteriographic trials have shown that, although aggressive lipid lowering results only in very small increases in lumen diameter, it promptly decreases acute coronary events (Brown et al, 1993). Aggressive lipid lowering therapy may prevent acute events through
its positive effects on the arterial wall it corrects endothelial
dysfunction, corrects abnormal vascular reactivity (spasms), and
improves plaque stability.

Atherosclerotic lesions containing a large lipid core, large numbers
of macrophages, and a poorly formed fibrous cap (Brown et al, 1993
Gutstein and Fuster, 1999) and prone to plaque rupture and acute
thrombosis. Aggressive lipid lowering appears to alter plaque
architecture, resulting in lesser lipid, fewer macrophages, and a
larger collagen and smooth muscle cell-rich fibrous cap.
Stabilization of plaque susceptibility to thrombosis appears to be a
direct result of LDL-C lowering or an indirect result of changes in
cholesterol and lipoprotein metabolism or arterial wall biology.

Hyperlipidemia (hypercholesterolemia) is a major cause of increased
atherogenic risk, and both genetic disorders and diets enriched in
saturated fat and cholesterol contribute to the elevated lipid levels of
our population and many other developed countries around the
world.

Recognition of hypercholesterolemia as a risk factor has led to the
development of drugs that reduce cholesterol levels. These drugs
have been used in well-controlled studies of patients with high
cholesterol levels caused primarily by elevated levels of low density lipoproteins (LDL). The results of these trials indicate that CHD mortality has reduced as much as 30% to 40% and that non fatal events are similarly reduced when hypercholesterolemic patients are treated with moderate doses of hypolipidemic drugs (Scandinavian Simvastatin Survival Study Group, 1994 Shepherd et al, 1995. The long term intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group ;1998)

Are there total and LDL cholesterol levels below which adverse health consequences begin to increase? Observational studies were initially confusing. In the United States and Western Europe, low cholesterol levels appeared to be associated with an increase in noncardiac mortality from chronic pulmonary disease, chronic liver disease, cancer (many primary sites), and hemorrhagic stroke. However more recent data indicate that it is the noncardiac diseases that cause the low plasma cholesterol levels and not the low cholesterol levels that cause the noncardiac diseases (Law et al 1994). One exception may be hemorrhagic stroke. In the Multiple Risk Factor Intervention Trial (MRFIT), hemorrhagic stroke occurred more frequently in hypertensive patients with total cholesterol levels below 160 mg/dl however, the increased incidence
of hemorrhagic stroke was more than Offset by reduced CHD risk due to the low cholesterol levels (Neoton et al, 1992). In addition in a study of the Chinese population, in which the cholesterol levels rarely exceeded 160 mg/dl, lower levels of cholesterol were not associated with increases in hemorrhagic stroke or any other cause of noncardiac mortality (Chen et al, 1991).

The present study was a randomized controlled comparative clinical study, aimed at assessing the role of some of the different preparations of simvastatin currently in use in the country, including multinational as well as local drug companies.

In group A we conducted trial of Zocor manufactured by a multinational company, which is brand leader in simvastatin tablets marketed in this country. To group B patients we administered Atcol, which is the product of a local company. Group C patients were given limitrol, which is also the simvastatin produced by a local company. Our objective was to assess the extent of efficacy and safety of these study drugs in patients suffering from hyperlipidemia.

We got highly significant results in all parameters, i.e. Serum Total Cholesterol, Serum Triglycerides, Serum Low Density Lipoprotein
Cholesterol (LDL-C), and Serum High Density Lipoprotein Cholesterol (HDL-C) at the end of 90-day study period, with p-value <0.001 in all these parameters, as shown in tables 5, 6, 7, 8 and figures 5, 6, 7, 8.

Present study, like scores of other clinical trials, has proven the benefit and safety of lipid lowering with simvastatin in patients with established atherosclerotic disease, particularly CHD. As cholesterol-lowering therapy appears to be highly efficacious for reducing risk for recurrent coronary syndromes, its initiation at the time of discharge from the hospital can be considered, provided the patient is metabolically stable.

Scandinavian Simvastatin Survival Study (4S, 1994), in which hypercholesterolemic patients with CHD received simvastatin therapy, documented a 34% reduction in major coronary events, a 42% decrease in coronary mortality, and a 30% reduction in total mortality. Investigators in the Cholesterol and Recurrent Events (CARE) study by Sacks et al (1996) likewise observed significant benefits when pravastatin was given to CHD patients with average serum cholesterol levels. Several other trials, including those by The Post Coronary Artery Bypass Graft Trial Investigators (1997), Brown et al (1993), and Buchwald et al (1990) in which
angiographic end points were used; show that cholesterol-lowering therapy retards progression of coronary atherosclerosis a decrease in acute thrombotic events in coronary arteries was also noted. The summed results of these different categories of trials justify aggressive cholesterol management in most patients with CHD. The results of the present study also match with results of above studies.

The National Cholesterol Education Program (NCEP, 1994) calls for intensive cholesterol-lowering therapy in patients with any form of clinical atherosclerotic disease, specifically, acute myocardial infarction or angina pectoris, coronary artery angioplasty, peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease, or a history of coronary artery bypass graft. These patients carry a fivefold to sevenfold elevated risk for developing new or recurrent CHD and thus need intensive risk reduction.

According to current guidelines, the goal of therapy in patients with clinical atherosclerotic disease, including CHD, is to decrease LDL cholesterol to ≤100 mg/dL. This level is considered optimal for patients with CHD by the American College of Cardiology (27th Bethesda Conference, 1996), the American Heart Association Secondary Prevention Panel (headed by Smith Jr et al, 1995), and the NCEP Expert Panel (NCEP, 1994). The consensus opinion on
the optimal target goal for LDL cholesterol in patients with atherosclerotic disease is supported on both theoretical and experimental grounds, including clinical trials by The Post Coronary Artery Bypass Graft Trial Investigators (1997), Sacks et al (1996), Byington et al (1995), Scandinavian Simvastatin Survival Study Group (1994), Brown et al (1993) and Buchwald et al (1996). In the present study a highly significant decrease is observed (p<0.001) in Serum Low Density Lipoprotein Cholesterol (LDL-C) in all three groups in 90-day study period, which diminished by the treatment with Zocor (in group A) from 192.92±3.31 on day-0 to 125.00±1.94 on day-90. It diminished by taking Atcol (in group B) from 185.52±2.19 on day-0 to 123.00±1.44 on day-90, and reduced with Limitrol use (in group C) from 186.31±1.15 on day-0 to 124.00±1.10 on day-90. Although the LDL-C levels of our study patients could not touch the optimal level of ≤100 mg/dL according to current guidelines, but the continued treatment beyond the 90 days or co-administration of diet therapy can be expected to bring these values down to the desired level.

In our study highly significant improvement (p<0.001) is observed in Serum High Density Lipoprotein Cholesterol (HDL-C) in all three groups, which increased from 30.83±0.57 on day-0 to 36.33±0.64 on
day-90 in group A treated with Zocor. It was noted to rise from 31.80±0.56 on day-0 to 37.01±0.63 on day-90 in group B taking Atcol, and from 31.14±0.60 on day-0 to 37.00±0.54 on day-90 in group C receiving Limitrol.

Our results differ a bit from some of those researchers in % change in the therapeutic effect and p-values, which may be different in different trials, having variable designs and coverage.

As far as safety is concerned, the results of our short term study show that Zocor, Atcol, as well as Limitrol caused no serious adverse event in this 90-day trial. According to our final results, side effects were reported by 7 patients (12.39%) in Group A, treated with Zocor.

Patients in group B (15.83%), treated with Atcol, and patients in group C (17.83%), treated with Limitrol in this 90-day study. No adverse effect was serious to cause worsening of any lab finding, hospitalization of the patient, or discontinuation of the study. The reported side effects were overcome by reassurance and symptomatic therapy. Even though we can not exclude the possibility of the occurrence of any serious adverse effects with any of the study drugs. There may be any serious adverse event with the
long term use of any of the study drug, or with the use by the patients on risk. This can be determined by the large scale trials extending for longer time periods and by the use of more sensitive assessment methods.

In the present study after taking the drugs for 90 days no statistically significant difference was detected in blood LDL-cholesterol between the (Zocor treated) and the (Atcol treated) and (Limitrol treated) groups i.e. A, B and C groups respectively. Only minor side effects, mainly dizziness and nausea, were observed in all the three groups.

In the present study no significant differences in the therapeutic effect and safety were demonstrated between the generic and original simvastatin products. Decrease in the blood LDL-cholesterol can slow down and reduce the incidence of CAD, and thus mortality rate associated with the disease (Rackley, 2000).

HMG-CoA reductase inhibitors are widely used in the treatment of hypercholesterolemia due to its efficacy in reducing blood cholesterol (Pederson 1998; Jones 1990).

To help alleviate the rising cost of imported drugs, one strategy of the National Drug Policy is to promote the usage of locally made
generic products (Supakankunti et al. 2001). Simvastatin is the drug of which the local production and utilization are strongly encouraged, provided it can give equivalent safety and efficacy to the original product. In the present study here we report the outcome of the first randomized study conducted in Pakistan on the LDL-cholesterol lowering effect of locally manufactured generic simvastatin products in comparison with the innovators product Zocor.

To cope with the problems of increasing demand for medicines and to help reduce the costs of imported finished pharmaceutical products, a number of developing countries including Pakistan have set up various strategies, one of which is to promote the local manufacture and usage of quality generic drugs.

In general, study to establish bioequivalence between the original and the generic products involves measurements of the drug level or active metabolite(s) in the blood, which is based on a pharmacokinetic approach. However measurements of Plasma simvastatin concentration proved to be more difficult because the drug is an inactive lactone form which is preferentially taken up by the liver, the target site of action. Simvastatin has a high liver uptake after gastrointestinal absorption, with hepatic extraction ratio greater
than 90%. less than 5% of the simvastatin dose was reported the systemic circulation in healthy human volunteers (Duggan and Vickers, 1990). Thus most of the drug will accumulate in the liver, where it is metabolized to several active compounds, the major one of which is simvastatin acid. The active metabolites will act by inhibiting hepatic enzyme HMG-CoA reductase, thereby interfering with the synthesis of endogenous cholesterol in the liver. Apparently, accurate determination of extremely low concentrations of simvastatin metabolite(s) in the blood could be very difficult to achieve. And even if it is possible, it may not represent the actual amount of drug accumulating in the target organ and thus, it may not provide good correlation to the drug therapeutic result. In the present study, the indirect study by measurements of its pharmacodynamic or therapeutic effect can provide a good resolution (Marzo, 1999).

A study design based on a clinical approach was utilized here to compare the safety and efficacy of a generic simvastatin with that of the original product. Similar to the general bioequivalence study based on plasma drug concentration measurements, studies employing a clinical/pharmacodynamic approach can provide useful information on the quality of the locally made products so as to assure both the physicians and the patients that the products can
produce equivalent therapeutic outcome (The 4S study 1994, Bocuzzi et al 1993).

A number of variables are concerned in this type of study. Differences in the individual subjects, physiology, age, sex, lifestyle, diet, and exercise control as well as drug compliance, can lead to great variation in the therapeutic response. Control of these factors is very important. Keeping in view these factors, a strict inclusion and exclusion criteria was observed throughout this study. Closed monitoring of the patient compliance was also carried out by direct interview of the individual subjects as well as by checking the amount of tablets remaining after each visit.

A part from direct evaluation of the therapeutic result, another advantage of the clinical study over the conventional bioequivalence is the ability to compare the drug side effects. The side effects reported (dizziness and nausea) may or may not relate to the drug. Some reported side effects in clinical trials may also originate from the placebo known as the placebo effects. However it is also possible that the side effects may be due to the presence of impurities or the inclusion of inappropriate “inert” excipients in the drug formula (Wiwanitkit et al, 2002).
Epidemiological studies have demonstrated the importance of the relationship between excess saturated fat consumption and elevated Cholesterol levels. Reducing the consumption of dietary saturated fat and cholesterol is the cornerstone of population-based approaches to the management of hypercholesterolemia (NCEP 1990). In addition it is clearly established that higher the cholesterol levels, the higher the CHD risk (Stamler et al, 1986).

Cholesterol, a simple lipid found in cell membranes, is a precursor of steroids, bile acids, and vitamin D and a major part of atherosclerotic plaques.

Most circulating blood cholesterol is synthesized from liver acetyl CoA and is excreted as bile salts. Only 25% of blood cholesterol is from the diet, but high-fat diets increase liver cholesterol production and blood cholesterol levels.

HMG-CoA formation from HMG-CoA reductase, the rate-determining step in cholesterol synthesis, is regulated via feed back inhibition. When cholesterol uptake is low, the liver and small intestine increase cholesterol synthesis. The plaque forming ability of cholesterol is related to LDLs, which promote plaque formation; HDLs remove cholesterol from arteries and transport it to liver.
HDLs remove cholesterol from plaques and slow atherosclerosis. Control of cholesterol and LDL levels is a major goal in heart disease therapy. Primary goal of therapy are lower LDL levels and higher HDL levels. The best drugs for such therapy are statins. They interfere with the cholesterol production of the liver by blocking HMG-CoA synthesis so liver can better remove cholesterol from circulating blood. Statins lower LDL cholesterol by 60% side effects can occur. Nicotinic acid (or niacin) lowers total and LDL cholesterol and raises HDL cholesterol levels, but it can be toxic because the therapeutic dose is 100 fold greater than recommended daily allowance.

Resins (e.g. cholestyramine and colestipol) bind intestinal bile acids and prevent recycling through the liver. The liver needs cholesterol to make bile, so it increases uptake of cholesterol from blood. Fibric acid derivatives decrease triglyceride and increase HDL levels. Low doses of aspirin block platelet thromboxane A2 synthesis, which leads to reduced platelet aggregation and blood viscosity (Raffa Robert, B et al 2005).

A study of mortalities in late 1970s suggested that mortality due to ischemic heart disease was significantly lower in vegetarian males than in their non-vegetarian counterparts (Phillips et al., 1978).
The first article published about influence of diet on plasma lipids by Thorogood et al (1987) compared concentrations of total cholesterol and various lipoprotein fractions in 4 diet groups: vegans, who never ate animal products, vegetarians, who never ate meat or fish but did eat dairy products, eggs, or both fish eaters, who ate fish but no meat, and meat eaters. Both total and LDL-cholesterol concentrations were significantly lower in vegans than in meat eaters, whereas vegetarians and fish eaters had similar, intermediate values. HDL-cholesterol concentrations were highest in fish eaters but did not differ among the other diet groups. Mean cholesterol concentrations for vegans, vegetarians, fish eaters, and meat eaters, adjusted for age and sex. On the basis of these results, it was predicted that the incidence of ischemic heart disease might be 24% lower in lifelong vegetarians and 57% lower in lifelong vegans than in meat eaters.

The Oxford Vegetarian Study by Appleby et al (1999) is a prospective study of 6000 vegetarians and 5000 non-vegetarian control subjects recruited in the United Kingdom between 1980 and 1984. Cross-sectional analyses of study data showed that vegans had lower total- and LDL-cholesterol concentrations than did meat eaters, vegetarians and fish eaters had intermediate and similar
values. Meat and cheese consumption were positively associated, and dietary fiber intake was inversely associated, with total-cholesterol concentration in both men and women. After 12 y of follow-up, after adjusting for smoking, body mass index, and social class, death rates were lower in non-meat-eaters than in meat eaters for each of the mortality endpoints studied. Mortality from ischemic heart disease was also positively associated with estimated intakes of total animal fat, saturated animal fat, and dietary cholesterol. Other analyses showed that non-meat-eaters had only half the risk of meat eaters of requiring an emergency appendectomy, and those Vegans in Britain may be at risk for iodine deficiency. Thus, the health of vegetarians in this study is generally good and compares favorably with that of the non-vegetarian control subjects.

Immediate institution of non pharmaceutical therapy is warranted in all patients with CHD and LDL cholesterol levels >100 mg/dL (Grundy et al, 1997). Non pharmaceutical therapy includes a maximal reduction in daily intake of saturated fats (to ≤7% of total calories) and cholesterol (to <200 mg/d), weight loss in persons who are overweight, and physical activity appropriate for cardiac status. Individualized dietary therapy by a registered dietitian or other qualified nutritional professional will often improve dietary
adherence. Maximal dietary therapy typically reduces LDL cholesterol levels by 15 to 25 mg/dL. (National Cholesterol Education Program, 1994)

If the baseline LDL cholesterol level in patients with CHD is >130 mg/dL, cholesterol-lowering drug therapy is often needed in addition to maximal non pharmaceutical therapy to achieve the target LDL cholesterol level of ≤100 mg/dL. The major drugs used for LDL reduction are statins, bile acid sequestrants, and nicotinic acid. (Grundy et al, 1997)

Current guidelines by the American College of Cardiology (27th Bethesda Conference, 1996) suggest use of nicotinic acid, because of its potential for increasing HDL, for the patients with CHD and a baseline LDL cholesterol level ranging from 100 to 129 mg/dL having a low HDL cholesterol level (<35 mg/dL).

In the last decade as a result of sedentary life style, junk foods and stressful life there has been an increase in cardiac events. Each increase by 1 unit of LDL-C/HDL-C ratio increases the risk of myocardial infarction by 53%. Cardiologists rely on lipid profile specifically LDL-C and HDL-C to predict chances of cardiac event, since dyslipidemia could be a major determinant of premature
atherosclerosis. The severity of atherosclerosis is strongly related to the LDL-C (Jabbar J et al, 2006).

Recent studies provide clear and convincing evidence that psychosocial factors contribute significantly to the pathogenesis and expression of CHD (Nishter, S; 2002). This evidence is composed largely of data relating CHD risk to depression, anxiety, personality factors and character traits such as anger, social isolation and chronic life stress. Emotionally stressed younger patients are also known to represent high risk group.

Individuals who engage in regular physical activity have lower prevalence rates of cardiovascular risk factors; exercise has also been found to yield beneficial effects on several risk factors and is therefore considered an important factor modification. For the South Asian population this offers a cost effective opportunity for risk reduction.

As more effective lipid-lowering drugs and better combination of therapies are developed, we will be able to lower lipid levels more effectively. Will lower level cholesterol levels translate into a further reduction of clinical events? Many researchers believe the answer is yes. In addition as statin become generic drugs more aggressive
treatment of wider segments of the population will become more cost effective.

There are self surface proteins named low density lipoprotein receptors or LDL-receptors. Individuals with a deficiency or absence of LDL-receptors are prone to atherosclerosis and premature CHD. It can be concluded that LDL-receptors are needed to help transfer the body's atherogenic LDL-particles to the liver for excretion. However, a diet rich in cholesterol and saturated fatty acids apparently signals the body to manufacture fewer LDL-receptors. It is therefore suggested that lifestyle induced deficiency of LDL-receptors results in an increased LDL-concentration and a greater risk of CHD.

In our study it was interesting to note that although the drugs have a pivotal role but the diet and physical activity has shown a significant role in decreasing the blood cholesterol level. From the data it was noted that the individuals who converted the diet mainly to vegetables and increased the physical activity and abandoned the sedentary life style, had significantly reduced the levels of LDL-C. It was astonishing to note that 170 subjects who severely cut the saturated fats and increased the fruits in their diet and substantially increased the physical activity, showed a very significant decrease of
LDL-C and generally felt more fit, active and alert after adopting the vegetarian diet and reducing the weight.

It is therefore to remarkably note from this study that individuals willing to add vegetable diet reducing saturated fats can significantly maintain an ideal Cholesterol level. A very classical group of this study was a group of individuals who in addition to diet and physical activity had a religious fervor and offered the prayers (Salat) regularly in the mosque. It was specifically noted that this small group of 22 individuals has drastically reduced the Cholesterol level as compared to those who did not offer the regular prayers. From this data it can be concluded that non Pharmacological measures adopted adequately and rationally can benefit more than 80% of people in initial stages of hypercholesterolemia, however when cholesterol levels have increased to certain level then of course drugs are valuable.

As with all things truly evil, the very essence of plaque vulnerability the modern plague that claims the lives of millions- continues to elude us. However, on the basis of many reported sightings, the
composite sketch of the serial killer is slowly coming up in to focus (Zorina S. Ghalis 2004)

It can therefore be strongly suggested that avoiding saturated fats, increasing physical activity and adopting religious means i.e. offering regular prayers certainly have an extremely significant effect in the management of hypercholesterolemia.
CONCLUSION:

We conclude from this study that Zocor, Atcol, as well as Limitrol possess comparable efficacy. The safety and tolerability of statins supports their use as first-line treatment for hypercholesterolemia. Myopathy and its serious complication, rhabdomyolysis, are a potential effect of therapy with the available statins, but occur very rarely. The molecular and biochemical mechanisms of myopathy and rhabdomyolysis caused by statins are yet to be fully elucidated. Appropriate awareness and attention to the potential for myopathy with statin therapy, in particular when they are given in combination with other drugs, should reduce the risk of this adverse event considerably. The different pharmacokinetic profile among the statins should be carefully considered to understand the different spectrum of drug interactions. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are a well established class of drug in the treatment of hypercholesterolemia, and member of this class have been shown to reduce the risk of cardiovascular morbidity and mortality in patient with or at risk of coronary heart disease (CHD).

All three study drugs are safe for the short term patients free from metabolic diseases; where as At col and Limitrol are cost effective.

It can therefore be strongly suggested that avoiding saturated fats, increasing physical activity and adopting religious means i.e. offering regular prayers certainly have an extremely significant effect in the management of hypercholesterolemia.

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APPENDIX – 1

DEPARTMENT OF PHARMACOLOGY
FACULTY OF PHARMACY
UNIVERSITY OF KARACHI

PROFORMA

Serial No_______ Reg. No_______ Date_______

Patient’s Name_______ W, D, S/o__________

Age: ______ Sex: ______ Weight Kg): ______

Height (cms): ______ BMI: ______

Occupation: ________________________________

Address: _________________________________

Presenting Complains: ____________________

Previous Medication: _____________________

PRETREATMENT PHYSICAL EXAMINATION:

Blood Pressure (sitting): ______ pulse Rate: ______

CVs: ________________________________

Respiratory System: ________________
GIT: ____________________________

CNS: ____________________________

Others: ____________________________

**BASELINE LABORATORY OBSERVATION (DAY 0)**

**LIPID PROFILE:**

Triglycerides: ____________________________

HDL: ____________________________

LDL: ____________________________

**TREATMENT GIVEN:**

______________________________

______________________________

______________________________
PATIENTS FOLLOW UP  
(FORTNIGHTLY)

FIRST VISIT (DAY 15)

SERIAL NO: __________________________ DATE: ________________________
DOSE REGIMEN: ________________________________________________________
COMPLIANCE: _________________________________________________________

SECOND VISIT (DAY 30)

SERIAL NO: __________________________ DATE: ________________________
DOSE REGIMEN: ________________________________________________________
COMPLIANCE: _________________________________________________________

THIRD VISIT (DAY 45)

SERIAL NO: __________________________ DATE: ________________________
DOSE REGIMEN: ________________________________________________________
COMPLIANCE: _________________________________________________________

Lipid Profile:

Cholesterol: ____________________________ (mg/dl)
Triglycerides: __________________________ (mg/dl)
HDL- Cholesterol: ______________________ (mg/dl)
LDL- Cholesterol: ______________________ (mg/dl)
Fasting Blood Sugar: ____________________ (mg/dl)
October 17, 2007

Dr. Assistant Registrar
ASR
University of Karachi
Karachi

I am submitting here with the thesis of Mr. Nazir Ahmed Solangi, a candidate for Ph.D. in Pharmacology.

I certify that all necessary corrections as suggested by the external examiners have been made in the thesis.

I am requesting the Viva voce examination of the candidate may be held at earliest.

[Signature]

Prof. Dr. Shahida F. Ahmed
Research Supervisor
Department of Pharmacology
Faculty of Pharmacy
University of Karachi

[Signature]

[Stamp]