Coronary heart disease (CHD) results from atherosclerosis, a slowly progressive condition of the medium arteries that begins early in life but rarely produces symptoms until middle age.

Although there has been a decrease in mortality from the disease, CHD is responsible for more than 550,000 deaths in the United States each year. There are over 5.4 million Americans with symptomatic CHD and a large number of others undiagnosed, many of whom are young and highly productive. It is estimated that CHD costs the United States over $60 billion a year in direct and indirect costs much of which must be borne by the insurance industry.

A number of risk factors have been identified as strongly associated with atherosclerotic heart disease. Heredity plays an important role in predisposition; adverse family history is more than just a strong genetic component and reflects a learned way of life that bridges generations. A positive family history, particularly for cardiovascular events which have effected one or more of the immediate family below the age of 60, is indication for careful assessment of other risk factors.

Cigarette smoking, high blood pressure and high blood cholesterol clearly predispose to the disease. The risk is greater in males and increases with age; obesity, diabetes, elevated uric acid, physical activity and behavior patterns are also implicated.

Indeed, the Framingham study further identified a cardiovascular risk profile using blood pressure, cholesterol, blood sugar, EKG and cigarette smoking history.

Using this set of variables, the risk for coronary artery disease can be estimated over a 30 fold range and 10% of the asymptomatic population identified in whom 25% of the coronary artery disease, 40% of the occlusive peripheral arterial disease and 50% of strokes will evolve.

However, from a review of current concepts, lipid metabolism has now been identified as fundamental to the process.

**LIPID METABOLISM**

Cholesterol, triglycerides and phospholipids are all lipids which are insoluble in water. When complexed with proteins (apoproteins) they form spherical macromolecules called lipoproteins which are soluble and can be transported throughout the body. Lipoproteins can be separated into five classes by ultra centrifugation according to their densities:

1. chylomicrons
2. very low density lipoproteins (VLDL)
3. intermediate density lipoproteins (IDL) (Remnant particles)
4. low density lipoproteins (LDL)
5. high density lipoproteins (HDL)

The density differences reflect the different proportions of triglycerides, cholesterol phospholipids and apoproteins in each. In the fasted state most of the serum cholesterol is carried in the LDL and most serum triglycerides in VLDL.

<table>
<thead>
<tr>
<th>Lipoprotein Class</th>
<th>Core Lipids</th>
<th>Major Apoproteins (Electrophoretic Mobility Pattern)</th>
<th>Phenotype</th>
<th>Electrophoretic Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>Dietary ABC</td>
<td>Triglycerides</td>
<td>I</td>
<td>Stay at origin</td>
</tr>
<tr>
<td>VLDL</td>
<td>Endogenous BCE</td>
<td>Triglycerides</td>
<td>IIb</td>
<td>Pre-Beta band</td>
</tr>
<tr>
<td>IDL</td>
<td>Cholesterol B, CIII, E</td>
<td>Triglycerides</td>
<td>III</td>
<td>Broad beta band</td>
</tr>
<tr>
<td>LDL</td>
<td>Cholesterol B</td>
<td>Triglycerides</td>
<td>IIa (with LDL IIb)</td>
<td>Beta band</td>
</tr>
<tr>
<td>HDL</td>
<td>Cholesterol A</td>
<td>Triglycerides</td>
<td>Alpha Band</td>
<td></td>
</tr>
</tbody>
</table>

*Fredrickson Classification*
Role of Cholesterol in Atherosclerosis

Cholesterol is a key component of cell membrane and a precursor of bile acids and steroid hormones. 80% of serum cholesterol is endogenous, the other 20% is affected by diet. Serum levels in the plasma are determined partly by inheritance and partly by diet. Obesity and physical activity also play a part.

Primary hypercholesterolemia is most commonly due to elevated LDL, and may be clinically classified as follows:

— familial hypercholesterolemia — heterozygotic — 1 in 500 of the caucasian population in North America — homozygotic 1 in 1,000,000

— polygenic (very common)

— familial combined hyperlipoproteinemia (common) 1-2% of population and 15-20% of patients with increased VLDL

— dysbetalipoproteinemia (abnormal apoprotein E) 1 in 10,000

Secondary hyperlipoproteinemia may result from diet, hypothyroidism, diabetes mellitus, end stage renal disease, hepatic cellular disease, glycogen storage disease, hyperuricemia, acute intermittent porphyria or drugs (corticosteroids, sex hormones, retinoids, beta blockers and diuretics).

Evidence that LDL Cholesterol is a Cause of CHD

1. Epidemiological — both the Framingham study and the Multiple Risk Factor Intervention Trial (MRFIT) correlate the extent of CHD with the serum LDL cholesterol level. Indeed the Framingham Study reported increased risk of CHD at cholesterol levels over 150 mg/dl (4.2 mmol/l), which is further increased when smoking and hypertension are present.

2. Genetic — in familial hypercholesterolemia, deficiency of LDL receptors in the liver and other organs results in defective LDL cholesterol removal and an increased serum LDL level. The natural history of this disorder is premature atherosclerosis that occurs in the 30’s and 40’s in males and in the 40’s and 50’s in females. The discovery of LDL receptors was an important contribution to the understanding of cholesterol metabolism.

3. Pathological — the major constituents of the atherosclerotic plaque are cholesterol containing lipids derived from plasma lipoproteins.

4. Animal studies — in non-human primates fed on a diet high in saturated fats, serum cholesterol levels rise, and atherosclerosis develops. This situation is reversed by decreasing the plasma cholesterol with a diet low in saturated fats.

5. Human studies — prolonged starvation has been shown to lower serum cholesterol levels and reduce atherosclerotic plaques. The Japanese who migrated from Japan to Hawaii began to consume more cholesterol and saturated fat. This was related to higher serum cholesterol levels and to an increase in the incidence of atherosclerosis. Similarly, comparison of autopsy reports on young American and Korean soldiers in the Korean war showed that the Americans, on a diet high in animal fat had a very much higher incidence of atheroma than the Koreans on a vegetarian diet.

Evidence that Reducing LDL Cholesterol Levels will Prevent CHD

Several primary and secondary intervention clinical trials have shown the benefits of lowering serum cholesterol and the prevention of progression of atherosclerotic disease.

(1) Lipid Research Clinic Coronary Primary Prevention Trial. This important double blind, placebo controlled multi-centre trial studied the effects of lowered LDL cholesterol on the natural history of CHD. 3,806 middle aged males with hyperlipidemia enrolled; 1,900 were placed on diet and placebo and 1,906 on diet and cholestyramine. All subjects were followed for 7.4 years.

Regardless of whether LDL cholesterol reduction was by diet or by cholestyramine, there was a decrease in CHD. Furthermore, the decrease in disease was directly proportional to the decrease in the LDL cholesterol.

(2) Oslo Heart Study. 1,200 middle age men were chosen because of high serum cholesterol levels and smoking habits, one half of whom followed a low saturated fat, low cholesterol diet for 5 years. This intervention group had 14% reduction in serum cholesterol, 40% reduction in smoking and 60% reduction in cardiovascular events. Although reduction of serum cholesterol did not account for all the cardiovascular improvement it played a major role.

(3) National Heart, Lung and Blood Institute Study was randomized and placebo-controlled in which 116 patients were divided into two groups. One group was treated with diet plus placebo and the other was diet plus cholestyramine. Coronary angiograms were carried out before the study and five years later. In the study there was a significant difference in the progression of coronary atherosclerosis between the placebo and cholestyramine group.

(4) Coronary Artery Bypass Graft Study. The relationship of risk factors to the development of atherosclerosis in saphenous vein bypass grafts and the progression of disease in the native circulation was studied. Patients were reviewed 10 years after surgery and it was demonstrated that the likelihood of developing atherosclerosis in the graft was higher in those with a high LDL or VLDL and low HDL cholesterol.
Diet and placebo was compared with diet and gemfibrozil in middle aged men; results showed significant reduction in the level of total cholesterol, LDL cholesterol and triglycerides and marked increase of HDL cholesterol as compared with the placebo group.

Epidemiological studies and clinical trials are remarkably consistent in supporting the projection that for individuals with serum levels initially in the 250-300mg/dl range, each 1% reduction in serum cholesterol level yields approximately 2% reduction in CAD rates.

The absolute magnitude of these benefits in reduction of elevated cholesterol levels is probably greatest in patients who are at high risk because of other risk factors such as cigarette smoking and hypertension.

Low HDL Cholesterol as a Risk Factor

The inverse relationship between lower HDL and greater risk of CHD has been clearly established; although the precise pathogenesis is unclear it would appear that HDL performs a scavenging effect returning excess LDL cholesterol to the liver to be metabolized. Because of this paradox in which increase LDL and decrease in HDL both result in atherosclerosis the term dyslipoproteinemia is now being used.

Causes of decreased serum HDL cholesterol include genetic factors, cigarette smoking, obesity, hypertriglyceridemia, lack of exercise, some cholesterol lowering drugs and other medications (thiazide diuretics, certain beta blockers and anabolic steroids, and progestational steroids).

Factors which increase serum HDL cholesterol are weight reduction in obese subjects, cessation of smoking, correction of hypertriglyceridemia, improving glucose metabolism, reduction to moderate consumption of alcohol, physical training and certain hypolipemic drugs, e.g., nicotinic acid, clofibrate and gemfibrozil.

The Helsinki Heart Study has now established that raising HDL cholesterol decreases the risk of developing CHD.

Hypertriglyceridemia as a Risk Factor

Hypertriglyceridemia results from the accumulation of triglyceride-rich lipoproteins: chylomicrons, VLDL, and/or IDL. The role as a risk factor remains controversial, the most recent conclusions suggests —

1. Hypertriglyceridemia due to excess chylomicrons is not associated with increased risk of atherosclerosis but may cause pancreatitis.

2. Hypertriglyceridemia due to excess VLDL may be associated with increased risk of atherosclerosis if there is excess VLDL-apoB or high LDL cholesterol in the patient or a member of the patient's family.

3. Hypertriglyceridemia due to excess IDL or remnant particles is associated with increased risk of atherosclerosis.

The evaluation of hypertriglyceridemia should be considered in light of other risk factors.

It is uncertain whether the atherogenic effect of elevated triglycerides is mediated through a low HDL, although correcting the elevated triglycerides often increases the serum HDL cholesterol level.

Lipid and Apoprotein Ratios As Risk Factors

Free cholesterol and phospholipid ratio

Recent evidence suggests that increase in the free cholesterol/phospholipid ratio is associated with reversal of cholesterol transport at the cellular level, resulting in a net transport of cholesterol into the cell instead of out of the cell. Patients with atherosclerosis due to hypercholesterolemia, hypertriglyceridemia and dysbeta lipoproteinemia, type II diabetes and patients on hemodialysis all have this metabolic defect but all hypertriglyceremic patients without atherosclerosis do not. Thus, this free cholesterol/phospholipid ratio may become a useful discriminator for identifying patients with atherosclerosis.

Apo B/apo A-1 ratio

Apo A-1 is the major apoprotein in HDL cholesterol and apo B in LDL cholesterol.

Patients with CHD have a lower apo-1 level and have a higher level of apo B than those without the disease.

An elevated Apo B/Apo A-1 ratio indicates increased risk of CHD.

Apo B/apo A-1 ratio has also been reported to be higher in offspring of patients with CHD than in offspring of patients without.

However, good technology is not readily available to measure apoproteins and most of the lipid experts favor using traditional lipid tests (total cholesterol, LDL, cholesterol and total cholesterol/HDL ratio) rather than apoproteins to assess future risk of CHD. Apoprotein levels are not currently available for underwriting.

PRACTICAL APPLICATION OF EVIDENCE

The 1987 report of The National Cholesterol Education Program Expert Panel formulated recommendations from the evidence which has been outlined in this paper. Similar recommendations were proposed by the recent Canadian Consensus Conference and also by panels in Britain and Europe and are worth reviewing.
"Increased blood cholesterol levels or more specifically increased levels of low density lipoprotein (LDL) cholesterol, are causally related to an increased risk of CHD. Coronary risk rises progressively with an increase in cholesterol level, particularly when cholesterol levels rise above 200 mg percent. There is also substantial evidence that lowering total and LDL cholesterol levels will reduce the incidence of coronary heart disease."

The Report recommends a massive public health awareness program using two approaches to lower blood cholesterol levels. The first is directed towards the individual patient that seeks to identify individuals at high risk who will benefit from intensive intervention efforts. The second approach aims to shift the distribution of cholesterol levels in the entire population to a lower range.

In addition to having serum cholesterol measured at least once every five years, it is recommended that all adults should be evaluated for the presence of risk factors including hypertension, cigarette smoking, diabetes mellitus, severe obesity and a history of heart disease in the patient or of premature heart disease in family members.

Patients with high blood cholesterol should undergo lipoprotein analysis when the focus of attention should shift from total cholesterol to LDL cholesterol.

Lipoprotein analysis involves measurement of the fasting levels of total cholesterol, total triglycerides and HDL cholesterol. From these values LDL cholesterol is calculated as follows: LDL cholesterol = total cholesterol – HDL cholesterol – (triglycerides/5).

Patients with high risk LDL cholesterol levels and those with borderline high risk LDL cholesterol levels who have definite CHD, or two other risk factors should have a complete clinical evaluation and begin cholesterol lowering treatment. Part of this evaluation will aim to determine whether the high LDL cholesterol level is secondary to another disease or a drug, and whether or not a familial lipid disorder is present.

Recommended Cholesterol Levels

The Report suggested that “desirable” LDL cholesterol levels are those below 130 mg/dl (4.0 mmol/l). Levels between 130-159 mg/dl are “moderate risk” and levels of 160 mg/dl and over are considered “high risk”. Although LDL cholesterol levels give a more accurate assessment, serum cholesterol is easier to obtain. Serum cholesterol bears a close correlation with LDL cholesterol levels and for practical purposes is therefore used more frequently to reflect lipid status.

Desirable serum cholesterol levels are those that are less than 200mg/dl (5.2 mmol/l). The following table lists serum cholesterol levels and the relative risk of coronary heart disease.

<table>
<thead>
<tr>
<th>Risk of Coronary Heart Disease</th>
<th>Moderate Risk (75-90% centile)</th>
<th>High Risk (&gt;90% centile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>(mg/dl) (mmol/l)</td>
<td>(mg/dl) (mmol/l)</td>
</tr>
<tr>
<td>2-19</td>
<td>&gt; 170 4.4</td>
<td>&gt; 185 4.8</td>
</tr>
<tr>
<td>20-29</td>
<td>&gt; 200 5.2</td>
<td>&gt; 220 5.7</td>
</tr>
<tr>
<td>30-39</td>
<td>&gt; 220 5.7</td>
<td>&gt; 240 6.2</td>
</tr>
<tr>
<td>40+</td>
<td>&gt; 240 6.2</td>
<td>&gt; 260 6.7</td>
</tr>
</tbody>
</table>

Adapted for the NIH Consensus Conference — 1985 Conversion factors: multiply mg/l by 0.02586 to convert to mmol/litre (Standard International units).

Treatment

While low cholesterol diet is the mainstay of treatment, improvement of other modifiable risk factors such as hypertension, cigarette smoking, diabetes and obesity is also important.

Exercise, in addition to providing cardiovascular benefits, decreases serum triglycerides and increases serum HDL cholesterol, but, of course, must be assessed on an individual basis.

Drug therapy has been recommended in high risk or in moderate risk where two or more risk factors are present.

The commoner drugs for lowering cholesterol are:

1. Bile Acid Sequestration — Colestipol (Colestid), Cholestyramine (Questran). By binding the bile acids these drugs force the liver to divert cholesterol away from the blood stream, reducing unwanted LDL and raising HDL.

2. Nicotinic Acid and Analogs. These inhibit synthesis of a precursor of LDL in the liver and block triglycerides breakdown in fatty tissue — reducing LDL and raising HDL.

3. Fibrates — Clofibrate (Atromid S), Gemfibrozil (Lopid). These drugs increase activity of an enzyme which removes triglyceride rich lipoprotein from the blood cutting LDL and raising HDL. Long term administration of Clofibrate is associated with significant toxicity and indications for its use are limited. The long term effect of Gemfibrozil is of course not yet known.

4. HMG — Co A reductive inhibitors — (Lovastatin). This group blocks an enzyme the liver needs to manufacture the body’s own cholesterol, lowering LDL and raising HDL. This is now generally available in the United States and is felt by many to be the most promising of the cholesterol lowering drugs.
5. Others - Probucol (Lorelco). Cuts the levels of both LDL and HDL by unknown mechanisms.

Metamucil has also been shown to lower serum cholesterol by inhibiting its absorption from the bowel.

Polyunsaturated omega 3 fatty acids found in marine or fish oil have been shown to have marked hypotriglyceridemic and mild to moderate hypocholesterolemic effects.

Several human clinical studies suggest that diets high in monounsaturated fat may reduce LDL cholesterol while maintaining HDL cholesterol levels. Olive oil and canola oil are good sources of monounsaturated fat.

**Summation of Evidence in the cholesterol Question**

From a review of the current concepts of lipid metabolism it is established that cholesterol is of fundamental importance in the genesis of CHD. It is also evident that cholesterol is a significant risk factor at lower levels than previously believed and that risk may be reduced by the lowering of serum cholesterol. However, there have been some interesting observations from closer examination of some of the studies.

Although patients who had blood cholesterol lowered by drug therapy suffered fewer heart attacks and coronary deaths, there was no decrease in the overall mortality over the duration of the study. Rather, the same number of people died but from other causes. While accidental and violent death was the main cause of mortality there is also an increased incidence of gastrointestinal cancers, liver problems and cholelithiasis in the Lipid Research Clinic Trial.

There is doubt over reasons for these results and although some attributed it to a chance occurrence it is probably multifactorial.

It has been postulated that these lipid lowering medications cause gastrointestinal symptoms which reinforce patients' belief they have a "dis-ease." They possibly become unconsciously introspective, preoccupied, inattentive or depressed and are therefore more prone to accidents or suicide.

There has also been concern that the recent recommendations regarding universal testing for cholesterol by the National Education Program are too aggressive and will produce unnecessary fear in the population.

However there is agreement that diet is the mainstay in treatment for hyperlipidemia and that cholesterol lowering drugs be reserved for those who do not respond, have several other risk factors present and/or have very high cholesterol levels.

With accumulation of this evidence in lipid hypothesis, a review of the current underwriting philosophy with specific regard to cholesterol's proven role in CHD is timely.

**CURRENT UNDERWRITING PHILOSOPHY**

Underwriting philosophy has undergone major evolution in recent years. The competitive market place of the 1970's encouraged an aggressive approach which undoubtedly compromised the process of risk selection.

This was evident in the 1983 Medical Impairment Study which revealed a greater than anticipated mortality in several of the impairments studied. More specifically, there was a greater than expected mortality in applicants with a history of CHD and also in applicants with a family history of two or more cardiovascular events.

Claims and profits were adversely affected and the return to prudent risk selection has been necessary.

While there is substantial evidence to incriminate cholesterol as a major risk factor there is no consensus as to the practical application of the information to the risk selection process.

At the recent Triennial Meeting of the Board of Insurance Medicine at The Wigwam, there was considerable difference of opinion with the Medical Directors at which cholesterol levels debits or credits would be applied.

We may, however, gain some comfort from a recent survey with physicians in practice which showed that more than 80% of physicians thought that controlling hypertension and discontinuing cigarette smoking were important in cardiovascular disease whereas only 39% thought that lowering serum cholesterol was important.

In a recent blood profile survey involving 29 Life Insurance Companies, one third issued standard insurance when the cholesterol was in the region of 301-450 mg %; most regard this degree of hypercholesteremia as minimally substandard.

When cholesterol exceeds 450 mg %, minimal to moderate substandard was offered by half of the respondents, 40% offered standard and 7% declined.

Credits were used to offset cardiovascular impairments when cholesterol-HDL ratio (62%), cholesterol (40%) and/or triglycerides (70%) are normal.

Triglyceride elevations were less severely treated and the majority would not rate triglyceride readings of less than 500 mg %.

When HDL is low (<35 mg/dl or 1 mmol/l) respondents split evenly between standard and mildly substandard.

**SUGGESTED UNDERWRITING ACTION**

With lipid levels being more readily available because of the more frequent use of Blood Profiles resulting from AIDS, we have an opportunity to apply the current concepts in lipid metabolism to underwriting.
The following suggestions are offered for consideration:

**Cholesterol:** As a rough guideline cholesterol levels of up to 300mg/dl would not be rated in the absence of other risk factors.

Levels of over 300mg/dl without risk factors and 260mg/dl where 2 or more risk factors are present would be debited accordingly, e.g., one table for every 50 mg of elevation above these indices.

Similarly with an absence of risk factors, levels less than 200 mg/dl would be considered for credit.

**HDL-Cholesterol:** The average HDL cholesterol level is in the region of 45 mg/dl. Levels below 35 mg/dl may be considered for debits and above 55 mg/dl for credits, e.g., one table for every 5mg/dl.

**Cholesterol/HDL Ratio:** The average ratio is approximately 5. Increased ratio indicates increased risk of coronary artery disease. Ratios over 10 without other risk factors and over 8 with other risk factors would merit rating.

Ratios below 3 in the absence of risk factors would be eligible for credits.

**Triglycerides:** Hypertriglyceridemia is not clearly established as an independent risk factor for coronary artery disease. However, elevated fasting triglyceride levels over 500 mg/dl with risk factors present and 750 mg/dl without merit debit consideration.

We must also be prepared to review substandard ratings when lipid levels have shown a satisfactory response to appropriate treatment.

Acceptance of this approach by clients, agents and attending physicians to whom we have increasingly to justify our decisions, will be facilitated by the National Education Program.

**CONCLUSIONS**

Cholesterol has been identified as a major risk factor in CHD at lower levels than previously believed.

Although many questions remain unanswered in the role of cholesterol in CHD Medical Directors must provide leadership in responsible risk selection by applying the information which is available to the underwriting process.

I would like to acknowledge the constructive comments by Dr. Len Hertko and Dr. Bob Pokorski in the preparation of this paper.

**References**


**Additional Reading**

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Medicine North America 1987; 2942-2951. — Hyperlipoproteinemia as a Cardiovascular Risk Factor.

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