# FOR YOUR INPHARMATION

PHARMACY NEWSLETTER

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**The Role of Statins in Hypercholesterolemia**

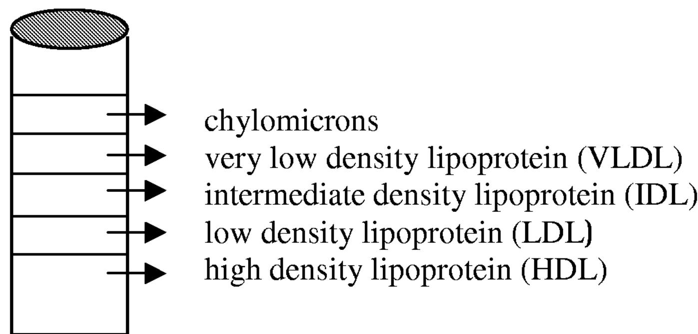
## Introduction

Coronary heart disease (CHD) continues to be the leading cause of death in North America and one-quarter to one-third of people will not survive their first heart attack. Clinical trials have demonstrated the benefits of lowering serum cholesterol levels in both primary (patients with no pre-existing CHD) and secondary (patients with a history of angina or myocardial infarction) prevention settings. The evidence from secondary prevention studies clearly supports the use of cholesterol-lowering strategies to reduce mortality in both men and women, young and old. Recently, the West of Scotland Study demonstrated that pravastatin reduced the incidence of myocardial infarction (MI) and death in middle-aged men with hypercholesterolemia and no history of CHD. Even small reductions in cholesterol are beneficial: for every 1% decrease in cholesterol levels, one can expect a 2% drop in the risk of CHD. Cholesterol accumulation in the vessel wall results in a progressive disorder known as atherosclerosis, which can eventually lead to occlusion of an affected vessel. The ensuing local ischemia may manifest clinically as angina, manifest clinically as angina, myocardial infarction or sudden cardiac death.

## Lipids and Lipoproteins

The two main lipid constituents of blood are cholesterol and triglycerides. Cholesterol is a cell-membrane component of all animal cells as well as a precursor of steroid hormones. Triglycerides (TG) are important in transferring energy from food into cells. Both cholesterol and triglycerides are carried in lipoproteins, which are classified on the basis of their density. A higher content of triglycerides in lipoproteins makes them less dense, while apoproteins (structural proteins) contained within lipoproteins makes them more dense. The least dense particles, chylomicrons, are generally found in the blood after a high-fat meal. (See diagram below)

Total cholesterol = HDL cholesterol + LDL cholesterol+VLDL cholesterol



The most important lipoproteins based on their contribution to CHD are LDL and HDL. LDL is the major cholesterol transport protein in blood. Excess LDL-cholesterol (ie. that which is not used to form bile acids, cell membranes or hormones) will preferentially deposit onto the walls of arteries to promote atherosclerosis, thereby being known as "bad cholesterol". About 1/3 to 1/4 of cholesterol in blood is transported by HDL, which is responsible for removing cholesterol from peripheral tissues and returning it to the liver for disposal. Since it helps to keep arteries unclogged, it is termed "good cholesterol". Lifestyle changes such as smoking cessation, exercise, weight loss, and limiting alcohol intake can help to raise HDL levels and subsequently reduce CHD risk. A HIGH plasma concentration of LDL-cholesterol or triglycerides is EACH a strong risk factor for CHD as is a LOW plasma concentration of HDL.

**Risk Factors**

| **Table I**<br>**Coronary Heart Disease Risk Factors** |
|---|
| *Positive risk factors (↑risk):* |
| • Age (male ≥ 45 ;female ≥ 55, or post-menopause/no hormone replacement therapy) |
| • Current cigarette smoking |
| • Hypertension (BP ≥ 140/90 or on anti-hypertensive drugs) |
| • Family history of premature CHD (MI or sudden death in first-degree relatives - male ≤ 55; female ≤ 65) |
| • Low HDL( < 0.9mmol/L) |
| • High LDL(see Table III) |
| • Diabetes mellitus |
| • Obesity( > 30% overweight) |
| *Negative risk factor(↓ risk) ie. subtract 1 risk factor from the total:* |
| • High HDL( ≥ 1.6mmol/L) |

Risk factors associated with CHD are shown in Table I. Epidemiologic studies have shown that the more risk factors present, the greater the likelihood that an individual will develop CHD during his or her lifetime (Table II). Those at higher risk of developing CHD should receive the most aggressive cholesterol-lowering drug treatments, while in low-risk patients, treatment is often limited to lifestyle modification (such as dietary therapy).

**Table II**
**Risk Stratification**

| *Number of risk factors* | *Risk level* | *Ten year CHD risk* |
|---|---|---|
| ≥4 | Very high | ≥40% |
| 3 | High | ≥20% |
| 2 | Moderate | ≥10% |
| ≤1 | Low | <10% |

## Treatment

Most treatment algorithms recommend diet therapy as the initial step for all patients with elevated cholesterol levels. However, the impact of a lipid-lowering diet varies considerably among individuals. Most patients will see only a modest decrease in LDL-cholesterol as a result of dietary changes, typically a 5-10% reduction. Thus the results of any dietary intervention should be

carefully monitored approximately 4 weeks after initiation.

3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors ("statins") inhibit the enzyme that catalyzes the rate-limiting step in cholesterol synthesis. They are the most highly effective class of drugs for lowering LDL-cholesterol and for this reason are recommended as a first-line therapy in patients with primary hypercholesterolemia when the response to a diet restricted in saturated fat and cholesterol is inadequate (Table III).

**Table III**
**Treatment Guidelines Based on LDL Levels**

| | Diet * | Drugs * | Goal * |
|---|---|---|---|
| Primary prevention<br>No CHD: | | | |
| < 2 risk factors | ≥4.1 | ≥4.9 | <4.1 |
| ≥ 2 risk factors | ≥3.4 | ≥4.1 | <3.4 |
| Secondary prevention<br>Patients with CHD | >2.6 | ≥3.4 | ≤2.6 |

*LDL units in mmol/L

## Adverse Effects

There are intrinsic differences in potency and pharmacokinetics between the statins, but as a class, the HMG-CoA reductase inhibitors have an excellent benefit-to-risk profile. The most serious side effects experienced are related to the liver and skeletal muscle. Patients may complain of muscle pain and have a slight elevation of creatine kinase (CK). Myopathy, characterized by muscle weakness and a CK increase of more than ten times the upper limit of normal, may necessitate discontinuation of the drug. Similarly, marked and persistent elevations in hepatic transaminases (ie. an increase in AST or ALT of more than three times the upper limit of normal) may require drug withdrawal in less than 1.5% of patients on a statin. It is important to note that statin-induced myopathy is dose-related and often caused by CYP3A4 drug interactions or by the combination of a statin with gemfibrozil.

## Choice of Statin

Drug selection should be based not only on cost but also on the extent of cholesterol-lowering needed (Table IV). The drugs with a lower potency require a higher dose to achieve the same reduction in cholesterol. Within the range of currently recommended dosages, atorvastatin has greater LDL and TG lowering effects compared to the other statins; it is also one of the more expensive agents. In contrast, simvastatin, according to a number of pharmacoeconomic studies, is the most cost-effective statin. Fluvastatin may be an appropriate choice when only a 15-25% reduction in LDL-cholesterol is desired, but when the desired reduction in LDL-cholesterol exceeds 25%, it is more efficacious to use another agent. In post-transplant patients receiving cyclosporine, safety has been documented for low doses of lovastatin and simvastatin, but when a higher dosage of statin is indicated for maximal cholesterol-lowering effect, pravastatin should be considered the drug of choice due to a lower incidence of myopathy. Since lovastatin and simvastatin undergo extensive first-pass metabolism by CYP3A4, they should be avoided in combination with interacting drugs (eg. HIV protease inhibitors) due to increased toxicity. With the exception of atorvastatin which can be taken any time of the day due to a long half-life, statins should be taken in the evening since

cholesterol production is greatest at night. It is important to use a statin in conjunction with a restricted diet as well as other risk-reducing strategies, while monitoring patients regularly for clinical efficacy and adverse effects.

**Table IV**

**Comparison of Lipid-Lowering Effects of Statins at Recommended Doses**

| | Average Change From Baseline (%) | | | |
|---|---|---|---|---|
| Drug & Dosage Regimen (mg/day) | LDL | HDL | TG | *Daily Cost ($) |
| Lovastatin (20-80) | 33 | 8 | 13 | 1.42-5.25 |
| Pravastatin (20-80) | 29 | 14 | 25 | 1.34-3.22 |
| Simvastatin (5-40) | 32 | 9 | 14 | 0.96-2.35 |
| Atorvastatin (5-80) | 48 | 7 | 28 | 0.86-4.60 |
| Fluvastatin (20-80) | 23 | 5 | 9 | 0.80-2.25 |
| Cerivastatin (0.2-0.3) | 31 | 7 | 22 | 1.28-1.55 |

*Average cost to Pharmacare –2001 (all statins presently covered).

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