HMG-CoA REDUCTASE INHIBITORS

A review of published clinical trials and pharmacoeconomic evaluations
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* Mr. Baladi was involved in previous drafts until his recent departure from CCOHTA.

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EXECUTIVE SUMMARY

The present study is a review of published clinical trials and pharmaco-economic evaluations of lipid-lowering agents, focusing mainly on HMG-CoA reductase inhibitors. This review is summarized throughout the text by summary points and propositions.

The report discusses the relationship between lipids and coronary events. It then examines the impact of lipid-lowering therapy on coronary events. This is accomplished by evaluating the important clinical trials published to date.

- Based on findings from epidemiological studies, an elevated total cholesterol level increases the risk of experiencing a coronary event. Low HDL and high LDL levels as well as an elevated TC/HDL ratio are also predictors for coronary heart disease.

- Coronary heart disease is a multifactorial disorder and, in addition to the dyslipidemia, other risk factors for CHD must be taken into account when determining treatment goals.

- Before HMG-CoA reductase inhibitors became available, lipid-lowering therapy significantly reduced coronary events (fatal and non-fatal CHD combined) in high risk populations in primary prevention. However, fatal CHD alone and overall mortality had not been shown to be significantly reduced. In secondary prevention, coronary events were significantly reduced and overall mortality was also reduced, although not significantly, by lipid-lowering therapy.

- Greater absolute benefits are more likely to be realized in patients at high risk of experiencing a coronary event. Even though secondary prevention trials demonstrated a larger impact on the incidence of CHD, results have been consistent, showing a decrease in coronary events in both primary and secondary prevention trials.

- There is no conclusive evidence that a low cholesterol level increases the risk of depression, cancer or trauma.

The report also examines the impact of lipid lowering in women, patients less than 35 years old and those over 60 years of age.

- The benefits of lipid-lowering therapy in hypercholesterolemic women with no evidence of CHD have not been determined conclusively. In secondary prevention, women appear to experience the same benefits of lipid lowering as men (i.e., a decrease in coronary events) although the number of participants in clinical trials have been too small to show an effect on mortality.

- The impact of starting lipid-lowering therapies in young hypercholesterolemic patients (i.e., less than 35 years old) is unknown.
• The association between CHD and serum cholesterol in the elderly is not as strong as that found in the middle-aged population. This may be due to the lack of data available on the elderly population. However, it appears to be beneficial to treat the young elderly (60 to 70 years old) with established cardiovascular disease. For those over 70, there is less information to assess the benefit to risk ratio of treatment.

The report provides an overview of the efficacy of HMG-CoA reductase inhibitors.

• All statins decrease total cholesterol and LDL levels, and increase HDL levels.

• Since all statins decrease total cholesterol and LDL levels, and increase HDL levels, although not to the same extent, it may be assumed that all will produce a decrease in coronary events. However, long-term clinical trials investigating lipid-lowering effects on the incidence of coronary events and mortality as primary outcomes have only been conducted with two of the five statins: The West of Scotland Coronary Prevention Study, has shown that pravastatin decreases nonfatal MI and overall mortality significantly in primary prevention patients. Furthermore, a secondary prevention trial, the Scandinavian Simvastatin Survival Study, reports that coronary events (nonfatal MI and fatal CHD) and overall mortality are significantly reduced with simvastatin. Another secondary prevention trial, the Cholesterol and Recurrent Events study, has shown that pravastatin significantly reduces nonfatal MI and fatal CHD in patients having mildly to moderately elevated LDL levels.

• Due to the lack of long-term clinical trials with the other statins and the lack of head to head trials in general, it has not been conclusively determined if some statins produce greater clinical benefits than others.

• Follow-ups in clinical trials have been limited to five years or less. Patients may take these drugs for longer than this period. Long-term safety remains to be established.

• If a statin is required, consideration should be given to choosing a statin based on its ability to lower LDL levels and raise HDL, the patient’s concurrent medical conditions and concomitant drug therapy, and cost. Clinicians must also keep in mind the information available for each statin as well as the generalizability of the evidence from clinical trials to the patient.

The following conclusions can be drawn from compliance studies.

• In actual practice, lipid-lowering therapy is often discontinued within the first year of therapy. Reasons for discontinuance include adverse effects, lack of effectiveness and non-compliance.

A review of pharmacoeconomic studies conducted to date is presented. The conclusions drawn from this are summarized below.

• Lowering lipid levels in secondary prevention will generally be more cost effective than doing so in primary prevention.
• The more likely the chance of experiencing a coronary event, the more cost-effective lipid lowering strategies will be.

• Cost-effectiveness of lipid lowering depends on pre-treatment cholesterol and LDL levels. If other risk factors are the same, the higher the pre-treatment levels, the more cost-effective cholesterol and LDL reduction will be.

• There is no evidence to indicate that one statin is more cost effective than another.
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1. INTRODUCTION

1.1 Background

Lipids are required for repairing cell membranes, for manufacturing vitamins at the cell surface and for synthesizing hormones such as estrogen and testosterone. High density lipoproteins (HDL), low density lipoproteins (LDL), very low density lipoproteins (VLDL) and chylomicrons are responsible for the transport of lipids, primarily triglycerides (TG) and cholesterol, through the plasma. The amount of cholesterol and triglycerides carried by the different lipoproteins varies. VLDL and chylomicrons are rich in triglycerides and LDL particles are the major carriers for cholesterol.

Hypercholesterolemia, hyperlipidemia and hyperlipoproteinemia are terms used to define elevated concentrations of serum cholesterol or lipoproteins. Hyperlipoproteinemia can be due to environmental factors (eg. diet high in cholesterol and saturated fat), genetic factors (eg. familial hypercholesterolemia), or can be secondary to drugs or other disorders such as hypothyroidism and diabetes mellitus.

A great deal of attention is being given to hyperlipidemia ever since a link has been established between cholesterol levels and coronary heart disease (CHD). Elevated levels of LDL and low HDL increase the risk of CHD. The roles of VLDL and triglycerides in CHD are not well established.

Numerous trials, evaluating the relationship between cholesterol reduction and CHD, have shown that decreasing lipid levels results in a decrease in coronary heart disease. However, early studies have failed to show a statistically significant reduction in the incidence of fatal CHD and overall mortality with lipid-lowering therapy. Findings of earlier studies have also raised concerns that cholesterol reduction may have a detrimental effect on mortality from causes other than cardiovascular disease.

Recent trials using selected HMG-CoA reductase inhibitors (commonly known as statins), a newer class of lipid-lowering drugs, have also shown a decrease in coronary events. Moreover, they showed a decrease in overall mortality in the treated group and no differences in mortality due to non-cardiovascular causes in the treated and control groups.

In general, the management of primary hypercholesterolemia (not caused by drugs or other diseases) depends on the individual's level of risk for CHD. For example, high lipid levels in the presence of other risk factors such as cigarette smoking and diabetes place an individual at a higher risk for CHD than having elevated lipid levels alone with no other risk factors.

Diet is recommended as first line therapy or as an adjunct to drug treatment in patients that have not reached treatment goals with diet alone.

Drug treatment should be started immediately in patients with multiple risk factors, with a history of coronary heart disease, or for patients with more severe forms of hypercholesterolemia such as the familial types.
Economic considerations must also be brought to mind for the management of hypercholesterolemia. Resources are limited, and maximum benefits need to be obtained from given budgets. Like any other drug (and any other health technology for that matter), lipid-lowering agents must be used in the most cost-effective manner.

1.2 Objectives

This study was undertaken at the request of the CCOHTA’S Pharmaceutical Advisory Committee. Its primary objectives were:

i) to review the efficacy of HMG CoA reductase inhibitors;
ii) to determine if differences exist between the statins;
iii) to determine which population would most likely benefit from statins
iv) to review the cost and cost-effectiveness of statins.

These objectives were met by: 1) reviewing the current literature including clinical trials, epidemiologic studies, meta-analyses, review articles, and guidelines; and 2) analysing pharmacoeconomic studies and utilization data.

Examining the cost effectiveness (CE) of cholesterol agents would mean (quite legitimately) studying the CE of lipid lowering agents as they compare with other interventions, examining whether HMG CoA reductase inhibitors are a CE alternative, and possibly determining from the class of HMG CoA reductase inhibitor agents, the one which is most cost-effective. As will be evident from the subsequent arguments, no simple answer exists to any of these specific questions. Cost-effectiveness depends on a number of factors and will vary for distinct groups of individuals. Rather than building a model which (although having its own merits) would add another set of CE ratios to the rather long list of already published ones, we decided, in this particular study, to answer the problem in a different manner.

It was decided that this study would concentrate on providing a set of (workable) propositions that would foster taking decisions for using lipid-lowering agents in a cost-effective way so that whatever the budget allocated to cholesterol reduction, it achieves the greatest benefit. This is tantamount to identifying, on the one hand, the particular groups of individuals who are the most likely to benefit from specific treatments, and on the other hand, the drug(s) which will produce the desired effect at minimum cost.

In doing so, the effects of cholesterol reduction on coronary events in general, and the similarities and differences of statins regarding cholesterol reduction, long-term outcomes, adverse events, long-term safety and compliance will be presented.

The present analysis does not consider secondary causes of hyperlipidemia such as diabetes mellitus, chronic renal failure, hypothyroidism and drug-induced hyperlipidemias, nor does it consider the genetic forms of this disorder such as familial hypercholesterolemia and familial combined hyperlipidemia.
1.3 Methods

This study relies on the review of clinical evidence and the pharmacoeconomic literature as well as an examination of market research data.

Extensive literature searches were conducted on the following databases:

- **Medline, Health Planning and Administration, Embase, International Pharmaceutical Abstracts, Economic Literature Index**, 1992-1995. Search for articles on the cost-effectiveness of cholesterol lowering agents. Keywords: anticholesteremic or cholesterol lower or hypercholesterolemia and cost or economic or benefit.
- **HSTAR** (excluding Medline and health references), no date limitation, anticholesteremic agents and cost.
- **Medline**, 1992-1996, limited to human, “Cholesterol and coronary disease” and “meta-analysis or review”.
- **Current Contents**, anticholester* or cholesterol or *statin.
- **Medline, Embase, International Pharmaceutical Abstracts**, hydroxymethylglutaryl coenzyme A reductase inhibitor or hydroxymethylglutaryl CoA reductase or statin or pravastatin or simvastatin or antilipemic agent or hypocholesteremic agent or anticholesteremic agent and class effect.
- **Medline**, 1985-1996, limited to human, coronary disease and cholesterol and meta-analysis or randomized controlled trial.
- **Medline**, 1985-1996, limited to human, coronary disease and cholesterol and mortality or survival.

In addition, the CCOHTA library was extensively searched. Different organizations and groups were contacted to obtain copies of guidelines, position statements or draft documents pertaining to the management of hypercholesterolemia.

Throughout the course of the project the recent literature was scanned using **Current Contents: Clinical Medicine**, and handsearching of journals received at the CCOHTA library. In addition, the references of all articles reviewed were scanned.

Estimates of the use and prescriptions of cholesterol lowering agents and statins have been kindly provided by “Intercontinental Medical Statistics” (IMS) Canada.
2. EPIDEMIOLOGY

2.1 Heart Disease

In 1992, ischemic heart disease accounted for 22% of total deaths and 38% of hospital admissions in Canada. (Heart and Stroke Foundation, 1995) The following table gives the incidence of deaths due to cardiovascular diseases by age and sex.

<table>
<thead>
<tr>
<th>SEX</th>
<th>AGE</th>
<th>all CVD</th>
<th>AMI</th>
<th>IHD</th>
<th>STROKE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>35-54</td>
<td>7.0%</td>
<td>9.2%</td>
<td>7.9%</td>
<td>4.6%</td>
</tr>
<tr>
<td></td>
<td>55-64</td>
<td>13.2%</td>
<td>16.7%</td>
<td>15.2%</td>
<td>8.5%</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>26.9%</td>
<td>30.0%</td>
<td>28.5%</td>
<td>22.4%</td>
</tr>
<tr>
<td></td>
<td>&gt;75</td>
<td>52.2%</td>
<td>43.6%</td>
<td>48.1%</td>
<td>63.7%</td>
</tr>
<tr>
<td>Women</td>
<td>35-54</td>
<td>2.4%</td>
<td>2.4%</td>
<td>2.0%</td>
<td>3.3%</td>
</tr>
<tr>
<td></td>
<td>55-64</td>
<td>5.2%</td>
<td>7.3%</td>
<td>5.8%</td>
<td>4.1%</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>16.2%</td>
<td>32.4%</td>
<td>18.1%</td>
<td>12.7%</td>
</tr>
<tr>
<td></td>
<td>&gt;75</td>
<td>75.6%</td>
<td>67.9%</td>
<td>74%</td>
<td>79.2%</td>
</tr>
</tbody>
</table>

CVD = cardiovascular disease; AMI = acute myocardial infarction; IHD = ischemic heart disease
Reproduced in parts from Heart and Stroke Foundation of Canada: Heart Disease and Stroke in Canada. Ottawa, Canada, 1995.

The risk of dying from cardiovascular diseases increases with age in both men and women, especially after menopause in women. However, women have a lower risk than men for all age groups except after the age of 75 years when the risk is higher.

2.2 Lipid Levels

The prevalence of hyperlipoproteinemia in Canada has been determined in a survey conducted between 1986 and 1990 in nine provinces which included a total of 16,924 participants aged 18 to 74 years: 46 percent of the population had a total cholesterol (TC) level above 5.2 mmol/L, 15% had a LDL level above 4.1 mmol/L, 15% had triglycerides above 2.3 mmol/L and 8% had a HDL level of less than 0.9 mmol/L, threshold values, after which the risk increases. (Connelly et al, 1992)

A higher percentage of men had elevated total cholesterol and LDL levels at ages 45 to 54 years and for women, at ages 55 to 64 years.

The tables below separate the results by age and sex.
### Table 2: Percentage of Canadian Men with Plasma Lipids Above Specified Levels

<table>
<thead>
<tr>
<th>AGE</th>
<th>TC&gt;5.2</th>
<th>TG&gt;2.3</th>
<th>LDL&gt;4.1</th>
<th>HDL&lt;0.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-24</td>
<td>14%</td>
<td>9%</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>25-34</td>
<td>34%</td>
<td>12%</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>35-44</td>
<td>58%</td>
<td>22%</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>45-54</td>
<td>65%</td>
<td>32%</td>
<td>26%</td>
<td>15%</td>
</tr>
<tr>
<td>55-64</td>
<td>61%</td>
<td>26%</td>
<td>21%</td>
<td>15%</td>
</tr>
<tr>
<td>65-74</td>
<td>65%</td>
<td>21%</td>
<td>26%</td>
<td>15%</td>
</tr>
<tr>
<td>All</td>
<td>48%</td>
<td>20%</td>
<td>14%</td>
<td>13%</td>
</tr>
</tbody>
</table>

* in mmol/L  
Reprinted from The Canadian Medical Association Journal 1992;146(11) with permission from the publisher.

### Table 3: Percentage of Canadian Women with Plasma Lipids Above Specified Levels

<table>
<thead>
<tr>
<th>AGE</th>
<th>TC&gt;5.2</th>
<th>TG&gt;2.3</th>
<th>LDL&gt;4.1</th>
<th>HDL&lt;0.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-24</td>
<td>18%</td>
<td>5%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>25-34</td>
<td>23%</td>
<td>5%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>35-44</td>
<td>31%</td>
<td>7%</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>45-54</td>
<td>60%</td>
<td>13%</td>
<td>17%</td>
<td>4%</td>
</tr>
<tr>
<td>55-64</td>
<td>81%</td>
<td>22%</td>
<td>33%</td>
<td>3%</td>
</tr>
<tr>
<td>65-74</td>
<td>80%</td>
<td>21%</td>
<td>40%</td>
<td>5%</td>
</tr>
<tr>
<td>All</td>
<td>43%</td>
<td>11%</td>
<td>14%</td>
<td>4%</td>
</tr>
</tbody>
</table>

* in mmol/L  
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2.3 Risk Factors

In the same survey by Connelly et al, 36 percent of men with a total cholesterol level above 5.2 mmol/L were hypertensive (diastolic blood pressure>90 mmHg), 61% smoked (1 cigarette or more per day), 85% were obese (body mass index\(\geq\)27) and 8% had diabetes.

Of Canadian women with a total cholesterol level above 5.2 mmol/L, 28% were hypertensive, 61% smoked, 70% were obese and 11% had diabetes.

The following table details the prevalence of risk factors in the Canadian population.

<table>
<thead>
<tr>
<th>RISK FACTORS IN MEN</th>
<th>18-24</th>
<th>25-34</th>
<th>35-44</th>
<th>45-54</th>
<th>55-64</th>
<th>65-74</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>33%</td>
<td>35%</td>
<td>32%</td>
<td>31%</td>
<td>22%</td>
<td>16%</td>
<td>30%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2%</td>
<td>9%</td>
<td>15%</td>
<td>25%</td>
<td>33%</td>
<td>27%</td>
<td>16%</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>14%</td>
<td>34%</td>
<td>58%</td>
<td>65%</td>
<td>61%</td>
<td>65%</td>
<td>48%</td>
</tr>
<tr>
<td>Obesity</td>
<td>18%</td>
<td>27%</td>
<td>37%</td>
<td>45%</td>
<td>47%</td>
<td>39%</td>
<td>35%</td>
</tr>
<tr>
<td>(\geq)1 risk factors(^a)</td>
<td>39%</td>
<td>57%</td>
<td>72%</td>
<td>80%</td>
<td>79%</td>
<td>80%</td>
<td>64%</td>
</tr>
<tr>
<td>(\geq)2 risk factors(^a)</td>
<td>5%</td>
<td>17%</td>
<td>28%</td>
<td>34%</td>
<td>30%</td>
<td>24%</td>
<td>22%</td>
</tr>
</tbody>
</table>

\(^a\) regular smoker, high blood pressure, total cholesterol\(>5.2\) mmol/L

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<table>
<thead>
<tr>
<th>RISK FACTORS IN WOMEN</th>
<th>18-24</th>
<th>25-34</th>
<th>35-44</th>
<th>45-54</th>
<th>55-64</th>
<th>65-74</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>32%</td>
<td>34%</td>
<td>33%</td>
<td>26%</td>
<td>18%</td>
<td>12%</td>
<td>28%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1%</td>
<td>3%</td>
<td>6%</td>
<td>19%</td>
<td>32%</td>
<td>38%</td>
<td>13%</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>18%</td>
<td>23%</td>
<td>31%</td>
<td>60%</td>
<td>81%</td>
<td>80%</td>
<td>43%</td>
</tr>
<tr>
<td>Obesity</td>
<td>13%</td>
<td>19%</td>
<td>27%</td>
<td>32%</td>
<td>42%</td>
<td>45%</td>
<td>27%</td>
</tr>
<tr>
<td>(\geq)1 risk factors(^a)</td>
<td>41%</td>
<td>49%</td>
<td>56%</td>
<td>74%</td>
<td>89%</td>
<td>89%</td>
<td>63%</td>
</tr>
<tr>
<td>(\geq)2 risk factors(^a)</td>
<td>6%</td>
<td>9%</td>
<td>14%</td>
<td>28%</td>
<td>36%</td>
<td>37%</td>
<td>19%</td>
</tr>
</tbody>
</table>

\(^a\) regular smoker, high blood pressure, total cholesterol\(>5.2\) mmol/L

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3. CLINICAL EVIDENCE

3.1 Lipids and Coronary Heart Disease

3.1.1 Atherosclerosis and CHD

Coronary atherosclerosis is the formation of plaques containing a lipid-rich core and a thin fibrous cap with inflammatory cells in coronary arteries. Coronary events due to atherosclerosis are usually related to the disruption or fissure of one or more plaques with the formation of a thrombus that occludes the artery. (Ambrose et Fuster, 1997)

3.1.2 Dyslipidemia as a Risk Factor for CHD

The relationship between lipids and coronary events has been evaluated for many decades.

In the Framingham Study, the risk for coronary heart disease (CHD) was shown to be proportional to serum cholesterol levels in subjects aged 30 and over. (Kannel et al, 1971) The incidence of CHD increased with age in men and women, with more men developing CHD than women.

The Multiple Risk Factor Intervention Trial (MRFIT) showed that the relationship between serum cholesterol and CHD mortality was continuous and graded in men 35 to 57 years old. Above a serum cholesterol level of 4.68 mmol/L, CHD mortality increased progressively with increasing cholesterol level, up to 6.54 mmol/L. Above this level, CHD mortality was markedly increased. (Stamler et al, 1986; Martin et al, 1986) Similarly, a follow-up study of Framingham showed an association between cholesterol levels and cardiovascular disease mortality in men and women younger than 50 years old. (Anderson et al, 1987)

The relationship between the different lipoproteins and CHD was later determined in various studies. The Framingham Study showed a statistically significant inverse relationship between HDL levels, and a positive association with LDL levels, with CHD incidence and CHD death in both men and women. In men, triglycerides were not correlated to CHD risk. In women, triglycerides were related to CHD risk when other risk factors were not considered. (Castelli et al, 1986; Gordon et al, 1977 and 1981)

Recent data however suggest that there is an independent association between triglycerides and future coronary events among individuals with a high LDL/HDL ratio. (Assmann et al, 1996; Stampfer et al, 1996) Similar findings were obtained in a meta-analysis of population-based, prospective studies which showed that triglyceride is a risk factor for cardiovascular disease in both men and women, independent of HDL levels. (Hokanson et Austin, 1996)

Another study, using data from the Lipid Research Clinics Prevalence and Follow-up Studies, showed that a decrease in HDL and increases in LDL and triglycerides were associated with an increase in CHD mortality. When looking at TC/HDL and LDL/HDL ratios, a rise in ratio was associated with an increase in CHD mortality. This study also showed that total cholesterol measurements alone were not very sensitive and that HDL levels were important to consider when evaluating risk. Finally, it recommended using TC/HDL ratios as a tool for identifying CHD risk. (Grover et al, 1994)

**Summary point 1:** Based on findings from epidemiological studies, an elevated total cholesterol level increases the risk of experiencing a coronary event. Low HDL and high LDL levels as well as an elevated TC/HDL ratio are also predictors for coronary heart disease.
3.2 **Assessment of CHD Risk**

3.2.1 **Risk Factors**

The Framingham Study looked at the relationship between risk factors and cardiovascular disease (CVD). Serum cholesterol levels, systolic blood pressure (SBP) and cigarette smoking were important factors in the development of cardiovascular disease, especially CHD in men. (Kannel et al, 1976)

In the MRFIT study, CHD mortality was higher in cigarette smokers and in individuals with a diastolic blood pressure (DBP) $\geq$ 90 mm Hg compared to non-smokers and to individuals with a DBP $< 90$ mm Hg respectively at comparable cholesterol levels. (Stamler et al, 1986)

Based on an extensive review of the literature, risk factors have been identified in the Canadian guidelines entitled “*Detection and Management of Hypercholesterolemia*” (Working Group on Hypercholesterolemia and other Dyslipidemias, draft March 1997):

- age: male $\geq$ 45 years; female $\geq$ 55 years or post-menopausal not on hormone replacement therapy
- diabetes mellitus
- family history of premature CHD in a first degree relative (males $\leq$ 55; females $\leq$ 65)
- smoking
- hypertension (SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg) or patients receiving antihypertensive medication
- HDL levels $\leq$ 0.9 mmol/L or LDL/HDL ratio $> 5.0$
- left ventricular hypertrophy

However, it is unclear how risk factors interact to produce atherosclerotic lesions. One hypothesis is that lipoproteins, which would normally enter and leave the inner layer of the arterial structure, are for some reason retained at certain sites. Increased quantities of lipoproteins along with an increase in tissue permeability would augment this process. Risk factors such as smoking, would somehow contribute to this through different mechanisms such as enhancing the tissue permeability. (Maher et al, 1997)

3.2.2 **Goals of Treatment**

The Canadian guidelines identify the 10-year risk of CHD based on the number of risk factors present and give targeted lipid values based on these. For example, a person with 4 risk factors or more or with a history of cardiovascular disease is at very high risk (≥ 40%) of experiencing CHD in the next ten years. In such cases, the target LDL level should be 2.5 mmol/L and TC/HDL ratio 4.

The table below gives details on the risk of CHD and targeted lipoprotein levels.
Table 6: Goals of Therapy (men aged 40 to 70 years; women aged 50 to 70 years)

<table>
<thead>
<tr>
<th>Number of Risk Factors</th>
<th>10 year risk of CHD</th>
<th>Criteria for Drug Therapy</th>
<th>Treatment Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LDL mmol/L</td>
<td>TC/HDL</td>
</tr>
<tr>
<td>≥ 4 or presence of CHD</td>
<td>very high (&lt;40%)</td>
<td>&gt;3.5</td>
<td>&gt;5</td>
</tr>
<tr>
<td>3</td>
<td>high (20-39%)</td>
<td>&gt;4.5</td>
<td>&gt;6</td>
</tr>
<tr>
<td>2</td>
<td>moderate (10-19%)</td>
<td>&gt;5</td>
<td>&gt;7</td>
</tr>
<tr>
<td>≤ 1</td>
<td>low (&lt;10%)</td>
<td>&gt;6</td>
<td>&gt;8</td>
</tr>
</tbody>
</table>

Based on a presentation at the International Conference of Preventive Cardiology, Montreal, Canada, July 1997. Reproduced with permission.

Attempts should also be made to alter modifiable risk factors and encourage lifestyle changes in patients. Smoking cessation and blood pressure control have been shown to have a positive impact on the cardiovascular risk profile. (Sytkowski et al, 1990) Weight reduction and regular exercise are also desirable.

**Summary point 2:** Coronary heart disease is a multifactorial disorder and, in addition to the dyslipidemia, other risk factors for CHD must be taken into account when determining treatment goals.

### 3.3 The Effects of Lipid Lowering

Many trials have studied the effect of lipid lowering on the incidence of morbidity and mortality from cardiovascular disease. Cholesterol reduction is associated with a decrease in coronary morbidity and mortality. Clinical benefits are usually seen within two years of starting therapy. Studies have been performed both in individuals with no underlying heart disease (primary prevention trials) and individuals with pre-existing clinical CHD (secondary prevention trials). Even though secondary trials demonstrated a larger impact on the incidence of CHD because the number of events are much higher, results have been consistent, showing a decrease in coronary events in both primary and secondary trials. Mortality from noncardiovascular causes however, has been shown to be increased in both observational studies and lipid lowering trials. The following sections describe some of the most important primary and secondary prevention trials conducted to date with an emphasis on trials using a statin drug.
3.3.1 Primary Prevention Trials

a) Non-statin drugs

Patients with no history of cardiovascular disease have a much lower risk of experiencing or dying from a coronary event. Lipid lowering in these patients was evaluated in trials such as the Lipid Research Clinics Coronary Primary Prevention (LRC CPP) Trial and the Helsinki Heart Study. Although both of these studies showed a significant decrease in coronary events (fatal and non-fatal CHD combined), fatal CHD and overall mortality were not significantly reduced.

In the LRC CPP trial, 3,806 men aged 35 to 59 years with total cholesterol of 7.6 mmol/L were randomized to receive cholestyramine 24 g/day or placebo. The average follow-up was 7.4 years. The primary end-points measured were definite CHD death and/or definite nonfatal MI. Total cholesterol levels and LDL levels were decreased by 13% and 20% in men at high risk for CHD and treated with diet plus cholestyramine compared to 5% and 8% for the placebo group. The treated group had a 19% relative risk reduction in non-fatal MI and a 24% relative risk reduction in fatal CHD. Overall mortality was reduced (7% relative risk reduction; (90% CI: -23 to 30%), but not significantly. (Lipid Research Clinics Program, 1984)

In the Helsinki Heart Study, 4,081 men aged 40 to 55 years were randomized to gemfibrozil 600 mg twice daily or placebo for 5 years. The primary end-points measured were fatal and nonfatal MI and cardiac death. Treatment with gemfibrozil decreased total cholesterol levels by 10% and LDL levels by 11%, and increased HDL levels by 10%. Clinical benefits were seen after one to two years of therapy. A 34% relative risk reduction (95% CI: 8 to 53%; p<0.02) in incidence of coronary events (non-fatal MI and fatal CHD combined) were obtained. Although triglycerides were decreased by 35%, it did not have a statistically significant effect on CHD. Overall mortality was slightly, but not significantly, increased. (Manninen et al, 1988)

A meta-analysis of primary prevention trials by Muldoon et al (1990) showed that mortality from CHD was reduced (OR:0.85; 95% CI: 0.69 to 1.05; p=0.06 one tailed) in men receiving lipid-lowering treatment. However, overall mortality was higher in the treated group (OR:1.07; 95% CI: 0.94 to 1.21; p=0.33) due to an increase in noncardiovascular deaths. When analysing diet and drug trials separately, cholesterol reduction was associated with a significant decrease in fatal CHD in the drug group (OR:0.78; 95% CI: 0.59 to 1.03; p=0.04 one tailed) and a non-significant decrease in the diet group (OR:0.95; 95% CI: 0.69 to 1.30; p=0.6 one tailed).

b) Statin Drugs

The only primary prevention trial evaluating a statin was the West of Scotland Coronary Prevention Study (WOS). (Shepherd et al, 1995)

The WOS compared pravastatin 40 mg daily to placebo in a double-blind, randomized control trial involving 6,595 men with no history of cardiovascular disease and a mean baseline total cholesterol of 7 mmol/L, LDL level of 5 mmol/L and TC/HDL ratio of 6.2. The average follow-up period was 4.9 years. The primary end-points measured were the occurrence of nonfatal myocardial infarction or death from coronary heart disease as a first event. LDL levels were decreased by 26% and HDL levels increased by 5%. Clinical benefits were apparent after 6 months of drug therapy.
The table below summarizes the results of the study.

### Table 7: Main findings of the West of Scotland study

<table>
<thead>
<tr>
<th>OUTCOME MEASURED</th>
<th>PLACEBO (n=3,293)</th>
<th>PRAVASTATIN (n=3,302)</th>
<th>SIGNIFICANCE LEVEL</th>
<th>RELATIVE RISK REDUCTION</th>
<th>ABSOLUTE RISK REDUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal MI (definite)</td>
<td>204 (6.5%)</td>
<td>143 (4.6%)</td>
<td>p&lt;0.001</td>
<td>31% (CI:15 to 45)</td>
<td>1.9%</td>
</tr>
<tr>
<td>Death from CHD (definite)</td>
<td>52 (1.7%)</td>
<td>38 (1.2%)</td>
<td>p=0.13</td>
<td>28% (CI:-10 to 52)</td>
<td>0.5%</td>
</tr>
<tr>
<td>Death from all cardiovascular causes</td>
<td>73 (2.3%)</td>
<td>50 (1.6%)</td>
<td>p=0.033</td>
<td>32% (CI:3 to 53)</td>
<td>0.7%</td>
</tr>
<tr>
<td>Death from non-cardiovascular causes</td>
<td>62 (1.9%)</td>
<td>56 (1.7%)</td>
<td>p=0.54</td>
<td>11% (CI:-28 to 38)</td>
<td>0.2%</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>135 (4.1%)</td>
<td>106 (3.2%)</td>
<td>p=0.051</td>
<td>22% (CI:0 to 40)</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

CI = 95% confidence interval
Note: These results are over approximately 5 years.

It should be noted that the study was carried out in men 45 to 64 years of age and the majority of the participants were at high risk of cardiovascular disease. The results are not necessarily applicable to women, young subjects, the elderly, and to those with hypercholesterolemia but no other risk factors.

### 3.3.2 Secondary Prevention Trials

#### a) Non-statin Interventions

Several trials such as the Coronary Drug Project and the Program on the Surgical Control of the Hyperlipidemias (POSCH) have evaluated the effect of lipid reduction in hyperlipidemic patients with established coronary disease.

The efficacy of clofibrate and niacin were evaluated in the Coronary Drug Project. 8,341 men aged 30 to 64 years were randomized to one of six treatment groups: conjugated estrogens 2.5 mg/day, conjugated estrogens 5 mg/day, clofibrate 1.8 g/day, dextrothyroxine 6 mg/day, niacin 3 g/day or placebo. Nearly half the patients had a total cholesterol level over 6.4 mmol/L. Length of follow-up ranged from 5 to 8.5 years. Primary end-point of interest was total mortality. Patients randomized to dextrothyroxine and estrogen were dropped from the study prematurely when it became evident that they were experiencing a high rate of adverse events. (Coronary Drug Project Research Group, 1974)

Clofibrate and niacin did not significantly reduce mortality from CHD and total mortality. At five year, the percentages of death in the placebo group was 20.9% compared to the clofibrate group 20.0% (z=-0.60) and the niacin group 21.2% (z=0.19). (The Coronary Drug Project Research Group, 1975) Nine years after termination of the trial, overall mortality in the clofibrate group was similar to that of the placebo group.
However, the benefits of niacin extended beyond treatment, with mortality 11% lower than the placebo group (52.0% for the niacin group compared to 58.2% for the placebo group; p=0.0004). (Canner et al, 1986)

The POSCH study compared surgery (partial ileal bypass) plus diet to diet alone in 838 men and women between the ages of 30 to 64 years. Average follow-up was 9.7 years. Baseline total cholesterol was 6.5 mmol/L (average LDL level of 4.6 mmol/L and average HDL level of 1.0 mmol/L). Surgery decreased cholesterol levels by 23% and LDL level by 37% and increased HDL level by 4% more than the diet group alone, resulting in significantly less coronary events (relative risk reduction of 35% for fatal and non-fatal CHD combined; p<0.0001). Although not statistically significant, there were 28% fewer deaths due to CHD (p=0.113) and a 22% relative risk reduction in overall mortality (p=0.164). (Campos et al, 1992)

However, the use of HMG-CoA reductase inhibitors results in higher reduction in cholesterol and LDL levels, and surgery is now rarely performed.

b) Statin Drugs

The Scandinavian Simvastatin Survival Study (4S) evaluated a statin drug in hyperlipidemic patients in secondary prevention. (Scandinavian Simvastatin Survival Study Group, 1994)

The 4S study compared 20 to 40 mg of simvastatin once daily to placebo in 4,444 men and women aged 35 to 70 years with a history of angina or MI and a baseline total cholesterol of 5.5 to 8 mmol/L (average LDL level of 4.87 mmol/L and TC/HDL ratio of 5.7) in a randomized double blind trial over a period of 5.4 years. The primary outcome measured was mortality. LDL levels were decreased by 35% and HDL levels were increased by 8%. Clinical benefits started to be seen after one year of continuous therapy.

Table 8 outlines the main results of the study.

<table>
<thead>
<tr>
<th>OUTCOME MEASURED</th>
<th>PLACEBO (n=2,223)</th>
<th>SIMVASTATIN (n=2,221)</th>
<th>RELATIVE RISK</th>
<th>RELATIVE RISK REDUCTION</th>
<th>ABSOLUTE RISK REDUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite acute MI (non-fatal)</td>
<td>270 (12.1%)</td>
<td>164 (7.4%)</td>
<td>0.63 (CI:0.54-0.73)</td>
<td>37%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Coronary deaths</td>
<td>189 (8.5%)</td>
<td>111 (5.0%)</td>
<td>0.58 (CI:0.46-0.73)</td>
<td>42%</td>
<td>3.5%</td>
</tr>
<tr>
<td>All cardiovascular deaths</td>
<td>207 (9.3%)</td>
<td>136 (6.1%)</td>
<td>0.65 (CI:0.52-0.80)</td>
<td>35%</td>
<td>3.2%</td>
</tr>
<tr>
<td>All non-cardiovascular deaths</td>
<td>49 (2.2%)</td>
<td>46 (2.1%)</td>
<td>0.94 (CI not reported)</td>
<td>5% (Not significant)</td>
<td>0.1%</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>256 (11.5%)</td>
<td>182 (8.2%)</td>
<td>0.70 (CI:0.58-0.85)</td>
<td>30%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

CI =95% confidence interval
Note: Results are over more than 5 years.
Also, patients treated with simvastatin were less likely to undergo coronary surgery or angioplasty (relative risk of 0.63; 95% CI: 0.54-0.74). There was a 30% relative risk reduction in stroke (relative risk 0.70; 95% CI: 0.52-0.96; p=0.024). Patients aged 60 to 70 years old and women had significantly fewer coronary events (see sections 3.4 and 3.6).

Contrary to other secondary prevention trials that had failed to show a statistically significant reduction in total mortality, the 4S had a decrease in total mortality due to a reduction in coronary death (p<0.01). Mortality from noncardiovascular causes was similar in both the treated group and the control group.

If extrapolating results of the 4S study to North Americans, it should be noted that patients in the 4S study had an average cholesterol level of 6.7 mmol/L and 37% of study participants were taking ASA regularly.

### 3.3.3 Meta-analyses of Combined Primary and Secondary Prevention Trials

Truswell (1994) pooled the results of 14 dietary trials evaluating CHD or death as the endpoints in both patients with no history of CHD (primary prevention) and in patients with established CHD (secondary prevention). Trials ranged from one year to 12 years duration and included between 52 to 57,460 participants. Dietary advice was different among trials. There were significantly fewer total deaths (OR: 0.94) and CHD events (OR: 0.87) in the treatment group. Analysing results from secondary prevention trials alone or primary prevention trials alone, showed a reduction in total deaths and CHD events, but these findings were not significant.

Other meta-analyses combining primary and secondary prevention trials of both diet and drug trials showed a significant reduction in CHD mortality but not total mortality. (Yusuf et al, 1988; Holme, 1990; Law et al (b), 1994)

A meta-analysis by Gould et al (1995) showed that mortality from CHD and total mortality were significantly reduced when combining results from primary prevention trials and secondary prevention trials of both dietary and pharmacological interventions. Thirty-five trials (including 2 trials with lovastatin) were included in the meta-analysis. They had to be randomized controlled trials of a duration of 2 years or more. A 10% reduction in cholesterol concentration significantly reduced CHD mortality by 13% (p<0.002) and total mortality by 10% (p<0.05). Pooling data from secondary prevention trials only, gave similar results. Although not statistically significant, mortality from CHD and total mortality were decreased when combining the results of primary prevention trials only. In this particular meta-analysis, the risk of noncardiovascular death was not related to lipid reduction.

It should be noted that the results vary between meta-analyses due to the inclusion of different trials, inadequate power, and heterogeneity among the trials.

In summary, it can be said that:

**Summary point 3:** Lipid-lowering therapy reduces the risk of experiencing a coronary event.

**Summary point 4:** Clinical benefits occur within two years of starting therapy.
Summary point 5: Greater absolute benefits are more likely to be realized in patients at high risk of experiencing a coronary event. Even though secondary prevention trials demonstrated a larger impact on the incidence of CHD, results have been consistent, showing a decrease in coronary events in both primary and secondary prevention trials.

3.3.4 Noncardiovascular Deaths

Some epidemiological studies have demonstrated that a low cholesterol level was associated with an increase in certain types of cancer, hemorrhagic stroke or trauma. Others have failed to show these associations. Some drug trials have also shown that the benefits of cholesterol reduction might be offset by an increase in deaths caused by factors other than cardiovascular disease when comparing the intervention group to the control group.

Some investigators have explained this as a chance finding, others have proposed that the cholesterol reduction produces these results, and still others have blamed the drugs themselves as causing these adverse events.

a) Epidemiological Studies

No significant excess of noncardiovascular mortality could be demonstrated at low total cholesterol concentration in a cohort study of 23,000 men and 26,000 women aged 30 to 54 years old. (Verschuren and Kromhout, 1995) The same observations were made in the British United Provident Association (BUPA) study. (Law et al, 1994)

However, the Honolulu Heart Program cohort study determined the relationship between serum cholesterol levels and overall mortality to be U shaped. At low cholesterol levels, noncardiovascular mortality was increased. In this study, the excess in mortality rates was due to cancer and hemorrhagic strokes. (Frank et al, 1992)

The MRFIT had similar findings. A low serum cholesterol was associated with an increased risk of intracranial hemorrhage, death from cancer of the liver and pancreas, suicide and alcoholism. There was no correlation between cholesterol levels and deaths from colon cancer. (Neaton et al, 1992)

In the Framingham Study, a low LDL level increased the risk of hemorrhagic stroke in women. (Gordon et al, 1981) As well, there was an inverse association between cholesterol levels and incidence of cancer, particularly colon cancer in men. (Williams et al, 1981) In contrast, a Swedish study that followed patients for 15 years, demonstrated the opposite: a high cholesterol level was associated with an increase risk of colon and rectal cancer. (Tornberg et al, 1986)

There has also been a concern that people with low cholesterol levels were more prone to depression and suicide. One group established a link between cholesterol levels and serotonin levels. Untreated men with low serum cholesterol had lower plasma serotonin levels, suggestive of an altered serotonin metabolism. This agrees with earlier studies done on primates showing that monkeys with low cholesterol levels had lower central serotonin metabolism. The authors concluded that, since low serotonin levels have been observed in patients experiencing depression and suicide, it may be that a low serum cholesterol affects serotonin concentration. (Steegmans et al, 1996)
Morgan et al (1993) demonstrated that depressive symptom scores were significantly and inversely correlated with cholesterol levels. Suicide risk was increased with elevated cholesterol levels in the Honolulu Heart Program. (Irribarren et al, 1995) Finally, other cohort studies determined that depression, suicide or mortality from accidents were not related to serum cholesterol levels. (Strandberg et al, 1992; Brown et al, 1994; Vartiainen et al, 1994; Freedman et al, 1995)

b) Drug Trials

There were also concerns that lipid-lowering drugs may cause adverse events.

In the W.H.O. clofibrate trial, it was determined that there was an increase in noncardiovascular mortality in the clofibrate group. When data was analysed 4.3 years after the trial, the increase was still apparent but had levelled off. The study had two control groups, one of which had participants with low cholesterol. This control group also had an increase in noncardiovascular deaths and mortality from all causes but not to the same extent as the treatment group. (W.H.O. Cooperative Trial, 1980)

The meta-analysis by Gould et al (1995) demonstrated that the use of hormones or fibrates increased the risk of noncardiovascular mortality and overall mortality. When the meta-analysis excluded studies with hormones or fibrates, the risk of noncardiovascular mortality was not increased with cholesterol reduction.

In a meta-analysis by Smith et al (1993), an increase in mortality from noncardiovascular causes was seen in drug trials but not in diet trials. Also, people at high risk of death from coronary heart disease were more likely to benefit from cholesterol reduction. Those at low risk experienced adverse treatment effects which outweighed the benefits of cholesterol lowering on CHD.

In the West of Scotland (pravastatin), the 4S (simvastatin) and the CARE (pravastatin) studies, the incidence of noncardiovascular deaths were similar for the intervention and placebo groups. However, post-trial follow-up of patients is required to fully understand the long-term impact of these drugs on mortality, as it was done in the W.H.O. clofibrate trial and the Coronary Drug Project.

In the meta-analysis by Muldoon et al (1990), there was a significant increase in deaths due to cancer and other illnesses. When the W.H.O. clofibrate trial was excluded, this association was lost.

Other meta-analyses showed no differences between the incidence of cancer in patients assigned to cholesterol-lowering treatment and the control group. (Davey Smith and Pekkanen, 1992; Law et al (a), 1994)

The LRC (cholestyramine) and the Helsinki (gemfibrozil) trials had an excess number of deaths from trauma such as violent deaths and accidents, although these findings were not statistically significant.

Simvastatin did not affect emotional well-being and lovastatin did not cause mood disturbances in two separate trials. (Wardle et al, 1996; Downs et al, 1993).
Finally, a review of meta-analyses (not including statin drugs) conducted by the United States General Accounting Office (1996) showed that there was a statistically significant increase in non-CHD deaths in treated patients with no evidence of coronary disease. Similarly, there was an increase in non-CHD deaths within secondary prevention trials but this increase was not statistically significant. (See Table 9)

**Summary point 6:** There is no conclusive evidence that a low cholesterol level increases the risk of depression, cancer or trauma. The increase in noncardiovascular deaths seen in some clinical trials may be related to the use of certain drugs such as clofibrate (although the evidence to support this is very weak) and not to cholesterol reduction itself. In any case, there is no consistent relationship between a low cholesterol level and noncardiovascular deaths.

### 3.3.5 Overall Mortality

As described previously, primary prevention studies have not shown that lipid reduction had an impact on overall mortality. In many trials, the reduction in CHD deaths was countered by an increase in noncardiovascular deaths. However, new evidence such as that obtained in the WOS (pravastatin) study shows that cholesterol reduction decreases the morbidity and mortality associated with CHD with no increases in noncardiovascular mortality, thus reducing overall mortality.

In secondary prevention, recent information obtained from the 4S (simvastatin) study has shown that cholesterol reduction is associated with a statistically significant decrease in overall mortality and a lack of effect on noncardiovascular mortality.

### 3.3.6 Angiographic Studies

Numerous trials (Lifestyle Heart Trial, Ornish et al 1990; FATS, Brown et al 1990; STARS, Watts et al, 1992; MARS, Blackenhorn et al, 1993; ACAPS, Furberg et al, 1994; SCRIIP, Haskell et al, 1994; CCAIT, Waters et al, 1994; MAAS, MAAS Investigators, 1994; REGRESS, Jukema et al, 1995; PLAC I, Pitt et al, 1995; Plac II, Crouse et al, 1995; CLAS, Azen et al, 1996; LCAS, Herd et al, 1997; and BECAIT, Ericsson et al, 1996) have evaluated the effects of lipid reduction (with or without risk factor modification) on atherosclerosis. Although these studies differed in terms of duration (trials lasted from one year to five years), selection of patients, type of intervention and type of measurements used to assess angiographic changes, they showed that modification of lipid levels altered the progression of coronary plaques, promoted their regression, or both (See section 4.2). The increases in lumen diameter were small. In several of these trials, clinical benefits were seen early on after initiation of therapy and were not in proportion with the reduction in angiographic coronary artery disease. Angiographic changes were not seen until after many years of treatment. In most studies, there was no correlation between severity of lesions and the risk of experiencing a future coronary event. Thus, it has been suggested that there may be some other mechanisms of action responsible for the benefits seen with lipid-lowering therapy. (Brown et al, 1993; Bjelajac et al, 1996; Levine et al, 1995) (See section 4.3)

**Summary point 7:** Angiographic studies show that lipid lowering induces the regression of atherosclerotic lesions and inhibits their progression but does not account for all of the clinical benefits.
3.3.7 **Patients with Mildly to Moderately Elevated Cholesterol Levels**

Several studies have evaluated the benefits of cholesterol reduction in patients with mildly to moderately elevated total cholesterol and LDL levels. (N.B. Levels at which to initiate treatment and LDL levels to be targeted are based on whether the population is being treated for primary vs. secondary prevention and the presence of risk factors. So, what is considered “normal” will vary according to the population treated.) (See section 3.2.2) However, in these studies, although total cholesterol or LDL levels were not very high, it should be noted that the TC/HDL or LDL/HDL ratios were elevated.

**Angiographic Trials**

The Cholesterol Lowering Atherosclerosis Study (CLAS) and the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT) did subgroup analyses of patients with normal to mildly elevated cholesterol. Baseline total cholesterol levels were less than 6.21 mmol/L and 6.36 mmol/L respectively. In the CLAS (colestipol/niacin) study, treatment effects were as significant as that of patients with elevated cholesterol. In CCAIT (lovastatin), there was a significant trend toward delayed progression of atherosclerosis. (Brown et al, 1995)

Another angiographic study specifically designed to measure cholesterol reduction in patients with “normal” cholesterol was the Harvard Atherosclerosis Reversibility Project (HARP) study. Seventy-nine participants with a mean average baseline total cholesterol level of 5.48 mmol/L (4.7-6.5 mmol/L) and baseline TC/HDL ratio of more than 4 were randomized to placebo or active treatment (niacin, cholestyramine, gemfibrozil and/or a statin). After 2.5 years of treatment, lowering plasma lipids was not associated with any benefits on coronary lesions. (Sacks et al, 1994)

The Lipoprotein and Coronary Atherosclerosis Study (LCAS) measured the rate of progression and the frequency of regression of coronary atherosclerosis in 429 patients with CHD and mild to moderately elevated LDL levels (range 2.9 to 4.9 mmol/L). Patients were randomized to fluvastatin 20 mg twice daily or placebo and followed for 2.5 years. All patients with LDL levels above or equal to 4.1 mmol/L received cholestyramine 8 g/day. Progression of atherosclerosis was slowed and regression of plaques was seen. Although the study was not designed to detect differences in clinical events, there was a trend toward decreased coronary events. (Herd et al, 1997)

**Clinical Trials**

The Cholesterol and Recurrent Events (CARE) study was a randomized, double-blind, placebo-controlled 5 year trial comparing pravastatin 40 mg to placebo in 4,159 North American men and women with a history of MI, an average total cholesterol of 5.4 mmol/L and a LDL level between 3.0 and 4.5 mmol/L. Baseline TC/HDL ratio was greater than 5, which is considered high. Clinical benefits were seen after 2 years of therapy. LDL levels were decreased by 32%. Fatal CHD and nonfatal MI combined was significantly reduced in the treatment group (13.2% incidence in the placebo group vs 10.2% incidence in the pravastatin group for a 3% absolute risk reduction and a 24% relative risk reduction, 95% CI: 9-36% p=0.03). Nonfatal MI were reduced by 23% (p=0.02) and CHD death by 20% (p=0.1). There was a 31% reduction in stroke (p=0.03). The reduction in coronary events was greater in women on pravastatin compared to men. (See section 3.5) Patients with higher pretreatment levels of LDL had a greater reduction in relative risk of coronary events. All-cause morality and noncardiovascular deaths were similar in both groups. (Sacks et al, 1996; Byrne et Wild, 1996)
The 4S (simvastatin) study carried out a sub-group analysis of patients with total cholesterol levels of 5.40 mmol/L to 6.18 mmol/L (n=240). A 29% relative risk reduction in overall mortality was seen in the treatment group compared to placebo. (Brown et al, 1995; Scandinavian Simvastatin Survival Study Group, 1995)

3.3.8 Summary

In conclusion, the following tables summarize the benefits of cholesterol reduction on clinical events before and after the introduction of HMG CoA reductase inhibitors.

Table 9: Effects of Cholesterol Reduction Before Statins in Patients with Hyperlipidemia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Primary Prevention</th>
<th>Secondary Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI</td>
<td>↓*</td>
<td>↓*</td>
</tr>
<tr>
<td>Fatal CHD</td>
<td>↓</td>
<td>↓*</td>
</tr>
<tr>
<td>Noncardiovascular Mortality</td>
<td>↑*</td>
<td>↑</td>
</tr>
<tr>
<td>Overall Mortality</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

This table is based on the results obtained in a review of meta-analyses conducted by the United States General Accounting Office (GAO), 1996.
* statistically significant

Summary point 8: Before HMG-CoA reductase inhibitors became available, lipid-lowering therapy significantly reduced coronary events (fatal and non-fatal CHD combined) in high risk populations in primary prevention. Fatal CHD alone and overall mortality had not been shown to be significantly reduced. In secondary prevention, coronary events were significantly reduced and overall mortality was also reduced, although not significantly, by lipid-lowering therapy.

Table 10: Effects of Cholesterol Reduction with Selected Statins in Hyperlipidemic Patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Primary Prevention</th>
<th>Secondary Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI</td>
<td>↓*</td>
<td>↓*</td>
</tr>
<tr>
<td>Fatal CHD</td>
<td>↓</td>
<td>↓*</td>
</tr>
<tr>
<td>Noncardiovascular Mortality</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Overall Mortality</td>
<td>↓*</td>
<td>↓*</td>
</tr>
</tbody>
</table>

* statistically significant
a from the WOS study (pravastatin)
b from the 4S study (simvastatin)

Summary point 9: A recent trial (WOS) has shown that pravastatin decreases nonfatal MI and overall mortality significantly in primary prevention patients. Furthermore, a secondary prevention trial (4S) reports that coronary events (nonfatal MI and fatal CHD) and overall mortality are significantly reduced with simvastatin.
For patients having mild to moderately elevated LDL or TC, the following can be concluded:

**Summary point 10:** In secondary prevention, lipid-lowering with pravastatin (CARE study) decreases coronary events in patients with mildly to moderately elevated LDL or total cholesterol levels.

### 3.4 Women

Women have been under-represented in epidemiologic studies and clinical trials of cholesterol-lowering treatments as the majority of studies have been carried out in middle-aged men. The few clinical trials that have included women participants lacked statistical power to show an effect of cholesterol reduction on mortality. In clinical practice, results from male-only trials have been extrapolated to women.

#### a) Epidemiologic Studies

The Framingham study showed that women have the same risk factors for CHD as men. (Murabito, 1995; Kannel et al, 1995) It also established that an elevated total cholesterol level was associated with an increased risk of CHD in women and a high HDL level was indicative of a reduced risk. (Castelli et al, 1986)

In a cohort study of more than 25,000 women with a mean age of 39.4 years, there was a positive association between cholesterol levels and mortality from coronary heart disease. (Verschuren et al, 1995) In the same study, mortality from coronary heart disease in men (n=23,389 and mean age 39.2 years) was five times higher than in women. However, these women were pre-menopausal and at low risk for cardiovascular disease. After menopause, there was a significant increase in myocardial infarction and coronary death. (Kannel et al, 1995)

#### b) Clinical Trials

Lowering lipids did not result in a significant reduction in coronary events in women with no evidence of cardiovascular disease as determined in a review of clinical trials that have included women. In women with pre-existing CHD, significant regression of atherosclerotic lesions occurred. (Moreno and Manson, 1993)

Two secondary prevention trials have included women and provided separate analyses. The 4S (simvastatin) study included women (n=827) with CHD and a total cholesterol level of 7.0 mmol/L. There were less major coronary events (35% relative risk reduction; p=0.01) in women treated with simvastatin. Total mortality was not decreased as more women died in the treatment group (n=27) than the control group (n=25). (Scandinavian Simvastatin Survival Study Group, 1994)

There was a greater relative risk reduction of fatal and non-fatal CHD in women (45%; p=0.04) compared to men (20%) in the CARE (pravastatin) trial. Also, there was a 59% relative risk reduction in the incidence of stroke in treated women compared to the placebo group. (Anon.(a), 1996)

Overall, due to the small number of women in these major trials, treatment effects in this sub-group should be estimated from the overall trial data.
Summary point 11: The benefits of lipid-lowering therapy in hypercholesterolemic women with no evidence of CHD have not been determined conclusively. In secondary prevention, women appear to experience the same benefits of lipid lowering as men (i.e., a decrease in coronary events) although the number of participants in clinical trials have been too small to show an effect on mortality.

3.5 Young Adults

The incidence of CHD in young adults is very low. Thus the potential benefits of lowering lipids in this group are small. In addition, no clinical trials have included young adults, and the impact of initiating lipid-lowering therapy at a young age is unknown.

One epidemiologic study was conducted in young men to evaluate the risk of cardiovascular disease associated with cholesterol level. One thousand and seventeen medical students, with a median age of 22 years and an average serum cholesterol level of 5 mmol/L, were followed over 27 to 42 years. Serum cholesterol levels at baseline were associated with risks of coronary heart disease, cardiovascular disease and total mortality in a continuous and graded fashion. At low cholesterol levels, there was no evidence of increased risk of death. (Klag et al, 1993)

Summary point 12: The impact of starting lipid-lowering therapies in young hypercholesterolemic patients (i.e., less than 35 years old) is unknown.

3.6 Elderly People

a) Epidemiologic Studies

The risk of CHD increases with age. However, an increase in cholesterol levels is less important as a risk factor in older patients. (Fey and Pearson, 1996)

A review of 22 cohort studies done at a workshop organized by the National Heart, Lung, and Blood Institute (NHLBI) in the United States determined that there was an association between total cholesterol and CHD in older men and women aged 65 years and over, although the associations were not as strong as for middle-aged men. The same was true for LDL cholesterol. (Manolio et al, 1992)

Framingham data demonstrated that the association between cholesterol levels and incidence of CHD is weaker after the age of 55 years. (Anderson et al, 1987)

Using data from the LRC study, Grover et al (1994) determined that total cholesterol, LDL and triglycerides were poor predictors of CHD mortality in people between the ages of 60 to 79 years.

A cohort study reported on the lack of correlation between elevated total cholesterol or low HDL, and CHD, CHD mortality and overall mortality in men and women 70 years and over. (Krumholz et al, 1994)

A larger cohort study, which included the participants from the Krumholz study, showed that low HDL was significantly associated with an increased risk of CHD mortality in people 71 to 80 years old. After the age of 80, the association, although not significant, was still apparent. (Corti et al, 1995)
These results need to be interpreted with the following differences in mind. The review by the NHLBI was not based on a meta-analysis and only included studies presented at the workshop. These studies were different in terms of end-point measured, study population and duration.

Studies by Krumholz et al and Corti et al were based on one serum sampling only and the sampling was done when participants had already reached old age. Findings by Grover al were also based on single lipid values and patients were followed for 12 years.

In Framingham, levels were collected at numerous intervals in subjects as young as 31 years old and followed for 30 years.

The Whitehall study showed that the earlier the age at which cholesterol level was measured, the stronger the association with CHD. Hence, it was concluded that reducing cholesterol levels in middle age may have an impact on the risk of CHD in old age. (Shipley et al, 1991) The reverse was demonstrated in the Honolulu Heart Program where CHD risk was the same whether measurements were obtain early on or later in life.

b) Clinical Trials

Very few clinical trials have evaluated lipid-lowering therapy in the elderly.

The Cholesterol Reduction in Seniors Program (CRISP) randomized 431 patients (mean age 71 years) to lovastatin or placebo. It was demonstrated that adequate lipid-lowering effects could be obtained in older subjects. Few side effects were reported. However, the study collected but did not analyze data on CHD morbidity and mortality. (LaRosa et al, 1994)

The Stockholm Ischaemic Heart Disease Secondary Prevention Study, a five-year open-label study, compared clofibrate and niacin to placebo in 555 patients below 70 years of age and with a history of MI. Total cholesterol level was lowered by 13%. A 28% relative risk reduction in total mortality (p<0.05) in subjects 60 to 69 years of age was obtained. (Carlson and Rosenhamer, 1988)

The 4S (simvastatin) study did a subgroup analysis of their subjects aged 60 to 70 years (n=2,282). There was a 27% relative risk reduction in overall mortality and a 29% relative risk reduction in major coronary events. (Scandinavian Simvastatin Survival Study Group, 1994)

In the CARE (pravastatin) study, patients over the age of 60 (n=1,075) had a 27% relative risk reduction in major coronary events (95% CI:12-38; p<0.001). (Sacks et al, 1996)

Summary point 13: The association between CHD and serum cholesterol in the elderly is not as strong as that found in the middle-aged population. This may be due to the lack of data available on elderly populations. However, it appears to be beneficial to treat the young elderly (60 to 70 years old) with established cardiovascular disease. For those over 70, there is less information to assess the benefit to risk ratio of treatment.
4. HMG CoA REDUCTASE INHIBITORS

4.1 General Information

HMG CoA reductase inhibitors inhibit the rate-limiting enzyme in cholesterol synthesis. This leads to a compensatory increase in the number of hepatic LDL receptors, thereby resulting in an increase in uptake of LDL and a decrease in its plasma level. (American Medical Association, 1995)

There are four HMG CoA reductase inhibitors available in Canada: fluvastatin (Lescol®), lovastatin (Mevacor®), pravastatin (Pravachol®) and simvastatin (Zocor®). A fifth one, atorvastatin (Lipitor®), has recently been released on the market.

Table 11: Availability of Statins

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE FORM</th>
<th>DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin*</td>
<td>10, 20 and 40 mg tablets</td>
<td>10 to 80 mg daily</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20 and 40 mg capsules</td>
<td>20 to 40 mg daily at bedtime or 40 mg twice daily</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>20 and 40 mg tablets</td>
<td>20 to 80 mg daily with the evening meal</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10, 20 &amp; 40 mg tablets</td>
<td>10 to 40 mg daily at bedtime</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>5, 10 and 20 &amp; 40 mg tablets</td>
<td>5 to 40 mg daily in the evening</td>
</tr>
</tbody>
</table>

Source: CPS 1997 and *product monograph 1997

Trials have been conducted to compare the lipid-lowering effects and safety of the different statins (See Appendix 2). It was shown that all statins effectively lower total cholesterol and LDL levels (although to different extents depending on dosage) and that they share a similar side effect profile. Major clinical endpoints such as coronary events and mortality have not been compared in head to head trials.

4.1.1 Effect on Lipoproteins

The reduction in total cholesterol and LDL levels depend on the dosages being compared such that fluvastatin 40 mg is approximately equivalent to simvastatin 10 mg, pravastatin 20 mg, or lovastatin 20 mg. (Illingworth and Tobert, 1994) The following table describes the percent change in lipid and lipoprotein levels obtained with HMG CoA reductase inhibitors at the usual recommended dosage range in placebo-controlled trials. (Hsu et al, 1995)

Table 12: Comparison Of Lipid-lowering Properties Of HMG CoA Reductase Inhibitors

<table>
<thead>
<tr>
<th>DRUG AND DOSE (mg/d)</th>
<th>CHANGE FROM BASELINE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TC</td>
</tr>
<tr>
<td>Lovastatin 20-80</td>
<td>↓17-29%</td>
</tr>
<tr>
<td>Pravastatin 10-40</td>
<td>↓12.9-27%</td>
</tr>
<tr>
<td>Simvastatin 10-40</td>
<td>↓16.1-32.5%</td>
</tr>
<tr>
<td>Fluvastatin 10-40*</td>
<td>↓14.6-19.5%</td>
</tr>
</tbody>
</table>

* fluvastatin 10 mg capsules not marketed in Canada; fluvastatin 80 mg not reported but may decrease LDL by up to 35%.

Reprinted from The Annals of Pharmacotherapy 1995;29 with permission from the publisher.
The newer agent, atorvastatin, reduces total cholesterol by 29 to 45%, LDL levels by 39 to 50% and triglycerides by 19 to 37%. HDL levels are increased by 5 to 9%. (Product monograph, 1997)

4.1.2 Pharmacokinetics

Physicochemical properties and pharmacokinetic characteristics such as absorption, plasma protein binding, hepatic extraction and renal excretion differ among the statins. The clinical relevance of this has not been fully elucidated.

Statins have a nonlinear dose-response relationship. At higher doses, the dose-response curve becomes flatter. Therefore, their effect on LDL does not increase proportionally with dose and most of the lipid lowering effect can be obtained with lower doses. (Farmer et Gotto, 1996; McMillan, 1996; Schectman et Hiatt, 1996)

Statins are contraindicated in patients with active hepatic disease or with increased serum aminotransferase levels. In patients with severe renal impairment, statin therapy should be instituted with caution. It should be noted however that simvastatin and fluvastatin do not undergo extensive renal excretion. (Garnett, 1995)

4.1.3 Adverse Events

All comparative studies have demonstrated that HMG CoA reductase inhibitors were similar in terms of side effects. Although the first statin (lovastatin) became available in the mid 1980's, the effects of life-time use are still unknown.

The incidence of adverse events is low with HMG CoA reductase inhibitors. Headache, dizziness, rash, diarrhea, abdominal pain, constipation and flatulence are the most common side effects. They may cause an increase in hepatic transaminases usually within the first few weeks of treatment but this is reversible by decreasing the dose or stopping treatment. Increases in creatine kinase and myopathy have also been reported and are dose dependent. Rhabdomyolysis and hepatotoxicity are rare. Discontinuation of treatment is recommended at the first sign of muscle symptoms. (Farmer et Gotto, 1996; Gonzalez, 1996; McMillan, 1996; Semchuk, 1996)

4.1.4 Drug Interactions

Statins are metabolized in the liver by the microsomal P-450 system. There is thus the potential for interaction with any other drugs that have an effect on this system. (Garnett, 1995)

Some of the drug interactions reported to date implicate anticoagulants, bile acid sequestrants, cyclosporine, erythromycin, fibrates, itraconazole and nefazodone. (Garnett, 1995; Trenque et al, 1996; Anon.(c), 1996; Segaert et al, 1996; Neuvonen et Jalava, 1996; Jacobson et al, 1997) It should be noted that these drug interactions have not been reported for all of the statins. Some authors have postulated that this may be due to differences in their pharmacokinetic properties. (Garnett, 1995) A review of the possible drug interactions is needed when selecting a statin.
4.2 Placebo Controlled Trials

Studies have evaluated the cholesterol lowering effects of the different statins alone or in combination with other lipid-lowering drugs on atherosclerosis and/or clinical events. The major ones are described below:

4.2.1 Atorvastatin

Data on the effect of atorvastatin in primary and secondary preventions are not available.

4.2.2 Fluvastatin

Large scale clinical trials have not been conducted and are required to fully evaluate the effects of fluvastatin on clinical outcomes.

a) Primary Prevention

There have been no studies evaluating fluvastatin in primary prevention.

b) Secondary Prevention

The LCAS study was an angiographic secondary prevention trial evaluating the effect of fluvastatin on atherosclerosis. Results are reported in section 3.3.7.

4.2.3 Lovastatin

Angiographic studies such as the Atherosclerosis Carotid Artery Progression Study (ACAPS), the Familial Atherosclerosis Treatment Study (FATS), the Monitored Atherosclerosis Regression Study (MARS) and the CCAIT have measured the effect of lovastatin on atherosclerosis. The CCAIT study is described in section 3.3.7.

Coronary plaques were reduced in size or their progression affected, with a reduction in lipid levels. These studies were principally designed to examine coronary angiographic changes as a primary outcome, and clinical events as secondary or tertiary outcomes. Large-scale clinical trials are required to fully evaluate the clinical benefits of lovastatin.

a) Primary Prevention

ACAPS assessed the effect of lovastatin in patients with carotid atherosclerosis with no evident symptoms of CHD. Nine hundred and nineteen men and women with mean average LDL levels of 4.1 mmol/L were randomized to receive lovastatin 20 or 40 mg per day in a double-blind placebo control trial.

Carotid wall thickness was reduced significantly. There were significantly fewer major cardiovascular events in the treatment group compared to the placebo group (5 vs 14; p=0.04) and less deaths (1 vs 8; p=0.02). (Furberg et al, 1994)
b) **Secondary Prevention**

FATS was a 2.5 year study which included 146 men of 62 years of age and younger with established coronary atherosclerosis and a family history of CHD who were randomized to receive lovastatin and colestipol, niacin and colestipol, or placebo with or without colestipol. Baseline total cholesterol was 6.99 mmol/L and LDL level was 4.9 mmol/L on average. Lovastatin (20 mg to 40 mg twice daily) combined with colestipol (5 to 10 g three times daily) decreased LDL levels by 46%. LDL levels were decreased by 32% in the niacin (125 mg twice daily to 500 mg four times daily)-colestipol group. Progression of coronary lesions was less frequent and regression was more frequent in the treatment groups. The incidence of coronary events was reduced by 73% (95% CI: 23 to 90 %). (Brown et al, 1990)

MARS was a two-year randomized double-blind control trial which included 270 patients with CHD and total cholesterol ranging from 4.9 to 7.6 mmol/L. Lovastatin (80 mg/day) decreased LDL levels by 38%. There were less progression of stenosis and greater regression of lesions than placebo treated patients. Although the lovastatin group experienced less coronary events than the control group, the difference was not significant (22 lovastatin patients vs 31 placebo patients experienced one or more clinical coronary events). (Blakenhorn et al, 1993)

4.2.4 **Pravastatin**

a) **Primary Prevention**

The West of Scotland Coronary Prevention Study, the Pravastatin Multinational Study, and the Kuopio Atherosclerosis Prevention Study (KAPS) were trials conducted in patients with no history of cardiovascular disease. The West of Scotland study described in section 3.3.1 measured clinical events. All other trials examined coronary angiographic changes as a primary outcome, and clinical events as secondary or tertiary outcomes.

The Pravastatin Multinational Study examined the efficacy and safety of pravastatin 20 to 40 mg in 1,062 patients with total cholesterol level of 5.2 to 7.8 mmol/L and two or more risk factors for CHD. This study only lasted 26 weeks after which time patients were given the opportunity to continue open-label pravastatin for an additional 26 weeks. In the first 26 weeks, there were less serious cardiovascular events in the treatment group than the placebo group (1 vs 13 events in the placebo group; p<0.001). (Pravastatin Multinational Study Group for Cardiac Risk Patients, 1993)

KAPS was a 3 year, randomized double-blind placebo-controlled study evaluating the effect of pravastatin 40 mg on the progression of atherosclerosis in carotid and femoral arteries in 447 men aged 44 to 65 years. Baseline LDL levels were 4.9 mmol/L. Although patients never experienced a coronary event, they had evidence of atherosclerosis. There was a greater reduction in the rate of progression in the carotid atherosclerosis with pravastatin than placebo, with the effect greater in smokers. Pravastatin had no significant effect on femoral segments. The number of cardiovascular events were less in the pravastatin group compared to placebo (11 vs 17 respectively). (Salonen et al, 1995)
b) Secondary Prevention

The Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I), the Pravastatin, Lipids, and Atherosclerosis in the Carotids (PLAC II), the Regression Growth Evaluation Statin Study (REGRESS), the Harvard Atherosclerosis Reversibility Project (HARP), and the Cholesterol and Recurrent Events (CARE) studies were secondary prevention trials. The HARP and CARE studies are described in section 3.3.7. Only the CARE trial was designed to measure clinical events as primary outcomes. All other studies were angiographic trials.

Four hundred and eight patients (mean age 57 years) with a history of CHD were randomized to receive pravastatin 40 mg or placebo in PLAC I. This study of 3 years duration examined the effect of pravastatin on the progression of atherosclerosis. Patients had an average total cholesterol level of 5.97 mmol/L and LDL level of 4.24 mmol/L. Progression of atherosclerosis was reduced in the pravastatin group compared to the placebo group. The risk of MI (fatal and nonfatal) was reduced in the treatment group by 60% (8 with pravastatin vs 17; p≤0.05). (Pitt et al, 1995)

In PLAC II, 151 patients with CHD and an average total cholesterol of 6 mmol/L and LDL level of 4.3 mmol/L received pravastatin 10 to 40 mg or placebo for 3 years. The study was designed to measure the progression of atherosclerosis in carotid arteries. Pravastatin treatment resulted in a reduction in the rate of progression of atherosclerosis in the common carotid artery. There was a 60% relative risk reduction in clinical events in the pravastatin group (4 vs 10 events in the placebo group; p=0.09) and fewer deaths (3 in the treatment group vs 5). (Crouse et al, 1995)

Pooling the results of PLAC I and II showed that fatal and non-fatal MI combined (3.6% with pravastatin vs 9.7% with placebo; p=0.003), and non-fatal MI and coronary deaths combined, (5.0% with pravastatin vs 10.4% with placebo; p=0.014) were significantly reduced. (Anon.(b), 1996; Furberg et al, 1995)

In REGRESS, 885 men (mean age 56 years) were randomized to receive pravastatin 40 mg or placebo for two years to assess the effect of treatment on the progression and regression of atherosclerosis and on clinical events. The study lasted two years. Half of the patients had a history of MI and the majority had multivessel coronary disease. Baseline total cholesterol and LDL levels were 6 mmol/L and 4.3 mmol/L respectively. Pravastatin promoted the regression of lesions significantly (p=0.019) and prevented the progression of lesions (p=0.001) compared to placebo. Clinical events were also reduced in the treatment group compared to the placebo group but did not reach statistical significance (8 nonfatal and fatal MI combined in the treatment group vs 13 in the placebo group). (Jukema et al, 1995)

Byington et al (1995) pooled the results of KAPS, PLAC I, PLAC II and REGRESS for a total of 1,891 patients. Clinical benefits were apparent after one year of therapy. There was a significant reduction in nonfatal and fatal MI combined (62% relative risk reduction, 95% CI: 38 to 80% p=0.001) and a significant reduction in nonfatal MI and CHD death combined (51% relative risk reduction; 95% CI: 24 to 71%; p=0.006). The reduction in overall mortality was greater in the treatment group but this was not statistically significant (46% relative risk reduction, 95% CI: 9 to 76%; p=0.168).
4.2.5 Simvastatin

a) Primary Prevention

There have been no studies evaluating simvastatin in primary prevention.

b) Secondary Prevention

The Multicentre Anti-Atheroma Study (MAAS), an angiographic trial, randomized 381 patients with coronary heart disease (mean age 55 years) to receive 20mg of simvastatin or placebo for four years. Baseline total cholesterol and LDL levels were 6.4 mmol/L and 4.4 mmol/L respectively. Treated patients had a decrease of total cholesterol of 23% and LDL levels of 31%. Although most patients had nonsignificant changes in the regression and progression of atherosclerotic lesions, fewer lesions developed with simvastatin. There were more MI in the simvastatin group compared to placebo (11 vs 7) and less deaths (4 vs 11). (MAAS Investigators, 1994)

The 4S study was the only secondary prevention trial evaluating the effect of simvastatin on clinical events. Details of the study are described in section 3.3.2.

4.2.6 Summary

The trials described above are mostly angiographic trials. Long-term clinical trials investigating cholesterol-lowering effects on the incidence of coronary events and mortality as primary outcomes in primary and secondary preventions have not been conducted for all statins.

Tables 13 and 14 below summarize the clinical evidence regarding the efficacy of statins.

**Table 13: Efficacy of Specific Statins on Coronary Events in Hyperlipidemic Patients**

<table>
<thead>
<tr>
<th>Statin</th>
<th>In Primary Prevention</th>
<th>In Secondary Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>no study</td>
<td>no study</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>no study</td>
<td>probably effective (LCAS*)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>probably effective (ACAPS*)</td>
<td>probably effective (MARS*)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td><strong>shown effective</strong> (WOS)</td>
<td>-probably effective (PLAC I &amp; II; REGRESS*)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-shown effective in patients with “normal cholesterol” (CARE)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>no study</td>
<td><strong>shown effective</strong> (4S)</td>
</tr>
</tbody>
</table>

* Studies were angiographic trials and measured clinical benefits as secondary or tertiary outcomes only.
Table 14: Efficacy of Statins in Different Populations

<table>
<thead>
<tr>
<th></th>
<th>In Primary Prevention</th>
<th>In Secondary Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Young (&lt; 35)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Women</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td><strong>Adults (35 - 60)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men with high cholesterol and CHD risk factors*</td>
<td>Effective in coronary events (WOS)</td>
<td>Effective in coronary events (4S)</td>
</tr>
<tr>
<td>Women with high cholesterol and CHD risk factors*</td>
<td>No data</td>
<td>Effective in coronary events (4S)</td>
</tr>
<tr>
<td>Men with normal cholesterol and with CHD</td>
<td>--</td>
<td>Effective in coronary events (CARE)</td>
</tr>
<tr>
<td>Women with normal cholesterol and with CHD</td>
<td>--</td>
<td>Effective in coronary events (CARE)</td>
</tr>
<tr>
<td><strong>Elderly (60 - 70)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men with high cholesterol and CHD risk factors*</td>
<td>Inadequate data to conclude that statins are effective in coronary events.</td>
<td>Effective in coronary events (4S)</td>
</tr>
<tr>
<td>Women with high cholesterol and CHD risk factors*</td>
<td>Inadequate data to conclude that statins are effective in coronary events.</td>
<td>Effective in coronary events (4S)</td>
</tr>
</tbody>
</table>

* Individuals with no risk factors are seldom included in cardiovascular clinical trials

4.3 **Class Effect**

The most recent debate with HMG-CoA reductase inhibitors deals with the issue of similarity between the agents. All statins decrease total cholesterol and LDL levels and increase HDL levels. They all alter the course of atherosclerosis. However, lesion regression occurs slowly and to a minimal extent, and cannot alone explain the clinical benefits reported. This suggests that statins and other lipid-lowering drugs may affect other processes which may explain the reduction in cardiac morbidity and mortality. (Levine et al, 1995)

It has been postulated that the clinical benefits of cholesterol reduction may be due to some effects other than lipid lowering and regression of atherosclerosis. Increasing evidence (i.e, in vitro and ex-vivo studies) suggest that statins and other lipid-lowering drugs affect biochemical processes other than lipid lowering. Plaque stabilization, (Brown et al, 1993), inhibition of platelet mural thrombi, (pravastatin: Lacoste et Lam, 1996), improvement in vascular endothelial function, (cholestyramine: Leung et al, 1993; pravastatin: Egashira et al, 1994; lovastatin: Treasure et al, 1995; lovastatin with probucol: Anderson et al, 1995), improvement in myocardial perfusion (fluvastatin: van Boven et al, 1996), direct antiatherosclerotic effect on the arterial wall such as a decrease in the migration and proliferation of smooth muscle cells (fluvastatin,
lovastatin, simvastatin: Corsini et al, 1996) have been proposed as possible mechanisms contributing to the benefit of lipid-lowering therapy.

However, the interactions among these different mechanisms in the evolution of coronary artery disease are complex. Statins and other lipid-lowering agents have been shown to modulate the effects of some of these processes to different extents. Whether this means that selected statins confer more clinical benefits because of their effects on these processes is still unknown.

There is little evidence for or against a statin class effect. Lipid reduction obtained with diet or other classes of lipid-lowering agents has been associated with a reduction in coronary events. The relative risk reduction of coronary events obtained in the randomized controlled trials are similar. (see Tables 7 and 8). At the present time, there is no evidence from randomized controlled trials to suggest that one statin is more effective than another. However, not all statins have been evaluated in clinical trials. Randomized trials need to be conducted to determine if any of the statins have a greater effect upon clinical events (MI, death) than others.

4.4 Selecting a Statin

The following factors need to be considered when selecting a statin:

- All statins effectively lower total cholesterol and LDL levels, and increase HDL. (section 4.1.1)
- Pharmacokinetic characteristics vary among the statins. (section 4.1.2)
- Their safety profile is comparable. (section 4.1.3)
- Statins may interact with other drugs. (section 4.1.4)
- Clinical trials measuring clinical outcomes have not been conducted for all statins. Also, they have not been studied in every population to determine their long-term impact on coronary events and mortality. (tables 13 and 14)

Until trials identify specific benefits for individual statins, it is reasonable to assume that the selection of a statin should be based on its ability to lower LDL levels and raise HDL, the patient’s concurrent medical conditions and concomitant drug therapy, and the cost. (Gonzalez, 1996; McMillan, 1996; Semchuk, 1996) Clinicians must also keep in mind the information available for each statin as well as the generalizability of the evidence from clinical trials to the patient.

4.5 Summary

The following points can be concluded from the discussion in Section 4:

**Summary point 14:** All statins decrease total cholesterol and LDL levels, and increase HDL levels.

**Summary point 15:** Since all statins decrease total cholesterol and LDL levels and raise HDL levels, although not to the same extent, it may be assumed that all will produce a decrease in coronary events. However, this has not been conclusively demonstrated. Long-term clinical trials investigating lipid-lowering effects on the incidence of coronary events and mortality as primary outcomes in primary and secondary preventions have only been conducted in two of the five statins: pravastatin in primary prevention and in secondary prevention in patients having mildly to moderately elevated LDL levels, and simvastatin in secondary prevention.
Summary point 16: Due to the lack of long-term clinical trials with the other statins and the lack of head to head trials in general, it has not been conclusively determined whether some statins produce greater clinical benefits than others.

Summary point 17: Follow-ups in clinical trials have been limited to five years or less. Patients may take these drugs for longer than this period. Long-term safety remains to be established.

Summary point 18: If a statin is required, consideration should be given to choosing a statin based on its ability to lower LDL levels and raise HDL, the patient’s concurrent medical conditions and concomitant drug therapy, and cost. Clinicians must also keep in mind the information available for each statin as well as the generalizability of the evidence from clinical trials to the patient.
5. ADHERENCE TO LIPID-LOWERING DRUGS

In general, adherence to treatment in clinical trials is approximately 80% or more. (Horwitz and Horwitz, 1993) This differs significantly with actual practice where it has been determined that compliance with long-term treatment (> one year) is 50%. (Haynes and Dantes, 1987) Four studies concerning the discontinuation of lipid-lowering therapy are reviewed.

An American retrospective cohort study measured the rates of discontinuation of lipid-lowering drugs in 2,369 new users at two health maintenance organizations (HMO) for data collected between January 1, 1988 to December 31, 1990, and compared them to those reported in clinical trials. Seventeen randomized trials and 13 open-label trials published between 1975 and 1993 were analyzed. The one year probability of drug discontinuation in HMO patients was 46% for niacin, 41% for bile acid sequestrants, 37% for gemfibrozil, 15% for lovastatin and 38% for all treatments combined. The main reasons given for discontinuing the drugs, in order of importance, were: adverse effects, lack of effectiveness and noncompliance. Discontinuation rates were higher in women due to a higher incidence of adverse effects. In contrast, discontinuation rates in randomized clinical trials were: 4% for niacin, 31% for bile acid sequestrants, 15% for gemfibrozil and 16% for lovastatin. Discontinuation rates in open label trials were similar to the rates seen in primary care setting. (Andrade et al, 1995)

An Australian utilization study, which assessed dispensing data collected between June 1994 to June 1995, established that 60% of patients discontinued lipid-lowering agents after 12 months. Rates of discontinuation were 56% for pravastain, 57% for simvastatin and 78% for gemfibrozil. Half of the discontinuation had occurred within three months of starting treatment. Thirty-two percent of patients discontinued treatment because they did not feel they required treatment. Thirty-two percent of the discontinuations were physician-initiated because of lack of effectiveness but only half of these patients were switched to another drug. Only a small percentage (7%) of patients stopped treatment due to adverse effects. Discontinuation was not related to gender. Those over 65 years of age and those receiving cardiovascular drugs or analgesics were less likely to discontinue treatment, perhaps due to the fact that they were used to chronic therapy. (Simons et al, 1996)

Another population-based study was done using the Saskatchewan prescription drug database. 11,002 new users of lipid-lowering drugs were followed for one to 2.5 years (May 1991 to August 1993) to determine their adherence to treatment. Nonadherence was established as being 90 days without obtaining a prescription refill. It was determined that median time on medication was 3.7 months. Discontinuation rates were 69% for niacin, 53% for cholestyramine, 35% for gemfibrozil, 26% for lovastatin, 25% for pravastatin and 24% for simvastatin after only one prescription. Seventy-five percent of new users had discontinued their lipid-lowering agent at one year. Subjects aged 45 to 74 years were less likely to discontinue treatment than those younger than 45 years. Results were not affected by gender. (Health Services Utilization and Research Commission, 1995)

Using information from the “Régie de l’assurance-maladie du Québec” (RAMQ) database for the years 1990 to 1993, compliance with cholestyramine and colestipol was determined to be between 63.6% to 66.1% compared to 77.8% to 80.2% for the statin drugs (lovastatin, pravastatin and simvastatin). The probability of being on treatment after one year was 41% with the bile acid sequestrants and 77.2% with the statins. (Lacour and Le Lorier, 1996)
Misuse of lipid-lowering drugs has been reported in at least one study where patients receiving HMG CoA reductase inhibitors (mostly lovastatin) were often prescribed subtherapeutic doses. Ninety patients at a large university-affiliated medical centre who had received statin therapy for at least one year were enrolled in the study. It was determined that only 52% of patients with two or more risk factors and 24% of patients with existing heart disease had LDL levels less than 2.6 mmol/L. Considering LDL levels less than 3.1 mmol/L, 50% of patients with existing CHD did not reach that goal. It should be noted that 31% of patients were deemed to be non-compliant. These patients were included in the analysis (Marcelino and Feingold, 1996).

These studies show that discontinuation rates are different for each drug type. Patients receiving niacin are most likely to discontinue their medication and those on statins are most likely to continue treatment. Reasons for discontinuance are adverse effects, lack of effectiveness, patient perception that they don’t require therapy and noncompliance. It should be noted that lipid-lowering agents have different administration schedules which could explain the differences in compliance. For example, statins are administered mostly on a once daily basis whereas niacin regular release is administered two to four times a day. In two studies, age seems to be a factor, with older patients being more likely to stay on their medication than younger patients.

Furthermore, stopping treatment is most likely to occur in the earlier part of treatment. If benefits of lipid-lowering therapy are only accrued after one year of therapy, discontinuance of treatment within the first year is costly with little gain. Similarly, the fact that some patients receive lipid-lowering drugs but are inadequately monitored and treated creates an expense with no benefits.

In summary, one can conclude that:

**Summary Point 19:** In actual practice, lipid-lowering therapy is often discontinued within the first year of therapy.

**Summary Point 20:** Reasons for discontinuance include adverse events, lack of effectiveness and non-compliance.
6. UTILIZATION OF LIPID-LOWERING AGENTS

In this section, information on prescribing patterns of lipid-lowering agents (LLA) is presented. This discussion aims at providing some information on one hand, about the place that statins hold among lipid-lowering agents, and on the other hand, about whether some differences are revealed regarding the use of particular statins. Lastly, some tentative remarks are attempted in relation to the appropriate use of lipid-lowering agents. Lipid-lowering agents include gemfibrozil, clofibrate, cholestyramine and the four statins (fluvasatin, lovastatin, pravastatin and simvastatin).

The data have been kindly provided by Intercontinental Medical Statistics (IMS) Canada. IMS data is not derived from population-based databases nor from epidemiologic information. Also, the data does not represent actual use but rather is estimated from non-random samples of prescribers and pharmacies. IMS does not validate the diagnosis or the appropriateness of use. More importantly, the effectiveness of therapy cannot be determined. As such, this data must be interpreted with caution. They are, at best, relatively precise estimates and their precision lies, depending on the database from which the estimates are drawn, between ± 3% to ± 8% at 95% confidence level.

6.1 Prescription Patterns of Lipid-lowering Agents

This section focuses on the prescription of lipid-lowering agents and more particularly on the relative use of statins compared to other lipid-lowering agents. Usage patterns, specialties of prescribers, regional variations and principal diagnoses for prescription of lipid-lowering agents are examined.

6.1.1 Trends

Lipid-lowering agents and statins in particular are increasingly being used. Tables 15 and 16 show the trends in the prescriptions of LLA and statins from 1991 to 1995. Table 15 includes both new and refill prescriptions whereas Table 16 focuses on new prescriptions only. Then, Table 17 shows, that most prescriptions dispensed in Canadian pharmacies are refills of previously dispensed medications and are not new prescriptions. As can be observed from all these tables, the use of lipid-lowering agents is increasing.

| Table 15: Trend in Prescriptions for LLA (new and refills) |
|-----------------|-------|-------|-------|-------|-------|
| Statin drugs    |       |       |       |       |       |
|                 | 1259  | 1686  | 2007  | 2223  | 2771  |
| % of change among statin drugs | -     | +34%  | +19%  | +11%  | +25%  |
| All LLA         |       |       |       |       |       |
|                 | 2084  | 2480  | 2752  | 2977  | 3469  |
| Percentage change among all LLA | -     | +19%  | +11%  | +8%   | +17%  |

All lipid-lowering agents include, fluvastatin, lovastatin, pravastatin, simvastatin, as well as gemfibrozil, clofibrate and cholestyramine.

Source: IMS Canada
Table 16: Trend in New Prescriptions of LLA

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin drugs</td>
<td>336</td>
<td>396</td>
<td>428</td>
<td>493</td>
<td>637</td>
</tr>
<tr>
<td>% of change among statin drugs</td>
<td>-</td>
<td>+18%</td>
<td>+8%</td>
<td>+15%</td>
<td>+29%</td>
</tr>
<tr>
<td>Total of all drugs</td>
<td>514</td>
<td>558</td>
<td>597</td>
<td>665</td>
<td>786</td>
</tr>
<tr>
<td>% of change among all LLA</td>
<td>-</td>
<td>+9%</td>
<td>+7%</td>
<td>+11%</td>
<td>+18%</td>
</tr>
</tbody>
</table>

All lipid-lowering agents include fluvastatin, lovastatin, pravastatin, simvastatin as well as gemfibrozil, clofibrate and cholestyramine.

Source: IMS Canada

Table 17: New Prescriptions as Percentage of all Prescriptions of LLA

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>27%</td>
<td>23%</td>
<td>21%</td>
<td>22%</td>
<td>23%</td>
</tr>
<tr>
<td>All LLA</td>
<td>25%</td>
<td>23%</td>
<td>22%</td>
<td>22%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Source: IMS Canada

Statins represent a high percentage of all lipid-lowering prescriptions. Not only do statin prescriptions represent more than half of all LLA prescriptions, but this proportion is increasing over time. (Table 18)

Table 18: Statin Prescriptions as a Percentage of Prescription of LLA

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of statin Rx.</td>
<td>60%</td>
<td>68%</td>
<td>73%</td>
<td>75%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Source: IMS Canada

6.1.2 Prescribers

Lipid-lowering agents are prescribed by a number of specialists. General practitioners are the most important group of prescribers as they prescribe approximately 65% of all prescriptions. This is true of all lipid-lowering agents. (Table 19) In addition, all specialists prescribe statins more frequently than other lipid-lowering agents, but cardiologists are those that choose statins more often than other specialists as is indicated in Table 20.

Table 19: Prescribers

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Prescribed Cholesterol Reducers (%)</th>
<th>Prescribed Statins (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Practitioner</td>
<td>65.7</td>
<td>64.9</td>
</tr>
<tr>
<td>Family Medicine</td>
<td>16.4</td>
<td>16.2</td>
</tr>
<tr>
<td>Cardiologist</td>
<td>7.4</td>
<td>8.1</td>
</tr>
<tr>
<td>Internist</td>
<td>5.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Endocrinologist</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Others</td>
<td>2.9</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Others include: nephrologists, gastroenterologists, general surgeons, infectious disease, and emergency medicine.

Source: IMS, 1995 data
Table 20: Prescribers’ choice of LLA

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Statins (%)</th>
<th>Other LLA (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Practitioner</td>
<td>80.0</td>
<td>20.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Family Medicine</td>
<td>80.0</td>
<td>20.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Cardiologist</td>
<td>89.3</td>
<td>10.7</td>
<td>100.0</td>
</tr>
<tr>
<td>Internist</td>
<td>81.7</td>
<td>18.3</td>
<td>100.0</td>
</tr>
<tr>
<td>Endocrinologist</td>
<td>81.4</td>
<td>18.6</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Source: IMS, 1995 data

6.1.3 Diagnosis

The most important diagnoses for which lipid-lowering agents are prescribed are indicated in Table 21.

Table 21: Diagnoses

<table>
<thead>
<tr>
<th>Diagnoses*</th>
<th>Statins</th>
<th>Other LLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia Oth+ Unspecified</td>
<td>79%</td>
<td>21%</td>
</tr>
<tr>
<td>Pure Hypercholesterolemia</td>
<td>84%</td>
<td>16%</td>
</tr>
<tr>
<td>Ch Isch Hrt Di Uns WO HT</td>
<td>92%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Other diagnoses include: Cor Atheroscler WO HTN, ESS Hypertension Unspec, Cor Atherosclerosis W HT, CH Isch Hrt DI W HTN Unspecified, Angina Pectoris, Unk+Unspec cause Oth, Dis Circulatory of Uns Site, Chest pain, Ch Isch Hrt DI Oth WO HT, Uns Dis Lipid Metabolism, Cardiac Dysrhythmia Uns

*Diagnoses used are from ICD-9

Source: IMS, 1995 data

6.1.4 Regional Variations

The use of lipid-lowering agents seems to be uniform among all Canadian regions. Table 22 indicates the proportional use of statins in the different regions.

Table 22: Prescription of Lipid-lowering Agents and Statins by Region

<table>
<thead>
<tr>
<th>Region</th>
<th>Statins</th>
<th>Other LLA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quebec</td>
<td>81%</td>
<td>19%</td>
<td>100%</td>
</tr>
<tr>
<td>Ontario</td>
<td>79%</td>
<td>21%</td>
<td>100%</td>
</tr>
<tr>
<td>Prairies</td>
<td>78%</td>
<td>22%</td>
<td>100%</td>
</tr>
<tr>
<td>Maritimes</td>
<td>79%</td>
<td>21%</td>
<td>100%</td>
</tr>
<tr>
<td>British Columbia</td>
<td>82%</td>
<td>18%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Source: IMS Canada, 1995 data

6.1.5 Significance of the Increase in Use of Lipid-lowering Agents

In spite of the apparent increase in use of lipid-lowering agents and statins, it is difficult to draw conclusions on the impact, relevance and significance of this increase. It is not known whether the increased use of these products have translated into improved health. A broader examination of the evidence would be required to relate usage to clinical benefits.

It may be worth noting that, in a review of the use of lipid-lowering agents in the Canadian population of 65 years and older enrolled in the British Columbia Pharmacare program, McCormack and Rangno (1994) noted that the use of lipid-lowering drugs in patients over age 65 has increased dramatically over
the last years. In 1991 usage was by 4.7% of the covered population, despite the fact that there is limited evidence available to support their use in this patient population. Sketris et al (1995) found that 4.8% of women and 2.8% of men age 65 and over enrolled in the Nova Scotia Pharmacare program were receiving prescriptions of LLA. Neither analyses examined the possible health benefits derived from such treatment.

6.2 Prescription Patterns of Individual Statins

Table 23 shows the percent utilization of fluvastatin, lovastatin, pravastatin, and simvastatin.

<table>
<thead>
<tr>
<th>Table 23: Utilization of Statins</th>
<th>Percentage*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td>17%</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>35%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>22%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

* Percentages are percentages of quantities of product dispensed.
Source: IMS Canada, 1995

Tables 24 to 28 seem to indicate that statins are not used differently. Table 24 shows how an individual drug is used for different conditions. Table 25 indicates how statins compare with each other in their use for a single condition. When equipotent daily dosages are compared, slight differences in the use of statins appear (Table 26). General practitioners and specialists (taken as groups) who prescribe statins, seem to prescribe all four of them (Table 27). All four statins seem to be prescribed for individuals of different age groups (Table 28). This could lend some support to the view that the statins’ actions seem to derive from their class effect rather than from their individual effect. In other words, evidence tends to indicate that prescribers are using the statins interchangeably.

<table>
<thead>
<tr>
<th>Table 24: Statin Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnoses</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Hyperlipidemia Oth+Unsp</td>
</tr>
<tr>
<td>Pur Hypercholesterolemia</td>
</tr>
<tr>
<td>Ch Isch Hrt DI Uns WO HT</td>
</tr>
<tr>
<td>Cor Atheroscler WO HTN</td>
</tr>
<tr>
<td>ESS Hypertension Unspec</td>
</tr>
<tr>
<td>Other*</td>
</tr>
<tr>
<td>100%</td>
</tr>
</tbody>
</table>

* Other diagnoses include: Cor Atherosclerosis W HT, CH Isch Hrt DI W HTN-Uns, Angina Pectoris WO HTN, Unk+Unspec cause Oth, Cardiac Dysrhythmia Uns, Dis Circulatory of Uns site, Chest pain, Ch Isch Hrt DI Oth WO HT, Uns Dis Lipoid Metabolis
Source: IMS, 1995 data
### Table 25: Statins Use by Diagnosis

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Lovastatin %</th>
<th>Simvastatin %</th>
<th>Fluvastatin %</th>
<th>Pravastatin %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia Oth-Unsp</td>
<td>30</td>
<td>27</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Pur Hypercholesterolemia</td>
<td>36</td>
<td>29</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Ch Isch Hrt Di Uns WO HT</td>
<td>73</td>
<td>9</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Cor Atheroscler WO HTN</td>
<td>48</td>
<td>32</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>ESS Hypertension Unspec</td>
<td>27</td>
<td>23</td>
<td>-</td>
<td>50</td>
</tr>
</tbody>
</table>

Source: IMS, 1995 data

### Table 26: Statins Use by Diagnosis, Equipotent Daily Dosages

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Lovastatin 20 %</th>
<th>Simvastatin 10 %</th>
<th>Fluvastatin 40 %</th>
<th>Pravastatin 20 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia Othh+Unsp</td>
<td>41</td>
<td>26</td>
<td>2</td>
<td>31</td>
</tr>
<tr>
<td>Pur Hypercholesterolemia</td>
<td>36</td>
<td>33</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>Ch Isch Hrt Di Uns WO HT</td>
<td>93</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cor Atheroscler WO HTN</td>
<td>50</td>
<td>40</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>ESS Hypertension Unspec</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>90</td>
</tr>
</tbody>
</table>

Source: IMS, 1995 data

### Table 27: Statin Use by Prescribers’ Specialty

<table>
<thead>
<tr>
<th>Prescribers Specialty</th>
<th>Lovastatin</th>
<th>Simvastatin</th>
<th>Pravastatin</th>
<th>Fluvastatin</th>
<th>All Statins</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Practitioner</td>
<td>65.7%</td>
<td>39.7%</td>
<td>26.5%</td>
<td>25.3%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Family Medicine</td>
<td>16.4%</td>
<td>43.8%</td>
<td>24.5%</td>
<td>21.3%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Cardiologist</td>
<td>7.4%</td>
<td>37.5%</td>
<td>35.3%</td>
<td>22.3%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Internist</td>
<td>5.4%</td>
<td>41.1%</td>
<td>30.5%</td>
<td>19.2%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Endocrinologist</td>
<td>2.2%</td>
<td>37.7%</td>
<td>32.8%</td>
<td>21.3%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Others*</td>
<td>2.9%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Others include nephrologist, gastroenterologist, general surgeon, infectious disease and emergency medicine

Source: IMS, 1995 data

### Table 28: Statin Use by Age Group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Lovastatin %</th>
<th>Simvastatin %</th>
<th>Fluvastatin %</th>
<th>Pravastatin %</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-39</td>
<td>32</td>
<td>16</td>
<td>9</td>
<td>44</td>
<td>100</td>
</tr>
<tr>
<td>40-59</td>
<td>32</td>
<td>23</td>
<td>24</td>
<td>21</td>
<td>100</td>
</tr>
<tr>
<td>60-64</td>
<td>30</td>
<td>37</td>
<td>12</td>
<td>21</td>
<td>100</td>
</tr>
<tr>
<td>65+</td>
<td>41</td>
<td>29</td>
<td>12</td>
<td>19</td>
<td>100</td>
</tr>
<tr>
<td>Unspecified</td>
<td>26</td>
<td>43</td>
<td>22</td>
<td>9</td>
<td>100</td>
</tr>
</tbody>
</table>

Source: IMS, 1995 data
It is very difficult to draw conclusions on the appropriateness of use of statins because information as to patient conditions is missing from this analysis. The only indication can come from an examination of the diagnoses. For example, statins seem to be prescribed for pure hypercholesterolemia to individuals 65 years old and over (Table 29). As implied in summary point 13, this might not be the most cost-beneficial use of statins.

**Table 29: Prescription of Statins in Certain Conditions for Patients of Different Age Groups**

<table>
<thead>
<tr>
<th>Pure Hypercholesterolemia</th>
<th>All Other Diagnoses</th>
<th>All Diagnoses Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-39 8%</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>40-59 44%</td>
<td>41%</td>
<td>40%</td>
</tr>
<tr>
<td>60-64 16%</td>
<td>16%</td>
<td>15%</td>
</tr>
<tr>
<td>65+ 29%</td>
<td>39%</td>
<td>33%</td>
</tr>
<tr>
<td>Unspecified 2%</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Source: IMS, 1995 data

In conclusion, it can be said:

**Summary point 21:** Upon examination of the prescription pattern of statins, there does not appear to be any difference in the way they are prescribed.
7. COST-EFFECTIVENESS CONSIDERATIONS

7.1 General Considerations Regarding the Cost-effectiveness of Cholesterol Reduction

7.1.1 Clinical Factors Which Impact Cost-effectiveness Analyses

The purpose of cost-effectiveness studies is to determine a cost per unit of improvement in health. Since, in the context of coronary heart disease, health benefits depend on risk factor modification, the cost-effectiveness of cholesterol reduction and of specific lipid-lowering agents will be particularly sensitive to the impact that health care interventions can have on risk. Because benefits from risk factor modification depend on the presence of risk factors (summary point 2), the cost-effectiveness of lipid-reducing agents will be different depending on the presence of known coronary heart disease or other risk factors. Therefore, (1) cost-effectiveness of a given lipid lowering strategy will depend on the presence of one or multiple risk factors, and (2) cost-effectiveness of primary prevention will differ from secondary prevention.

More specifically, cholesterol reduction has been proven to be most effective and cost-effective in decreasing coronary events in patients with greater risk of coronary heart disease (summary point 5).

For example, Hamilton et al (1995) estimated the cost per life-year saved (LYS) to be $34,000 in low risk men and $16,000 in high risk men. It can be said that:

**Proposition 1:** The more likely the chance of experiencing a coronary event, the more cost-effective lipid lowering strategies will be.

Furthermore, because serum cholesterol was shown to be an independent risk factor for fatal coronary events, the absolute risk reduction will depend on pre-treatment cholesterol values. Also, since the risk of experiencing a cardiac event is associated with lipid levels, lowering total cholesterol and LDL reduces the risk of coronary events.

Hay et al (1991) estimated the cost per life year saved to range between US$13,000 and $297,000 for lovastatin in low risk individuals depending on pre-treatment cholesterol levels. Another example is provided by Hjalte et al (1992). They estimated that, depending on pre-treatment cholesterol levels, cost-effectiveness ratios varied between SEK 150,000 and SEK 510,000 (approximately Cdn$ 27,000 and $92,000 respectively). Therefore,

**Proposition 2:** Cost-effectiveness of lipid lowering therapy depends on pre-treatment cholesterol levels. If other risk factors are the same, the higher the pre-treatment level, the more cost-effective cholesterol and LDL reduction will be.

The same reasoning can be applied to the cost-effectiveness of treating patients in primary prevention (i.e., to prevent a first coronary event) compared to treating patients in secondary prevention (i.e., to prevent a second event). Individuals with pre-existing coronary disease have been shown to benefit more than those with no such history (summary point 5). Published cost-effectiveness ratios have been generally much lower for secondary prevention than for primary prevention.
For example, Goldman et al (1991), estimated the cost-effectiveness of lovastatin to range between US$13,000 and $690,000 (depending on the specific population subgroup and the specific dosage) in primary prevention, whereas in secondary prevention, cost-effectiveness was estimated to range between $1,600 and $310,000 (depending again on the specific population and the specific dosage). Therefore,

**Proposition 3:** Lowering lipid levels in secondary prevention will generally be more cost effective than doing so in primary prevention.

Similarly, cost-effectiveness has been reported to be more favorable in men than in women in primary prevention because men have a higher absolute risk of coronary disease.

Taking HDL into account when assessing cost-effectiveness also has an impact on results. Raising HDL levels lowers the risk of CHD. Therefore, incorporating its effect into the cost-effectiveness analyses can be expected to improve the cost-effectiveness ratios. For example, Hamilton (1995) estimated that cost-effectiveness ratios can be improved by 40% if HDL effects are considered.

Table 30 give examples of reported cost-effectiveness ratios (cost per life-year saved) obtained in various studies. The table clearly shows the extent to which cost-effectiveness ratios depend on the presence of risk factors and the particular populations subgroup examined. The table is not meant to indicate precise costs per life-year-gained for different drugs but to show how sensitive these figures are to factors such as age, gender, pre-treatment cholesterol levels and presence of risk factors.
<table>
<thead>
<tr>
<th>Drug &amp; Dose</th>
<th>Population Characteristics</th>
<th>Cost-Effectiveness (Cost per LYS)</th>
<th>Dependent on</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin 20 mg</td>
<td>Primary prevention, men</td>
<td>US$13,000 - $690,000</td>
<td>Age, pre-treatment cholesterol level</td>
<td>Goldman et al. 1991</td>
</tr>
<tr>
<td>Lovastatin 40 mg</td>
<td>Pre-existing CHD, secondary prevention</td>
<td>US$8,600 - $310,000</td>
<td>Age, gender, pre-treatment cholesterol level</td>
<td></td>
</tr>
<tr>
<td>Simvastatin 20 mg</td>
<td>free of CHD</td>
<td>NLG 50,000 - 110,000</td>
<td>Age, gender, pre-treatment cholesterol level</td>
<td>Martens et al. 1989</td>
</tr>
<tr>
<td>Cholestyramine 12 g</td>
<td>free of CHD</td>
<td>NLG 220,000 - 510,000</td>
<td>Age, gender, pre-treatment cholesterol level</td>
<td></td>
</tr>
<tr>
<td>Simvastatin 20 mg</td>
<td>Men</td>
<td>NLG 46,000 - 98,000</td>
<td>Age, pre-treatment cholesterol level</td>
<td>Martens et al. 1990</td>
</tr>
<tr>
<td>Cholestyramine 12 g</td>
<td>Men</td>
<td>NLG 104,000 - 242,000</td>
<td>Age, pre-treatment cholesterol level</td>
<td></td>
</tr>
<tr>
<td>Lovastatin 20 mg</td>
<td>Low risk</td>
<td>$13,000 - $297,000</td>
<td>Age, gender, pre-treatment cholesterol level</td>
<td>Hay et al. 1991</td>
</tr>
<tr>
<td>Lovastatin 20 mg</td>
<td>High risk</td>
<td>$6,000 - $160,000</td>
<td>Age, gender, pre-treatment cholesterol level</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin 40 mg</td>
<td>Men, free of CHD</td>
<td>Cdn$21,600 - 63,900</td>
<td>Pre-treatment cholesterol level (LDL, HDL), age, presence of additional risk factors</td>
<td>Martens et al. 1994</td>
</tr>
<tr>
<td>Simvastatin 20 mg</td>
<td>Men, free of CAD</td>
<td>SEK 150,000 - 519,000</td>
<td>Age, initial serum cholesterol</td>
<td>Hjalte et al. 1992</td>
</tr>
<tr>
<td>Cholestyramine 16 g</td>
<td>Men, free of CAD</td>
<td>SEK 340,000 - 1,175,000</td>
<td>Age, initial serum cholesterol</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Condition</td>
<td>Cost Range</td>
<td>Risk Factors</td>
<td>Source</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------------</td>
<td>---------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Lovastatin 40 mg</td>
<td>Familial hypercholesterolemia primary prevention</td>
<td>US$2,000 - $120,000</td>
<td>Risk factors (smoking, weight, mild hypertension), age, gender, pre-treatment cholesterol level</td>
<td>Goldman et al. 1993</td>
</tr>
<tr>
<td>Lovastatin 20 mg</td>
<td>No familial hypercholesterolemia primary prevention</td>
<td>$2,000 - $1,000,000</td>
<td>Risk factors, age, gender, pre-treatment cholesterol level</td>
<td></td>
</tr>
<tr>
<td>Lovastatin 40 mg</td>
<td>Secondary prevention</td>
<td>$16,000 - $65,000</td>
<td>CAD history, age, gender, pre-treatment cholesterol</td>
<td></td>
</tr>
<tr>
<td>Cholestyramine 16g</td>
<td>Primary prevention, men, HDL level</td>
<td>$24,000 - $1,400,000</td>
<td>Age, pre-treatment cholesterol, risk level</td>
<td>Taylor et al. 1990</td>
</tr>
<tr>
<td>Lovastatin 40 mg</td>
<td>Primary prevention, men, HDL level</td>
<td>$20,000 - $1,000,000</td>
<td>Age, pre-treatment cholesterol, risk level</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Primary prevention, men, HDL level</td>
<td>$11,000 - $190,000</td>
<td>Age, pre-treatment cholesterol, risk level</td>
<td></td>
</tr>
<tr>
<td>Lovastatin 20 mg</td>
<td>High risk</td>
<td>Cdn$17,000 - $101,000</td>
<td>Age, gender, serum cholesterol</td>
<td>Hamilton et al. 1995</td>
</tr>
<tr>
<td>Lovastatin 20 mg</td>
<td>Low risk</td>
<td>Cdn$36,000 - $151,000</td>
<td>Age, gender, serum cholesterol</td>
<td></td>
</tr>
<tr>
<td>Lovastatin 20, 40, 80 mg, Cholestyramine 12, 16, 20 g and Gemfibrozil 1200mg</td>
<td>Blood pressure, smoking, glucose intolerance</td>
<td>Cdn $35,000 - $420,000 (approximately: Lov $70,000 - $170,000 Cho $110,000 - $250,000 Gem. $70,000 - $90,000)</td>
<td>Drug regimen, age, gender, serum cholesterol</td>
<td>Guibert et al. 1993</td>
</tr>
</tbody>
</table>

CE: cost-effectiveness; LYS: life-year saved; NLG: Dutch Guilders; SEK: Swedish Kroena; CHD: coronary heart disease; CAD: coronary artery disease

The cost-effectiveness ratios that are presented in Table 30 were all obtained by modeling LDL reductions onto life-years saved using risk functions obtained mostly from the Framingham Heart Study. Since then, some studies have estimated the cost-effectiveness of statins by direct measurement of the reduction in coronary events and changes in mortality in clinical trials.
One such example is the economic study which was conducted alongside the 4S trial (Jonsson et al, 1996). In this trial, which was a secondary prevention trial, the cost effectiveness of simvastatin 20 and 40 mg was estimated at SEK 56,400 (approximately Cdn$10,000) per life year saved based on data accruing over a period of 5.5 years.

Again, using data from the 4S study, Rivière et al (1997) modeled the long-term effect of simvastatin under three different premises regarding the long-term effectiveness of simvastatin. The cost-effectiveness ratios obtained ranged between Cdn$6,000 per life-year-saved (if the effectiveness of simvastatin continues over the full 15 years of the model) and Cdn$30,000 (if the effectiveness of long-term therapy stops after 5.4 years).

In summary, cost-effectiveness ratios presented to date range between a few thousands dollars to hundreds of thousands of dollars, depending on the specific patient population and on specific assumptions regarding LDL reduction and HDL increase. Lowest ratios are usually obtained for middle-aged men with multiple risk factors and least favorable ratios are usually obtained for young women with no risk factors.

7.1.2 The Impact of Including Different Cost Items in Cost-effectiveness Analyses

The majority of studies have considered only direct costs of therapies either to patients or to third party payers. Very few studies have taken into consideration the added health care costs associated with prolonged life consequent to lowering cholesterol and decreased mortality. When these costs were included into these analyses (for example, Oster et Epstein, 1987; Hamilton et al, 1995), cost-effectiveness ratios were higher than otherwise estimated.

Indirect costs (or time costs) were also rarely included in cost-effectiveness analyses. When they were, it had the effect of improving cost effectiveness ratios. As expected, the absolute change in cost-effectiveness ratios was greater in low risk individuals as compared to high risk individuals (e.g., Hay et al, 1991).

7.1.3 Common Assumptions Made in Cost-effectiveness Studies

Studies that have examined the cost-effectiveness of lipid-lowering agents have usually been based on multivariate logistic equations developed from the Framingham Heart Study except for the ones based on the 4S.

Published studies have usually used the same effectiveness measures for lipid-lowering agents irrespective of the particular patient group.

Published studies have usually assumed that cholesterol reduction does not increase morbidity and mortality from any other causes.

Health-related quality of life and dis-utility of treatment have seldom been examined.
7.2 Cost-effectiveness Considerations Regarding HMG-CoA Reductase Inhibitors

7.2.1 Are Statins Cost-effective When Compared to Other Lipid-lowering Agents?

Table 31 gives examples of conclusions reached in pharmacoeconomic studies comparing a statin to another lipid-lowering agent. The interpretation of the results is not straightforward because the conclusions of these analyses depend on factors such as the perspective of the analysis, end-point of the analysis, the actual effectiveness values used and the assumptions made regarding resource use, compliance, and cost values.

**Table 31: CE of Statins Compared to Other Drug Therapies**

<table>
<thead>
<tr>
<th>Author</th>
<th>Conclusions reached</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martens et al, 1990</td>
<td><strong>Simvastatin</strong> is substantially more cost effective than <strong>cholestyramine</strong>. In men, cost/LYS increases when therapy is initiated at a later age. There is an inverse relation between cost/LYS and the pre-treatment cholesterol level.</td>
</tr>
<tr>
<td>Hjalte et al, 1992</td>
<td><strong>Simvastatin</strong> is consistently found to be more cost-effective than <strong>cholestyramine</strong>.</td>
</tr>
<tr>
<td>Guibert et al, 1993</td>
<td>Irrespective of gender, initial TC/HDL level or age at the start of treatment, <strong>gemfibrozil</strong> has the lowest cost/LYS followed by <strong>lovastatin</strong> and <strong>cholestyramine</strong>. Costs/LYS are lower for men than for women. Costs/LYS are minimal when treatment is started between 50-55 years for men and between 55-60 years for women.</td>
</tr>
<tr>
<td>Heudebert et al, 1993</td>
<td>When <strong>lovastatin</strong> is used initially, the regimen becomes simpler albeit more expensive than other treatment approaches. The higher the initial LDL level, the more cost-effective a lovastatin therapy is. At low initial LDL levels, a <strong>niacin</strong>-first regimen is reasonably simple and substantially less expensive.</td>
</tr>
<tr>
<td>Oster et al, 1996</td>
<td>A stepped care regimen beginning with <strong>niacin</strong> is less costly than an initial therapy with <strong>lovastatin</strong> but is also less effective in lowering LDL, principally because of tolerability and compliance issues. Cost, compliance and efficacy considerations have to be taken into account.</td>
</tr>
<tr>
<td>Stinnett et al, 1996</td>
<td>Nearly all strategies that employ <strong>lovastatin</strong> as a first-line medication are dominated. In most cases, therapy with stepped care yields greater health gains at a lower cost. This result is explained by the fact that lovastatin has a smaller effect on HDL. <strong>Niacin</strong> on the other hand as a large effect on HDL.</td>
</tr>
</tbody>
</table>

Statins appear more cost-effective than cholestyramine and less cost-effective than stepped-care strategies that use niacin as initial therapy.
Effectiveness and cost-effectiveness in an actual setting depend also on compliance. In the above mentioned studies, only the studies by Stinnett et al (1996), Heudebert et al (1993) and Oster et al (1996), took compliance into consideration. Studies involving niacin (Stinnett et al, 1996; Heudebert et al, 1993) used compliance rates that were much lower than values reported elsewhere and mentioned in Section 5 of this report.

Furthermore, Drummond et al (1993) have shown that the actual cost-effectiveness of CHD interventions depend on the outcome or end point selected for the analysis. Relying on surrogate outcome measures such as LDL may show that certain interventions (for example statins) are cost-effective, whereas an analysis that uses QALYs as the outcome may indicate that another intervention (for example risk factor modification, such as lowering blood pressure or smoking cessation) is more cost-effective.

In summary, evidence is still incomplete regarding the cost-effectiveness of statins compared to other CHD interventions. Cost-effectiveness results depend highly on (1) the actual LDL and HDL impact assumed for each therapy, (2) the comparator chosen, (3) the outcome measure of the analysis and (4) the compliance rate assumed1.

7.2.2 Which Statin Is the Most Cost-effective?

Section 4.3 concluded that there is, at present, little evidence for or against a statin class effect, and that since cholesterol reduction obtained with diet, statins or other classes of lipid-lowering agents have been associated with a reduction in coronary events, it can legitimately be assumed, until proven otherwise, that since all statins decrease LDL levels and increase HDL, all would produce a decrease in coronary events. This is said with the caution that lipid level is a surrogate outcome, and that surrogate outcomes should be regarded in light of their limitations.

In theory then, one could opt to prescribe the least expensive statin since all factors that can cause differences in the cost of treatments, such as treatment patterns, side effects, indirect costs and compliance rates, are very similar. Potential differences are drug costs, exact effects on LDL levels and possibly drug interactions.

Another option would be to prescribe the statins that have been studied in large clinical trials and have been shown to have an impact on coronary events: pravastatin in primary prevention, pravastatin in secondary prevention in individuals having mildly to moderately elevated LDL levels, and simvastatin in secondary prevention, until similar studies have been conducted with the other statins.

However, there is no clear evidence that one approach is better than the other.

Table 32 indicates the prices of the different statins and dosages. This table is presented with the following caveats: 1) statins do not have a linear dose-response curve for LDL reduction; 2) the dosage that produces the maximum lipid-lowering effect on each patient is unknown; 3) concomitant medication may dictate the choice of another agent to avoid drug interactions; 4) HDL effects are not taken into account; 5) not all statins have been studied in clinical trials evaluating clinical benefits.

1 Note that these studies also differ on a number of other characteristics, such as the resources that were included, their perspective and the time horizon. However, these differences would not affect the conclusions of this section.
## Table 32: Cost per Equipotent Dosage

<table>
<thead>
<tr>
<th>% average reduction in LDL (Gonzales, 1996)</th>
<th>% reduction in LDL (range of reported values)*</th>
<th>Unit drug plan cost per tab (Drug acquisition cost only)**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>≤ 20% LDL reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluvarstatin 20 mg</td>
<td>-18%</td>
<td>$0.7500</td>
</tr>
<tr>
<td>pravastatin 10 mg</td>
<td>-20%</td>
<td>$1.5133</td>
</tr>
<tr>
<td><strong>21 - 29% LDL reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>simvastatin 5 mg</td>
<td>-24%</td>
<td>$0.9000</td>
</tr>
<tr>
<td>fluvarstatin 40 mg</td>
<td>-24%</td>
<td>$1.0500</td>
</tr>
<tr>
<td>pravastatin 20 mg</td>
<td>-25%</td>
<td>$1.7850</td>
</tr>
<tr>
<td>lovastatin 20 mg</td>
<td>-27%</td>
<td>$1.7313</td>
</tr>
<tr>
<td><strong>30 - 35% LDL reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lovastatin 40 mg</td>
<td>-30%</td>
<td>$3.1935</td>
</tr>
<tr>
<td>simvastatin 10 mg</td>
<td>-33%</td>
<td>$1.7800</td>
</tr>
<tr>
<td>pravastatin 40 mg</td>
<td>-34%</td>
<td>$2.1500</td>
</tr>
<tr>
<td><strong>36 - 40% LDL reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>simvastatin 20 mg</td>
<td>-36%</td>
<td>$2.2000</td>
</tr>
<tr>
<td>fluvarstatin 80 mg (2 x 40 mg)</td>
<td>--</td>
<td>$2.1000</td>
</tr>
<tr>
<td>lovastatin 80 mg (2 x 40 mg)</td>
<td>-40%</td>
<td>$6.3870</td>
</tr>
<tr>
<td>atorvastatin 10 mg</td>
<td>--</td>
<td>$1.6000§</td>
</tr>
<tr>
<td><strong>&gt; 40% LDL reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>simvastatin 40 mg</td>
<td>-41%</td>
<td>$2.7000</td>
</tr>
<tr>
<td>atorvastatin 20 mg</td>
<td>--</td>
<td>$2.0000§</td>
</tr>
<tr>
<td>atorvastatin 40 mg</td>
<td>--</td>
<td>$2.1500§</td>
</tr>
<tr>
<td>atorvastatin 80 mg (2 x 40 mg)</td>
<td>--</td>
<td>$4.3000§</td>
</tr>
</tbody>
</table>

* obtained from studies listed in Appendix 2
** combined mean LDL reduction of simvastatin 5 mg and 10 mg
§ Quebec Liste des médicaments no 47, July 1996.
§ 1997 prices
In general, it can be said that:

**Proposition 4: There is no evidence to indicate that one statin is more cost effective than another.**

7.2.3. **In Which Patients Should Statins Be Used?**

As presented in section 7.1, the most cost-effective use of statins can be obtained by using them in the population sub-groups identified below.

- In secondary prevention, for adults (35-70 years old) with high LDL levels;
- In secondary prevention, for adults (35-70 years old) with mild to moderately high LDL levels;
- In primary prevention, in adult men (35-65 years old) with high LDL levels and multiple CHD risk factors.

For these subgroups, effectiveness has been demonstrated in clinical trials for two of the five statins. Information is lacking for women, and no strong evidence exist for the elderly, especially in primary prevention. Even if lipid-lowering is effective in pre-menopausal women, it will be less cost-effective than in other women subgroups. All studies have shown that lipid lowering in the above mentioned subgroups is more effective, and cost-effective, than in other subgroups, even if there has been disagreement on the exact magnitude of the cost-effectiveness ratio (which as seen above depends on the types of analysis and various assumptions).

7.3 **Summary**

The cost-effectiveness ratios obtained in the various published studies, whether they are expressed as $ per LYS or as $ per 1% decrease in LDL, vary mostly as a result of the following factors:

- Magnitude of effect of the drug under consideration on LDL and HDL levels
- Resource items included in the analysis, and their cost
- Drug compliance
- The comparator used
- The end point of the analysis.

However, whatever assumptions are made regarding the above points, cost-effectiveness will be highly dependent on two crucial factors: (1) the presence of risk factors, and (2) the specific patient population under consideration (age and sex). These are the two essential determinants of the cost-effectiveness of lipid-lowering drugs and other lipid-lowering interventions.

The exact cost-effectiveness of statins ($ per life year saved) as compared to other lipid-lowering agents and among themselves has not been conclusively determined. It depends on the patient’s LDL and LDL/HDL responses, clinical outcomes and compliance.
8. CONCLUSION

Initiating lipid-lowering drug therapy depends on a patient’s lipid (cholesterol, LDL and HDL) and overall risk profiles. The choice of a particular agent depends on treatment goals, the patient’s concurrent medical condition and medication as well as the patient’s preference and anticipated compliance with the drug. Once it has been determined that a statin is needed, the choice of a particular agent should, in turn, depend on the ability of the agent to lower LDL to the targeted level, and on the cost of the agent. Consideration should also be given to the generalizability of the evidence from clinical trials to the patient.

All statins effectively lower cholesterol and LDL levels and raise HDL levels. Their safety profile is comparable. Differences exist in terms of pharmacokinetic properties and drug interactions which may be important in specific patients. Finally, not all statins have been studied to determine their long-term impact on coronary events and mortality.

Cost-effectiveness of lipid lowering will vary among patient groups according to their risk profile and cholesterol level. The higher the pre-treatment risk, the more cost-effective therapy will be. Accordingly, secondary prevention and the treatment of high risk individuals will have a more favorable cost-effectiveness ratio than treatment of other groups of individuals.

There is no evidence to indicate that one statin is more cost effective than another. However, the following factors need to be considered if statins are to be cost-effective: selecting the patient population that is most likely to benefit from treatment, maintaining treatment long enough to obtain clinical benefits, ensuring patient compliance, and selecting the agent that lowers LDL levels at the lowest cost.

Further work is needed to determine: 1) the benefits of statins in all population subgroups such as women and patients over 70 years of age; 2) how statins compare in head to head trials and; 3) whether they confer similar clinical benefits.
Appendix 1: Abbreviations

Miscellaneous
CHD  coronary heart disease
CI   confidence interval
CVD  cardiovascular disease
DBP  diastolic blood pressure
HDL  high density lipoprotein
HMO  health maintenance organization
IMS  Intercontinental Medical Statistics
LDL  low density lipoprotein
LLA  lipid-lowering agent
LYS  life-year saved
MI   myocardial infarction
OR   odds ratio
RAMQ Régie de l’assurance-maladie du Québec
SBP  systolic blood pressure
Statins HMG CoA reductase inhibitors
TC   total cholesterol
TG   triglycerides
VLDL very low density lipoprotein
W.H.O. World Health Organization

Trials
4S   Scandinavian Simvastatin Survival Study
ACAPS Asymptomatic Carotid Artery Progression Study
BUPA British United Provident Association
CARE Cholesterol and Recurrent Events
CCAIT Canadian Coronary Atherosclerosis Intervention Trial
CLAS Cholesterol Lowering Atherosclerosis Study
CRISP Cholesterol Reduction in Seniors Program
EXCEL Expanded Clinical Evaluation of Lovastatin
FATS Familial Atherosclerosis Treatment Study
FLARE Fluvastatin Angioplasty Restenosis
FLUENT Fluvastatin Long-term Extension Trial
HARP Harvard Atherosclerosis Reversibility Project
KAPS Kupio Atherosclerosis Prevention Study
LCAS Lipoprotein and Coronary Atherosclerosis Study
LIPID Long-term Intervention with Pravastatin in Ischaemic Disease
LRC CPP Lipid Research Clinics Coronary Primary Prevention Trial
MAAS Multicentre Anti-Atheroma Study
MARS Monitored Atherosclerosis Regression Study
MRFIT Multiple Risk Factor Intervention Trial
PLAC I Pravastatin Limitation of Atherosclerosis in the Coronary Arteries
PLAC II Pravastatin, Lipids, and Atherosclerosis in the Carotids
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>POSCH</td>
<td>Program on the Surgical Control of the Hyperlipidemias</td>
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<tr>
<td>REGRESS</td>
<td>Regression Growth Evaluation Statin Study</td>
</tr>
<tr>
<td>SCRIP</td>
<td>Stanford Coronary Risk Intervention Project</td>
</tr>
<tr>
<td>STARS</td>
<td>St Thomas’ Atherosclerosis Regression Study</td>
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<tr>
<td>WOS</td>
<td>West of Scotland Coronary Prevention Study (also called WOSCOPS)</td>
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Appendix 2: Safety And Efficacy Trials Comparing HMG-CoA Reductase Inhibitors

Lovastatin vs pravastatin


Lovastatin vs simvastatin


Lovastatin vs fluvastatin


Pravastatin vs simvastatin


Steinhagen-Thiessen E. Comparative efficacy and tolerability of 5mg and 10mg simvastatin and 10mg pravastatin in moderate primary hypercholesterolemia. Simvastatin Pravastatin European Study Group. *Cardiology* 1994;85(3-4):244-254.


**Simvastatin vs fluvastatin**


**Atorvastatin vs lovastatin**


**Atorvastatin vs pravastatin**


**Atorvastatin vs simvastatin**

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Pravastatin Multinational Study Group for Cardiac Risk Patients. Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. American Journal of Cardiology 1993;72(14):1031-1037.


