A CLINICAL AND ECONOMIC REVIEW
OF HMG-CoA REDUCTASE INHIBITORS
IN CORONARY HEART DISEASE

based primarily on the Technical Report:

HMG-CoA reductase inhibitors: a review of published clinical trials
and pharmacoeconomic evaluations

by

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This overview has been prepared by staff at CCOHTA and is based primarily on a technical report: **HMG-CoA reductase inhibitors: a review of published clinical trials and pharmacoeconomic evaluations.** This overview attempts to put the original study into a clinical perspective.

This overview does not necessarily reflect the opinions of the original investigators.

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SUMMARY REMARKS

BACKGROUND

Abnormalities in blood lipid levels, such as decreased high density lipoprotein (HDL) and elevated total cholesterol (TC), triglycerides (TG), low density lipoproteins (LDLs), very low density lipoproteins and TC/HDL ratios, have been linked to an increase in the risk of developing coronary heart disease (CHD). Pharmacological interventions aimed at lowering lipid levels have been demonstrated to decrease CHD and, more recently, to decrease coronary events and overall mortality. The degree of benefit that can be achieved in treating hypercholesterolemia is linked to the patient's inherent level of cardiovascular risk and remaining life expectancy. Whether a given patient should be started on lipid lowering therapy, the duration of treatment, and which agent to use has been difficult to answer due to the limited duration (< 5 years) of clinical trials, and the absence of data on long-term safety, effectiveness and cost-effectiveness.

This review attempts to address these issues, particularly as they relate to statin therapy. The primary objectives are:

- to review the efficacy of HMG-CoA reductase inhibitors (i.e. statins);
- to review whether there is evidence to suggest differences exist among the statins;
- to determine which population(s) would most likely benefit from statins;
- to review the costs and cost-effectiveness of statins.

This Overview is based primarily upon the CCOHTA report titled: “HMG-CoA reductase inhibitors: a review of published clinical trials and pharmacoeconomic evaluations” although additional information has been added since the publication of that report.

CONCLUSIONS

1) Epidemiologic studies demonstrate that changes in blood lipid levels (specifically decreased HDL and elevated TC, LDL and TC/HDL ratios) are associated with an increased risk of CHD. Given that CHD is a multi-factorial disease, additional risk factors (e.g. gender, age, family history, smoking status, presence of diabetes mellitus, obesity, or hypertension) will affect the risk of patients.

2) In general, early studies with non-statin lipid lowering agents showed a reduced risk of coronary events in both primary and secondary\(^a\) prevention trials. Coronary events (i.e. combined fatal and non-fatal CHD) were significantly reduced in primary prevention studies involving high risk populations; but there was no impact on fatal CHD alone or on overall mortality. Early secondary prevention trials involving non-statin drugs showed a significant reduction in the incidence of

\(^a\) Primary prevention: patient has no evidence of CHD.
Secondary prevention: patient has a history of CHD.
coronary events, and a non-significant reduction in overall mortality. The greatest benefits of therapy were realized in patients with the highest risk of a coronary event. These trials provided evidence that altering a patient’s lipid profile (raising HDL and decreasing LDL) improved cardiac outcomes. The statin trials strengthened this hypothesis by demonstrating that significant decreases in cardiac events and even mortality in high risk patients could be achieved.

3) In general, different patient subgroups tend to derive different absolute benefits from lipid lowering therapy. The benefit of primary prevention in hypercholesterolemic women has not been conclusively demonstrated; while with secondary prevention, women appear to derive similar decreases in coronary events as men. The impact of starting lipid lowering therapy in general in patients <35 years old is unknown. Despite the weaker association between lipid levels and CHD in elderly patients, it is still beneficial to provide secondary preventive treatment to those 60 to 70 years of age. Information on the benefits and risks of treatment is limited for those >70 years old.

4) It is generally accepted from experience gained over many years, that the risk of coronary events can be reduced by lowering TC and LDL and increasing HDL. Since all statins lower TC and LDL and increase HDL to varying degrees it may be assumed they will reduce the risk of coronary events. The effect of statins upon angiographic outcomes and coronary events is consistent. Indeed, in all major clinical trials conducted to date significant decreases in cardiac morbidity have been demonstrated [4S (simvastatin), WOSCOPS (pravastatin), CARE (pravastatin), AFCAPS/TexCAPS (lovastatin), LIPID (pravastatin)].

5) The question of whether some statins produce greater clinical benefits than others has not been determined as trials measuring clinical outcomes have not been conducted for all available statins, and their long term safety remains to be established. As well no head-to-head trials comparing different statins using clinical outcomes have been published. When making the choice between individual statins, variables such as the agent’s ability to lower LDL and raise HDL, concurrent medical conditions and/or drug therapy, cost, and the amount of information from clinical trials available for each statin should be taken into consideration. In addition, generalizability of data from clinical trials to the individual patient remains a challenge. The reported low to moderate rate of compliance within the first year with any type of lipid lowering therapy reduces the potential benefit of these agents.

6) The pharmacoeconomic literature related to lipid lowering therapy, in general, concludes that secondary prevention is more cost-effective than primary preventive therapy. A patient’s risk plays a role in determining cost-effectiveness, in that as the risk of a coronary event increases (e.g. with higher pre-treatment TC and LDL and/or lower HDL), the more likely it is that the lipid lowering therapy will be cost-effective.

\[ A \text{FCAPS/TexCAPS and LIPID have not been published yet but results were presented at the American Heart Association meetings November 1997.} \]
With regards to statins, there is no clear evidence as to whether a cost minimization approach (i.e. prescribing the least expensive statin) or a clinical approach (i.e. prescribing the statins which have been shown in large clinical trials to have an impact on coronary events) is the best method of using this group of agents in the most cost-effective manner. There is no evidence to indicate that one statin is any more or less cost-effective than another.

7) Limitations:
   • incompleteness of the available clinical data, i.e. absence of head to head statin trials, absence of long term efficacy and effectiveness data;
   • the absence of a systematic review of the data, i.e. this report is not a meta-analysis;
   • the absence of detailed economic information to assist decision makers in determining the applicability of the available evidence to their own settings.
CLINICAL REVIEW

Coronary Heart Disease and Lipids

Cardiovascular diseases (CVD)\(^c\) account for a large proportion of deaths and morbidity in Canada. For example, ischemic heart disease alone was responsible for 22% of total deaths and 38% of hospital admissions in 1992.\(^2\) The risk of death from CVD increases with age in both genders, with women having a lower absolute risk in all age groups except those >75 years of age. Given the aging population, the impact of CVD on the health care system can only be expected to increase with time.

Elevated blood lipid levels have been associated with an increased risk of CVD as well as CHD. In addition, a number of other risk factors which predispose individuals to these disease states have been identified. Canadian guidelines for the detection and management of hypercholesterolemia\(^3\) identify the following risk factors for CHD:

- **age:** male ≥ 45 years; female ≥ 55 years or post-menopausal not on hormone replacement therapy
- diabetes mellitus
- family history of premature CHD in a first degree relative (males ≤ 55 years; females ≤ 65 years)
- smoking
- hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) or patients receiving antihypertensive medication
- HDL levels ≤ 0.9 mmol/L or LDL/HDL ratio > 5.0
- left ventricular hypertrophy
- obesity (body mass index >27)

The interactions amongst these risk factors in creating the atherosclerotic plaque which ultimately leads to coronary events have not been clearly delineated; but it is clear that in the presence of multiple risk factors, there is compounding of the risk for coronary disease.

**The Potential Scope of the Problem**

The prevalence of elevated lipid levels in Canada has been determined.\(^4\) In a survey of almost 17,000 individuals between 1986 and 1990, the following rates of occurrence were found: 46% had a TC above 5.2 mmol/L, 15% had an LDL above 4.1 mmol/L, 15% had TGs above 2.3 mmol/L, and 8% had an HDL below 0.9 mmol/L.\(^d\)

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\(^c\) CVD: acute myocardial infarction, ischemic heart disease and stroke.
CHD: acute myocardial infarction and ischemic heart disease.

\(^d\) Note that lipid levels which are above the threshold values listed are associated with an increased risk of CHD, with the exception of HDL, where levels below that reported are related to increased risk.
Treating the Problem

The goal of treatment of hypercholesterolemia (i.e. the target lipid value[s]) varies depending on the number of other risk factors at play in the individual patient. Note that, both in defining treatment goals and in outcomes measured in many clinical trials, lipid levels are surrogate or intermediate markers of the impact of the intervention. Ideally, actual clinical outcomes, such as cardiovascular events, would be evaluated to assess the impact of an intervention as in more recent trials evaluating lipid lowering therapies.

Methods of Evaluation of Clinical Evidence

The CCOHTA report relied on the review of clinical evidence, pharmacoeconomic literature (see below) and examination of market research data. Literature searches were conducted using a variety of databases covering the period from 1966 to 1996. Estimates of the use and prescribing of cholesterol lowering agents and statins provided by Intercontinental Medical Statistics (IMS) Canada were included in the technical report, but are not discussed in this overview.

Results of the Clinical Review

Three large scale clinical trials of statins have been published: the Scandinavian Simvastatin Survival Study (4S)\(^5\), the West of Scotland Coronary Prevention Study (WOSCOPS)\(^6\), and the Cholesterol and Recurrent Events Study (CARE)\(^7\). Patient population and findings are described below.

**WOSCOPS**

This primary prevention trial evaluated pravastatin in men, with elevated baseline lipid levels, for an average of 4.9 years of follow-up. Significant risk reductions (absolute/relative) were demonstrated for the following outcomes: definite non-fatal MI (1.9%/31%) and death from all cardiovascular causes (0.7%/32%). Reduction in death from any cause almost achieved conventional statistical significance (p = 0.051).

**4S**

This secondary prevention trial evaluated simvastatin in patients (19% female) with elevated lipid levels and a history of angina or MI for 5.4 years. Significant risk reductions (absolute/relative) were demonstrated for the following outcomes: definite acute non-fatal MI (4.7%/37%), coronary deaths (3.5%/42%), all cardiovascular deaths (3.2%/35%), and overall mortality (3.3%/30%).

**CARE**

This secondary prevention trial evaluated pravastatin in patients (14% female) with normal to mildly elevated lipids and a history of MI for 5.0 years. Significant risk reductions (absolute/relative) were demonstrated for the following outcomes: death from CHD or non-fatal MI (3%/24%), non-fatal MI (1.8%/23%), and fatal MI or confirmed non-fatal MI (2.5%/25%). As well the pravastatin group had significantly lower rates of coronary bypass surgery, angioplasty, and stroke.

Results of two other trials, AFCAPS/TexCAPS and LIPID, using lovastatin and pravastatin respectively, have recently been presented; they also demonstrated a significant impact on cardiac events. In randomized trials, the effect of statins upon angiographic and clinical outcomes has consistently shown a beneficial effect of lowering LDL and raising HDL.
Summary

Table 1 provides an overview of the impact of each of the available statin medications (except atorvastatin) on lipid levels. While no true conversion factors have been developed, it has been suggested that the clinical effect of 40 mg fluvastatin is approximately equivalent to 5 - 10 mg simvastatin, 20 mg pravastatin or 20 mg lovastatin based on their ability to reduce LDL. 8, 9

Table 1: Comparison of lipid lowering properties of statins 10

<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 available in Canada

The following factors need to be taken into consideration when selecting a statin for lipid lowering therapy:

- all statins effectively lower TC and LDL levels, and increase HDL
- pharmacokinetic characteristics vary among the statins
- the safety profiles of statins are comparable
- statins interact to varying degrees with other drugs (via P-450 metabolism; e.g. anticoagulants, cyclosporine, erythromycin)
- clinical trials measuring clinical outcomes have not been conducted for all statins, nor have there been studies in every population to determine the long-term impact on coronary events and mortality

It is reasonable to select a statin based on its ability to lower LDL and raise HDL, the patient’s concurrent medical conditions and drug therapies, the amount of information from clinical trials available for each statin and cost. Support for the fundamental role of LDL in atherogenesis derives from several sources: epidemiology, animal research, genetic forms of hypercholesterolemia, laboratory studies, and clinical trials.11 The importance of LDL reduction is exemplified by the recent American Heart Association Medical and Scientific Statements regarding optimal target levels for LDL.12

Compliance with therapy is an important issue which is of particular concern when on-going drug treatment is required. The clinical effects of lipid-lowering drugs, specifically statins, do not become apparent for at least 6 to 12 months. Rates of discontinuation of statin therapy due to adverse effects, lack of effectiveness, or non-compliance ranged from 24 to 26% after one prescription to 22.8% after one year. These results are based on data from actual practice in two Canadian studies.13, 14 Thus, patient adherence to therapy (i.e. discontinuation of treatment within the first year) has an impact not only on clinical success but also on the cost-effectiveness of therapy.
REVIEW OF ECONOMIC EVALUATIONS

The technical report reviewed several cost-effectiveness evaluations involving a statin medication. The sections which follow put these studies into context by outlining the major clinical and economic issues as well as inferences derived from their results.

Clinical Factors Impacting on Cost-effectiveness

The prime factor affecting the cost-effectiveness of a given lipid lowering strategy is the baseline risk. Given this, it is reasonable to state that the greater the likelihood of experiencing a coronary event, the more cost-effective lipid lowering therapy will be. Studies indicate that the cost-effectiveness of lipid lowering therapy is most attractive with the higher pre-treatment cholesterol levels, all other risk factors being the same. Finally, it appears that secondary prevention treatment is generally more cost-effective than primary prevention, due to the higher absolute baseline risk of coronary events in the former.

Deriving Cost-effectiveness Ratios for Statin Therapy

A number of the economic evaluations that were reviewed derived cost-effectiveness ratios using a modelling approach. These studies "translated" the LDL reductions achieved by a given lipid-lowering therapy into life-years saved (LYS) by using data regarding risks for various coronary events which were obtained from the Framingham Heart Study (a very large, longitudinal study part of which evaluated the relationship between cholesterol levels and coronary risk). The use of estimates of major benefit when these benefits have not been shown in clinical trials has been criticized. However these studies helped to predict substantial benefit from lowering cholesterol before the clinical results from statins were known. More recent economic assessments have determined the cost-effectiveness of statin therapy concurrent with clinical trials, thus incorporating any direct measurement of reduction in coronary events and changes in mortality into the evaluation. For example a recent economic evaluation has been conducted on the data from the 4S study.\(^{15}\)

Irrespective of the source of clinical data (i.e. modelling versus direct measurement), the cost-effectiveness ratios for statin medications vary significantly based on the specific patient population, the timing of therapy (i.e. primary versus secondary prevention), and the degree of LDL lowering/HDL increase assumed or measured in the study. Generally, the more likely the chance of experiencing a coronary event, the more cost-effective lipid lowering strategies will be. For example, secondary prevention is more cost-effective than primary prevention. Also the 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.

In summary, evidence is incomplete regarding the cost-effectiveness of statins compared to other interventions aimed at CHD (i.e. other lipid lowering therapies, smoking cessation, blood pressure control, exercise, etc). Results of these economic evaluations depend highly on the impact that is assumed to occur on the lipid profile, the comparator chosen, the outcome measures selected and the compliance rate.

Which Statin is the Most Cost-effective?
As noted above, clinical trials have not been carried out with all agents. One might expect that all statins would produce a decrease in coronary events based on the total evidence available to date (i.e. that lipid lowering in general reduces coronary events, that all statins decrease LDL and increase HDL levels and that statins have consistently shown a beneficial effect on angiographic outcomes and clinical events.)

Keeping in mind the limitations of the trials in which clinical impact has been demonstrated, it can be said that the other main differences among the statins relate to costs, LDL/HDL impact and possible drug interactions. Clinicians should also keep in mind the information available for each statin. Table 2 outlines the cost per equipotent dosage for available statin therapies based on LDL reduction.

**Targeting the Use of Statins**

The CCOHTA report concludes that the most cost-effective use of statins can be obtained by their use in the following patient subgroups:

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

In each of these subgroups, the effectiveness of statins using clinical outcomes has been demonstrated. More information regarding the use of these drugs in women (in primary prevention) and elderly patients (in primary or secondary prevention) is needed.
### Table 2: Cost per equipotent dosage

<table>
<thead>
<tr>
<th>% average reduction in LDL(^{13})</th>
<th>% reduction in LDL (range of reported values)(^{14})</th>
<th>Unit drug plan cost per tablet (drug acquisition cost only)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 20% LDL reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluvastatin 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>21 - 29% LDL reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>simvastatin 5 mg - 10 mg</td>
<td>-24%</td>
<td>$0.9000 - $1.7800</td>
</tr>
<tr>
<td>fluvastatin 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>30 - 35% LDL reduction</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>36 - 40% LDL reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>simvastatin 20 mg</td>
<td>-36%</td>
<td>$2.2000</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 (1997 price)</td>
</tr>
<tr>
<td>&gt;40% LDL reduction</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 (1997 price)</td>
</tr>
<tr>
<td>atorvastatin 40 mg</td>
<td>--</td>
<td>$2.1500 (1997 price)</td>
</tr>
<tr>
<td>atorvastatin 80 mg (2 x 40 mg)</td>
<td>--</td>
<td>$4.3000 (1997 price)</td>
</tr>
</tbody>
</table>

* Québec Liste des médicaments, No. 47, July 1996.
** Combined mean LDL reduction of simvastatin 5 mg and 10 mg.

Note the following points as they pertain to this table: statins do not have a linear dose-response curve for LDL reduction; the dosage that produces the maximum lipid-lowering effect on each patient is unknown; concomitant medication dictates caution in drug selection due to potential drug interactions; HDL effects are not taken into account; and, not all statins have been studied in clinical trials evaluating clinical benefits.
LIMITATIONS OF THE EVALUATION

Limitations of this evaluation relate, to a large extent, to limitations of the available clinical data. Despite the fact that only two statins, pravastatin and simvastatin, have published clinical outcome trials with statistically significant results, the weight of evidence would indicate that statins may be regarded to have a class effect due to their abilities to decrease LDL and increase HDL, and their consistent effects upon angiographic and clinical outcomes. In addition, long term efficacy and effectiveness data (greater than 5 years) are not currently available in the literature for any of these agents. Direct comparative trials amongst the statins are also absent.

The clinical endpoints used in the statin trials that were available were highly variable from one study to the next. These included the use of LDL and HDL level changes to predict the impact on coronary events, angiographic changes in coronary artery diameter as a marker for the drug’s efficacy; or assessment of the impact of therapy on coronary events over a longer term. Differences in the selection of primary study endpoints, the duration of therapy, and differences in patient population studied (e.g. % of patients on concurrent ASA and beta blockers) make the interpretation of the true cost-effectiveness of these medications difficult, as this depends on demonstrated success of treatment in the general population in the long run.

The CCOHTA report itself is a review of the literature and does not systematically combine the information available (i.e. this is not a meta analysis). This is also not a formal pharmacoeconomic evaluation. Given that there were many such formal evaluations in the literature, the goal of the economic review was to develop conclusions based on the findings of these studies. Decision makers should refer to the original studies cited in the CCOHTA report to determine the applicability of these individual evaluations (i.e. comparability of costs, etc.) to their own setting.
REFERENCES


