Cost-effectiveness of lipid-lowering treatment according to lipid level
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined lipid-lowering treatment with simvastatin. Different dosages (mainly 20 or 40 mg/day) were considered.

Type of intervention
Primary and secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised individuals between the ages of 30 and 74 years. Two sub-groups of patients were considered. The CVD group comprised individuals with a history of acute myocardial infarction (AMI), stroke, or other heart disease who were taking heart medication. The non-CVD group included all other individuals.

Setting
The setting was primary care. The economic study was carried out in Canada.

Dates to which data relate
The effectiveness data were derived from studies published between 1979 and 1996. Much of the data on resource use and costs were derived from a study published in 1999. The price year was 1996.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Modelling
A published CVD life expectancy model was used to estimate the CVD risk of the representative population sample. The model calculated the annual probability of CVD events (fatal and nonfatal) and estimated the benefits (in terms of life-years saved) of risk factor modifications. The multi-factorial risk model incorporated the following risk factors: age, gender, smoking, cholesterol levels, blood pressure, diabetes mellitus and CVD. The Markov model was used to describe the yearly transition to a CVD end point, including angina pectoris, nonfatal MI, congestive heart failure, transient ischaemic attack or a nonfatal stroke, as well as related and non-related fatal events. The model considered a hypothetical cohort of 1,000 individuals, who were followed until death. Thus, the cycle length was 1 year and the time horizon was the patient's lifetime.

Outcomes assessed in the review
The outcomes assessed from the literature were:

the risk of CVD,

the probabilities of fatal and nonfatal events,

treatment effect, and

the proportions of patients receiving different drug doses.

**Study designs and other criteria for inclusion in the review**

It would appear that a systematic review of the literature was not undertaken and the primary studies might have been identified selectively. Data on CVD risk were derived from the Canadian Heart Health Survey (CHHS), which gathered data from 1986 and 1993 from a random sample representative of the Canadian population. The final sample used for this analysis comprised 2,212 individuals with CVD and 12,982 individuals without CVD. Event rates (angina pectoris, nonfatal MI, congestive heart failure, transient ischaemic attack, or a nonfatal stroke) came from the Lipid Research Clinic Coronary Primary Prevention Trial (LRC-CPPT). Treatment efficacy was derived from the Scandinavian Simvastatin Survival Study (4S). Extensive information on the CHHS was provided, but few details of the other studies were given.

**Sources searched to identify primary studies**

Not stated.

**Criteria used to ensure the validity of primary studies**

Not stated.

**Methods used to judge relevance and validity, and for extracting data**

Not stated.

**Number of primary studies included**

Five primary studies provided the clinical data.

**Methods of combining primary studies**

The primary estimates were not combined since each study provided a group of estimates.

**Investigation of differences between primary studies**

Not stated.

**Results of the review**

Simvastatin led to a 25% reduction in TC, a 35% reduction in low-density lipoprotein cholesterol, and an 8% increase in high-density lipoprotein.

The analysis of simvastatin doses showed that 61.6% of patients were given 20 mg/day, 31.6% were given 40 mg/day, 0.1% were given 10 mg/day, and 6.7% discontinued the drug.

Some data on the risk of CVD death were reported. For example, the 10-year risk of CVD death in individuals with TC levels higher than 6.2 mmol/L was 15.3% in men with CVD, 7.7% in men without CVD, 16.5% in women with CVD, and 8.2% in women without CVD.
In general, the 10-year risk of CVD death was 13.1% in individuals with CVD and 2.5% in individuals without CVD.

Other data used to populate the decision model were not reported.

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the life-years saved. These were obtained using the decision model. An annual discount rate of 3% was applied.

**Direct costs**
The authors did not explicitly state the perspective adopted in the study, but it appears to have been that of the third-party payer. The analysis of costs included simvastatin, other cardiovascular drugs, hospitalizations for surgical and non-surgical events, physician services for emergency, inpatient and outpatient care, and laboratory services. The unit costs and the quantities of resources used were not presented separately. Most details on the cost calculation had been published in 1999. The costs were mostly based on reimbursement fee schedules. The drug costs were derived from retail prices including a dispensing fee. Resource use appears to have been based on typical treatment patterns in the authors' setting. An annual discount rate of 3% was applied to future costs. The price year was 1996.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
Canadian dollars (CAD).

**Sensitivity analysis**
A univariate sensitivity analysis was carried out to assess the robustness of the estimated cost-effectiveness ratios to variations in treatment efficacy (+/- 10%).

**Estimated benefits used in the economic analysis**
The estimated life-years gained were not reported.

**Cost results**
The cost of the first year of treatment with simvastatin was reported and was extrapolated to the Canadian population.

For primary prevention in men, the annual cost was CAD 602 million for those with a TC level > 6.2 mmol/L, CAD 1.8 billion for those with a TC level >/= 5.2 mmol/L, and CAD 2.6 billion regardless of TC level.

For primary prevention in women, the annual cost was CAD 194 million for those with a TC level > 6.2 mmol/L, CAD 408 million for those with a TC level >/= 5.2 mmol/L, and CAD 473 million regardless of TC level.

For secondary prevention in men, the annual cost was CAD 90 million for those with a TC level > 6.2 mmol/L, CAD 303 million for those with a TC level >/= 5.2 mmol/L, and CAD 605 million regardless of TC level.

For secondary prevention in women, the annual cost was CAD 124 million for those with a TC level > 6.2 mmol/L, CAD 220 million for those with a TC level >/= 5.2 mmol/L, and CAD 333 million regardless of TC level.
Synthesis of costs and benefits

Incremental cost-effectiveness ratios (ICERs) were calculated to combine the costs and benefits of simvastatin therapy in comparison with no intervention.

For primary prevention in men, an ICER below the cut-off value of CAD 50,000 per life-year gained was obtained for those aged 45 to 59 years regardless of TC levels, those of all ages with a TC level > 6.2 mmol/L, and those older than 44 years with a TC level >/= 5.2 mmol/L. Primary prevention in women was never cost-effective (the ICERs were always higher than CAD 100,000).

For secondary prevention in men, an ICER below the cut-off value of $50,000 per life-year gained was observed in men of all ages and regardless of TC levels. For women, an ICER below the cut-off value was obtained for those of all ages with a TC level > 6.2 mmol/L, those older than 44 years with a TC level >/= 5.2 mmol/L, and those older than 44 years regardless of the TC level.

The proportion of individuals for whom primary and secondary prevention with simvastatin was cost-effective (according to cholesterol levels) was also estimated.

For primary prevention, simvastatin was cost-effective (given a threshold of CAD 50,000 per life-year saved) in:

- 85.6% of men and 28.7% of women with TC level > 6.2 mmol/L,
- 70.6% of men and 18.4% of women with TC level >/= 5.2 mmol/L, and
- 51.4% of men and 9.3% of women regardless of TC levels.

For secondary prevention, simvastatin was cost-effective (given a threshold of CAD 50,000 per life-year saved) in:

- 99.8% of men and 86.1% of women with TC level > 6.2 mmol/L,
- 99.2% of men and 77.1% of women with TC level >/= 5.2 mmol/L, and
- 94.7% of men and 55.5% of women regardless of TC levels.

The sensitivity analysis showed that changes in treatment efficacy did not substantially alter the conclusions of the base-case analysis.

Authors' conclusions

Lipid-lowering treatment with simvastatin was cost-effective for a high proportion of the population, even for primary prevention in Canada. In general, this treatment was more cost-effective in men and in secondary prevention. However, the cost of a population-wide treatment was high, even among high-risk individuals.

CRD COMMENTARY - Selection of comparators

The comparator selected (i.e., no treatment) was appropriate as it reflected the current preventive strategy for individuals not at risk for CVD events. Among all possible drugs available for lipid-lowering therapy, the choice of simvastatin was arbitrary. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness

The effectiveness evidence was derived from published sources, but the primary studies appear to have been identified selectively rather than through a systematic review of the literature. Limited information on the primary studies was reported, except for the CHHS. However, the treatment effect of simvastatin was taken from a well-known randomised controlled trial, and this should ensure the internal validity of the analysis. The authors assumed that the treatment effect of simvastatin was the same regardless of lipid levels. This, as the authors acknowledged, would appear to represent a limitation of the analysis. Limited sensitivity analyses were performed to address the issue of uncertainty in
the decision model.

**Validity of estimate of measure of benefit**
The summary benefit measure was appropriate as it reflected the most important dimension of health for patients at risk of CVD (i.e. survival). However, the estimates of life-years gained were not reported. Discounting was applied, as recommended by pharmacoeconomic guidelines.

**Validity of estimate of costs**
The perspective of the study was unclear, but only the direct medical costs were considered in the analysis. The source of the data was reported for all items, and further details of the cost analysis were published elsewhere. A breakdown of the costs was not provided and few unit costs were presented. There were limited data on utilisation rates, which will limit the possibility of replicating the analysis in other settings. No statistical analyses of the costs were carried out. Most of the costs were specific to the Canadian setting and the impact of alternative estimates was not investigated. The price year was reported, which will simplify reflation exercises in other time periods.

**Other issues**
The authors reported the results of published studies that showed the clinical benefits of lipid-lowering treatments in individuals not at high-risk of CVD events. The issue of the generalisability of the study results to other settings was not explicitly addressed and few sensitivity analyses were performed, which limits the external validity of the study. The study referred to different patient populations and this was reflected in the authors’ conclusions. The authors noted some limitations of their analysis, mainly related to the use of dated data and the need for some generalising assumptions. Unfortunately, the sensitivity analysis did not specifically address these points.

**Implications of the study**
The study results suggest that population-wide treatments for the prevention of cardiovascular events may not be affordable from the perspective of the health care system.

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**Other publications of related interest**


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