Comparison of efficacy and cost among lipid-lowering agents in patients with primary hypercholesterolemia

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Authors' objectives
To compare the efficacy and cost of lipid-lowering agents in patients with primary hypercholesterolaemia.

Searching
MEDLINE was searched up to January 1996 for articles using the keywords 'cholesterol', 'hyperlipidemia' and 'anticholesterolmic agents'. The search was limited to articles published in English, French or German. Additional references were identified by examining the bibliographies of those articles retrieved.

Study selection
Study designs of evaluations included in the review
Blinded, randomised and non-randomised trials evaluating single lipid-lowering monotherapy were included, whilst those examining combined therapies were excluded.

Specific interventions included in the review
The specific interventions included in the review were: bezafibrate (400 to 1,350 mg/day), cholestyramine (8,000 to 24,000 mg/day), ciprofibrate (50 to 100 mg/day), clofibrate (1,500 to 2,000 mg/day), colestipol (20,000 mg), fenofibrate (200 to 400 mg/day), fluvastatin (2.5 to 80 mg/day), gemfibrozil (800 to 1,600 mg/day), lovastatin (10 to 80 mg/day), pravastatin (5 to 80 mg/day), probucol (1,000 to 2,000 mg/day) and simvastatin (2.5 to 80 mg/day). The duration of the treatment ranged from 4 to 104 weeks. The control treatment was another monotherapy regimen.

Participants included in the review
The patients included in the review had to have primary hypercholesterolaemia, explicit or at least deducible on the basis of the patient exclusion criteria. All patients had to have abnormal lipid levels, in spite of appropriate diet therapy that was continued for the duration of the trial. The mean baseline total cholesterol (TC): high-density lipoprotein (HDL) ratio was 7.3 for the participants included in the review. The participants had an average age of 50.5 years and the mean proportion of men was 62.5%. No attempt was made to distinguish trials comprising patients with and without coronary artery disease because this clinical parameter was not included in many reports.

Outcomes assessed in the review
The treatment efficacy was assessed in terms of the percentage change from baseline in the TC:HDL ratio.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not state that they assessed quality.

Data extraction
Data were extracted from the primary studies on patient numbers, patient demographics, and the effect of treatment on TC and HDL levels. The data were tabulated according to the total daily dose, regardless of the treatment regimen.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis, with results combined across trials for each dose level, weighted by the sample size at each dose level.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
One hundred and twenty-four studies involving 25,157 patients were included in the review: 83 randomised trials and 41 non-randomised trials.

Information including the average percentage change in the TC:HDL ratio, the baseline TC:HDL ratio, the average duration of treatment, the number of participants and the number of studies, was provided for 47 different monotherapy regimens. Confidence intervals for the TC:HDL ratio could not be calculated due to insufficient information in the original studies. Given the small number of patients studied for some drugs, there may be broad confidence intervals. The effect of treatments on the TC:HDL ratio varied from a 23% increase in the ratio with probucol (1 g/day) to a 46% decrease with simvastatin (80 mg/day). The more recently introduced drugs appeared to have improved efficacy, and there was a trend towards a dose-effect relationship with a number of the drugs.

Cost information
Cost comparisons were carried out for each of the treatments using the acquisition price of lipid-lowering agents. The cost-effectiveness analysis assumes that the only important cost is the acquisition price of the drug, and that all patient management costs (diagnosis, treatment of adverse events, physician visits) are identical. Drug prices were obtained from the Quebec provincial drug formulary, Regie de l’Assurance Maladie du Quebec (RAMQ) for the first quarter of 1996. Various dose levels for each drug were evaluated separately. The analysis also assumes that within and among classes there are no meaningful differences in side-effects, which would otherwise alter the risk-to-benefit and cost-to-benefit ratios.

The results of the cost-effectiveness analysis were presented in graphical form using the decrease in TC:HDL ratio per dollar of daily drug cost. The drugs were divided into three categories according to their efficacy.

The first category were products which produced a less than 20% decrease in the TC:HDL ratio. These included cholestyramine, clofibrate and probucol; these are the three oldest products on the Quebec market and are now much less frequently prescribed due to their low efficacy and patient compliance.

The second category of drugs, which produced a 20 to 30% decrease in the TC:HDL ratio, included the largest number of treatments. The most cost-effective drugs within this category were fluvastatin (20 mg/day, acquisition cost $0.75), simvastatin (5 mg/day, $0.90) and fluvastatin (40 mg/day, $1.05).

For drugs with the most potent effect on the TC:HDL ratio, i.e. a greater than 30% decrease in the ratio (third category), the most cost-efficient treatments were fluvastatin (60 mg/day, acquisition cost $1.80), micronised fenofibrate (200 mg/day, $1.73), and simvastatin (20 mg/day, $2.20).

Authors’ conclusions
The results of this review could aid clinicians in selecting the cheapest agents to achieve a specified goal of therapy.

CRD commentary
In general, this review was clearly presented and incorporated well-defined criteria for the inclusion of studies and participants. Details of the keywords used to retrieve articles were provided, thus enabling other researchers to repeat the search strategy. However, the primary studies were retrieved by searching only one database, and the search was limited to German, French and English language articles; this may have resulted in relevant literature being excluded from the review. In addition, no attempts were made to locate potentially useful information from other sources,
including unpublished data. The authors clearly stated what information was extracted from the included studies, but they did not state how decisions on the relevance of primary studies were made. In addition, there appeared to be no assessment of study quality or heterogeneity before the studies were combined in the meta-analysis.

The results of the meta-analysis were presented without confidence intervals, which the authors stated was due to the lack of information in the primary studies. This, however, causes difficulties when interpreting the significance of the results. In addition, the results from the cost-effectiveness analysis were only presented in graphical form and no absolute values were provided. It is not possible to comment on the validity of the authors' conclusions as they fail to make any overall definitive comments on the effectiveness and cost-effectiveness of the various treatment regimens.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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