

## **The cost-effectiveness of statin treatment: can we synthesize evidence from economic evaluations?**

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### **Abstract**

Bayesian approaches to economic analysis of health care interventions could be a way towards synthesising evidence for economic evaluations. As part of the preparations for undertaking an economic evaluation of the Heart Protection Study(3), it was decided to explore the evidence on the cost-effectiveness of statin therapy in order to specify prior beliefs for parameters in the population of interest, as a necessary step towards a future Bayesian analysis. A systematic review of the published economic evaluation studies of statins and other cholesterol lowering interventions was performed to explore the prior knowledge of their cost effectiveness measured in cost per LY/QALY. The studies were critically appraised with respect to data employed and study methodology (study population(s), primary study, secondary study, types of modelling, assumptions made). The richness of economic evaluations in the area allowed issues related to the use of modelling and evidence synthesis for economic evaluations to be explored and discussed.

## Introduction

In the last decade there has been widespread interest in the use of cholesterol-lowering drugs (3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitors or 'statins') primarily in relation to the link between cholesterol levels and increased risk of heart disease. The general consensus to date seems to be that secondary prevention with statins for patients with hypercholesterolemia represents good value for money, but that primary prevention is probably not a good use of scarce health care resources – partly due to the potential scale of the eligible population if statins were used to treat all patients with elevated cholesterol levels.

Furthermore, the scope of potential treatment with statins is increasing as evidence accumulates as to their effectiveness. In particular, it has been observed that cholesterol levels in the Western world are much higher than cholesterol levels in the East and that Western populations experience much more heart disease. What is a 'normal' cholesterol level for us in the West might be considered rather high in an Eastern population. It has been hypothesised that statin therapy might also be worthwhile for patients with cholesterol levels in the 'normal' range but who have elevated risk of heart disease, e.g. through pre-existing heart disease, diabetes or through a family history of heart disease.

The Heart Protection Study (HPS) was designed to test just such a hypothesis, but also represents (with 20,000 patients randomised) one of the largest randomised controlled trials of the impact of statin treatment ever performed. The study includes 40-75 years old males or females at increased CHD risk (with history of CHD, diabetes, high blood pressure and/or other risk factors). Individuals with low to medium cholesterol levels ( $>3.5$  mmol/l) were also eligible provided that they are considered on the basis of other factors to be at substantial risk of CHD. Patients were randomly allocated to Simvastatin 40 mg/day or placebo in a 2x2 factorial design together with vitamin supplementation. The employment of minimum number randomisation at the baseline of this trial allows for valid analysis of subgroups of the population (3).

As a first step toward undertaking an economic analysis of the HPS study, we undertook a systematic review of the economic evaluation literature to identify cost-effectiveness analyses of statin therapies that reported results in terms of cost per life-year (or quality-adjusted life-year). There has been an increasing interest recently in the use of Bayesian methods for cost-effectiveness analysis and we were interested in seeing whether it would be possible to specify a true 'prior' on cost-effectiveness before analysing the HPS data (often Bayesian analyses proceed by 'imagining' that a prior had been specified before the data analysis!). However, we wanted this prior to be 'evidence based', reflecting what is

currently known in the scientific community about the cost-effectiveness of Statin therapy rather than representing our own subjective views about how cost-effective we thought the therapy might be. Furthermore, by reviewing the methods employed to analyses cost-effectiveness, we hoped to ensure that our analysis built on the state of the art methods for estimating cost-effectiveness.

However, our interest in synthesising the results of economic evaluations extends beyond the specific application to the analysis of the HPS. With the increasing use of economic evaluation it has become natural for analysts to consider how the results of economic evaluations might be synthesised in order to give an overview of the cost-effectiveness of a treatment intervention for a particular disease area. Recently, Nixon and colleagues (54) have proposed a 'new approach' to summarising cost-effectiveness results and we were keen to consider this method in addition to other potential approaches. In particular, the level at which synthesis is conducted could be an important issue. Nixon and colleagues favour summarising the evidence at the level of the cost-effectiveness ratio. However, we might also consider summarising costs and effects separately (or on the cost-effectiveness plane); synthesising individual parameters of the model (as with many 'Bayesian' cost-effectiveness models); or even synthesising based on individual patient level data (where such data are available). Given the wealth of economic evaluations addressing the cost-effectiveness of statin therapy, this topic area seems an ideal one in which to explore the potential for systematic review and synthesis of evidence.

## **The systematic review**

In this section the search strategy for identifying studies is described, descriptive results from that strategy are reported, the main areas of focus for the review are identified and finally the comparative analysis of the reviewed articles for those areas is reported.

### **Search strategy**

A systematic review of cost-effectiveness studies of HMG-CoA Reductase Inhibitors was undertaken. The studies were identified through searches of Medline, OHE HEED, CRDEED, developed databases in HERC as well as referenced studies in the bibliographies of previously identified studies. Broad search criteria were used in different databases (see Appendix 1) in order to identify published economic evaluations of statins. This resulted in the identification of 705 potentially relevant studies (Medline (362 references), CRDEED (75 references), OHE HEED (222 references), HERC (46 references)). The abstracts of the initially identified studies were obtained and assessed against the criteria for the review.

In order to be selected a publication needed to meet the follow criteria.

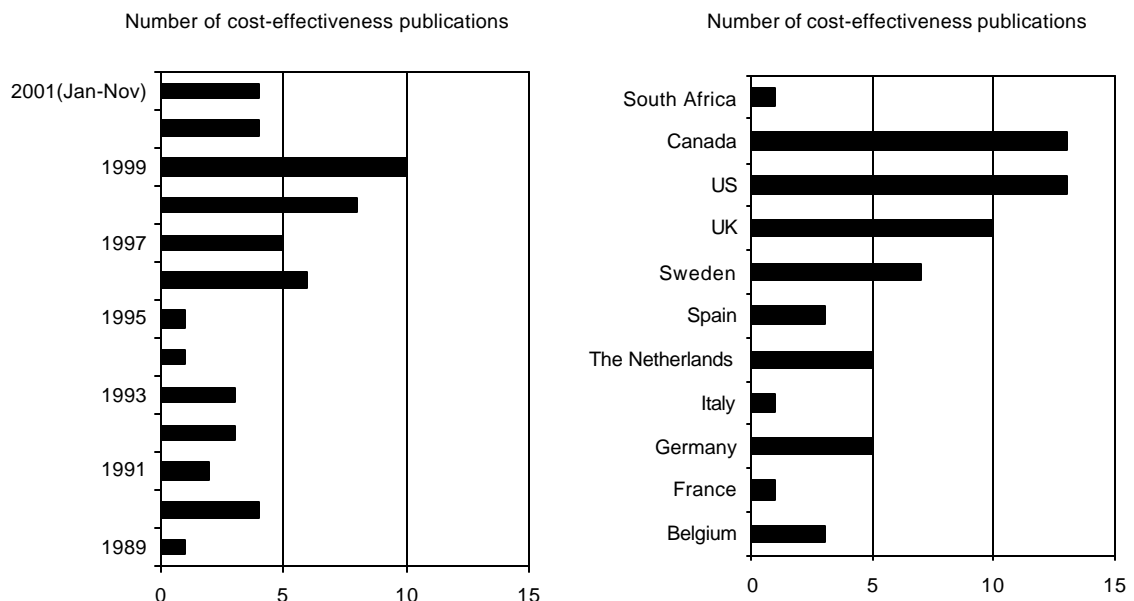
1. A statin intervention was one of the studied alternatives (possibly combined with other intervention(s)).
2. The benefits of intervention were estimated in terms of life-years (LYs) or quality-adjusted life-years (QALYs).
3. The interventions were homogeneously provided for the relevant intervention groups (pure screening studies aimed at identifying and treating subjects that will benefit most were excluded; guideline evaluation studies that differentially treat subjects were also excluded).
4. Adult populations were considered.
5. The study was fully published in English (publications in abstracts only were excluded).

In total, 53 studies were identified that met the above criteria. At the time of writing only 52 of these studies had been acquired and reviewed and these form the basis of the review results reported in this paper. The presented results are preliminary and since the final results may change, please do not quote the results of the review as it stands at present.

### Descriptive results of the review

The studies were predominantly published in 1996-99 (Fig. 1) and most of those stating the source of funding were supported by the Industry (28 out of 43). All reviewed studies were based on populations from developed countries with North American analyses representing over half of the total number of published studies (26 studies from US and Canada). Few of the European analyses were multinational with respect to the unit costs employed.

Fig. 1 Year of publication and country of application of the published EE studies\*



\* some of the studies address populations from more than one country

Although only two publications address exactly the same research question and provide the same results (61;62), some of the other studies are based on previously published models that were updated or used to address a slightly different question (17) (27) (49) (11).

### **Review methods: main areas for analysis**

There were three main ways in which we approached the review of the identified studies. Firstly, we were interested in the methods employed by analysts to obtain their results, secondly, we were interested in the scope of the study and finally in results themselves (and the extent to which they could be synthesised).

#### *Methods employed*

The US Panel on cost-effectiveness in Health Care(23) has proposed the use of a reference case of analytic methods in order to improve the comparability of results of cost-effectiveness studies and this technique has been used retrospectively to attempt to improve the comparability of results in a review of UK cost-effectiveness analyses(6). However, this reference case approach tends to focus on well-known methodological issues such as the categorisation of costs and health outcomes, the choice of valuation technique, and the choice of discount rate. We wanted to go beyond this basic set of methods available to analysts and look in more detail at specific methods of evaluation.

The starting point was the design of the study – in particular, whether there was a primary data source informing the economic evaluation (e.g. an economic analysis conducted alongside a single clinical trial) or whether the evaluation was composed of a number of data sources in a secondary analysis. Studies alongside a single well-designed and conducted clinical trial are generally considered the most reliable as they tend to use all the benefits that randomised controlled trials present. We adopted the following classification of study design:

- (i) Primary modelling studies (conducted alongside clinical trials directly estimating treatment effect on mortality and morbidity);
- (ii) Secondary modelling studies (multiple data sources)
  - (ii.i) Studies based on trial(s) estimates of the impact of treatment on mortality and morbidity;
  - (ii.ii) Studies based on intermediate events (i.e. impact of treatment on cholesterol level)

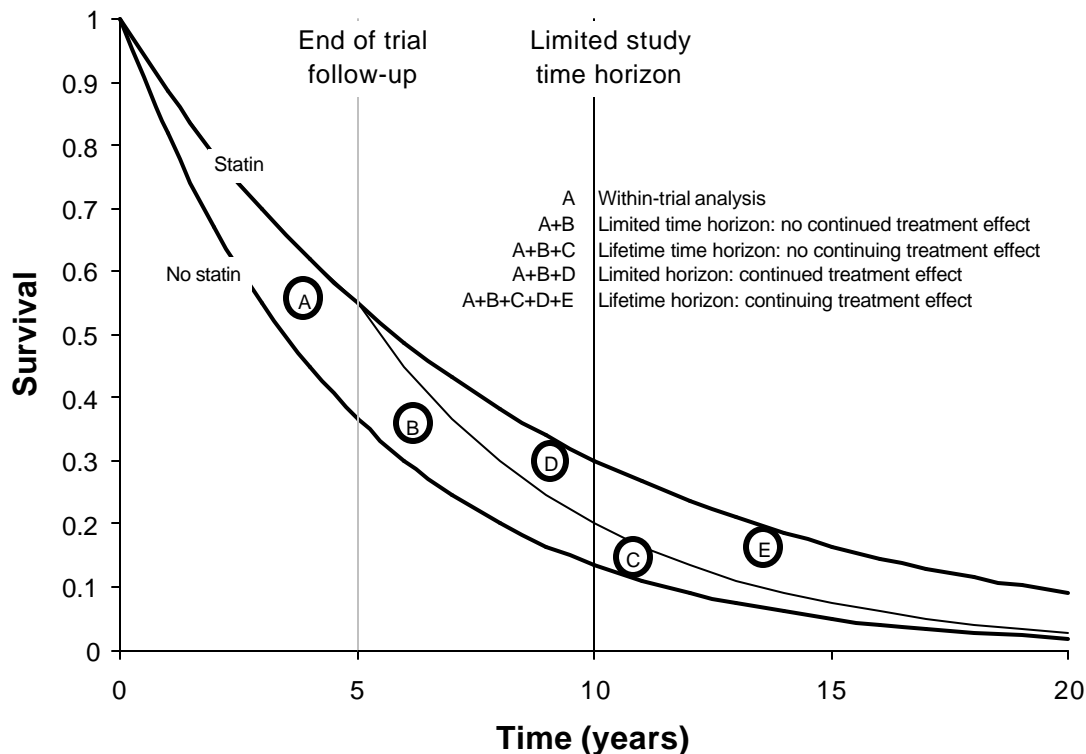
The next area of interest was whether data sources informing the secondary studies related to final or intermediate endpoints, i.e. was data available directly on mortality and morbidity, or was cholesterol lowering the chosen outcome. This defined the scope of the extrapolation exercise that studies undertook – where studies extrapolating short-term survival data to the

long-term or was the extrapolation from the effect of the drug on cholesterol to the estimated effect on mortality and morbidity? The method by which these extrapolation exercises were achieved was of primary interest. For example, when extrapolating observed survival in a clinical trial did authors assume no further benefit beyond the trial (i.e. only a within trial analysis was performed); or assume no continued treatment effect, but extrapolate from the observed separation of the survival curves; or did they model a continued treatment effect assuming a continued separation of survival curves beyond the trial period.

Figure 1 illustrates the main ideas behind extrapolation beyond the trial end (i.e. at 5 years in our example). If the analysis is based on costs and benefits in the period of the trial then the incremental benefit will be only area A on the figure. If the study extrapolates beyond the trial end but without assuming additional treatment effect (i.e. analysing only the increased life expectancy due to prevented mortality and morbidity during trial) then the incremental benefit will be areas A and B in the case of limited study horizon (i.e. 10 years) or areas A, B and C in the case of lifetime study horizon. In the case of extrapolates beyond the trial end with the assumption of additional treatment and effect (i.e. same relative impact on mortality and morbidity as during trial) then the incremental benefit will be areas A, B and D in the case of limited study horizon (i.e. 10 years) or areas A, B, C, D and E in the case of lifetime study horizon. The exact method of extrapolation could differ (i.e. parametric survival curves, life-tables, etc.) but the incremental benefits and costs will differ mainly based on these principal assumptions related to the extrapolation and study time horizon.

In addition, the studies that use trial end points were reviewed in respect to extrapolation assumption made beyond the end of the trial and classified into (a) no further treatment and no continued benefit (i.e. area A on Fig. 1), (b) no further treatment and no benefit but different future prospects because of prevented CHD events (i.e. areas A, B and C on Fig. 1), and (c) further treatment and benefits (i.e. areas A, B, C, D, E on Fig. 1) (possibly different assumptions, i.e. linear extrapolation, constant relative risk (RR), parametric survival analysis, life tables, etc.)). The secondary modelling studies based on intermediate events also extrapolate beyond the original data on cholesterol lowering and its impact on morbidity and mortality. This extrapolation was usually based on constant relative cholesterol reduction. The models employed (i.e. based on Framingham heart study) were extrapolating beyond the original cohort data and were additionally expanded to lifetime for the purposes of relevant economic evaluations.

**Fig.1 Main assumptions when extrapolating beyond clinical trials**



Finally, we considered how the studies handled the issue of compliance with the intervention, since the preventive interventions are generally affected by significant level of non-compliance that could affect the overall cost-effectiveness(36). The issue of compliance is potentially important for the cost-effectiveness of a prevention intervention. The compliance was evaluated in the major clinical trials and analysis employing the mean statin dose and impact according intention to treat criteria aimed to provide unbiased estimates. Unfortunately it is unclear what will be the pattern of compliance in usual practice with potentially less stringent monitoring protocol. The only way the issue of compliance is addressed in the cost-effectiveness studies is through the use of mean drug dose and effects from the main randomised controlled trials.

#### *Study scope*

The study scope addresses the internal validity and generalisability of the study results. The evidence from randomised controlled studies is often referred to as gold standard in terms of providing valid unbiased estimates for the study setting analysed. Frequently, the cost-effectiveness studies of statins aim to inform decision making on broader population groups than those included in the trials or in different settings (i.e. different countries) which could have had an impact on the validity of study results. As background, we considered the generalisability that the authors were attempting to achieve: did they attempt to generalise beyond the specific setting of the data sources, e.g. from one country to another; did they

attempt to generalise beyond the study population of the data sources, e.g. from men to women or from one age group to another?

It is also clear that the health care setting of the study may have an important impact on cost-effectiveness in terms of comparability, for example, US health care is generally considered more expensive than the European health systems. At this stage of the review we only attempted to directly compare results from a single country (the UK), thus avoiding problems of different health care systems generating different resource costs and the problems associated with estimating appropriate exchange rates (for example, using medical purchasing power parities).

### *Results reported*

In reporting the results of economic evaluation, the population group to which the study applies is of crucial interest and increasingly analysts are aware of the potential for the cost-effectiveness of interventions to vary across different patients. In attempting any comparison of cost-effectiveness results it is important to specify the patient groups to which the estimated results apply – including the purpose of the intervention itself (primary versus secondary prevention). Having attempted to make the results as comparable as possible, it was then possible to consider the extent to which the results of the different studies could be compared, and at what level they could be compared.

## **Comparative review of methods employed**

### *Study design*

Of the 52 studies reviewed to date, 7 were judged to be primary economic analyses related to an evaluation of a particular clinical trial – all of which were concerned with final mortality outcomes of patients. The remaining 45 studies were judged to be secondary modelling studies of which 16 had employed data on final endpoints from trials (CVD morbidity and mortality and non CV mortality) but employing additional assumptions, while 31 studies employed data on intermediate endpoints (cholesterol reduction) and modelled the final endpoints. One study compared modelling based on final events from trial and modelling based on the intermediate outcome from the same trial(50).

### *Extrapolation*

Most of the studies that extrapolate from the impact of statins on cholesterol level (total cholesterol (TC) or LDL-C/HDL-C) use predictive models developed based on epidemiological cohort data. The main assumption made is that epidemiological study across different individuals is a good predictor for the CAD risk reduction for individuals when medication is used to lower their cholesterol level. Two main data sources for extrapolation



from intermediate to final events were used in the reviewed studies (1) Framingham Heart Study Cohort(5;16;22;24;25;29-32;35;37;38;45-51;56;57;61-63;65;73;75) and (2) Lipid Research Clinic Cohort(26-28).

Evidence from clinical trials evaluating impact of statins on morbidity and mortality are considered a more reliable basis for cost-effectiveness analysis. Furthermore, studies conducted alongside randomised clinical trial (primary modelling studies) tend to be viewed as more reliable as they avoid assumptions about generalisability of trials to another population and setting (although this aspect cannot be avoided when interpreting the policy implications of the results of such trials).

The main review results in respect to the above-mentioned characteristics for the studies employing final events data are summarised in Table 1.

**Table 1 Study design and extrapolation assumption**

<i>Study</i>	<i>Main trial source(s)</i>	<i>Length of intervention/ Study time horizon</i>	<i>Type extrapolation</i>
<i>Study design: Primary modelling</i>			
(4)	PLACI and PLACII (men)	3 yrs/10yrs	No continuing treatment effect
(7)	WOSCOPS	5yrs/Lifetime	No continuing treatment effect
(39)	4S	5yrs/Lifetime	No continuing treatment effect
(41)	4S	5yrs/15yrs	No continuing treatment effect
(40)	4S	5yrs/Lifetime	No continuing treatment effect
(42)	Single centre RCT	4yrs/Lifetime	No continuing treatment effect
(77)	CARE	Lifetime/ Lifetime	Continuing treatment effect
<i>Study design: Secondary modelling (final end points)</i>			
(8)	WOSCOPS	5yrs/Lifetime	No continuing treatment effect
(9)	WOSCOPS	5yrs/Lifetime	No continuing treatment effect
(10)	4S	5yrs/5yrs 10yrs/10yrs	Within trial analysis Continuing treatment effect
(11)	4S	5yrs/5yrs 10yrs/10yrs	Within trial analysis Continuing treatment effect
(17)	Metaanalysis (WOSCOPS, AF/TexCAPS, LIPID, CARE) 4S,	Lifetime/ Lifetime	Continuing treatment effect Continuing treatment effect
(19)	4S	Lifetime/ Lifetime	Continuing treatment effect
(21)	CARE	Lifetime/Lifetime	Continuing treatment effect
(33)	WOSCOPS	5yrs/Lifetime	No continuing treatment effect
(43)	WOSCOPS	Not-stated	Not-stated
(50)	WOSCOPS	Lifetime/Lifetime	Continuing treatment effect
(53)	PLACI and PLACII (men)	3yrs/Lifetime	No continuing treatment effect
(58)	WOSCOPS	10yrs/10yrs	Continuing treatment effect

(59)	WOSCOPS, 4S	Lifetime/Lifetime	Continuing treatment effect
(64)	4S	15 yrs/15 yrs	Continuing treatment effect
(76)	WOSCOPS	10yrs/10yrs	Continuing treatment effect
(78)	4S, AFCAPS/TexCAP S, CARE, LIPID, WOSCOPS	Lifetime/Lifetime	Continuing treatment effect

The duration of statin intervention is an indication for the duration of treatments effect as well as for the drug consumption and cost. The study time horizon shows the maximum timeframe of benefits from continuing treatment effect or no continuing treatment effects. The size of the benefit is evaluated based on all assumptions (i.e. size of effects, extrapolation assumptions). Only one cost-effectiveness study (reported in two publications for US and UK) presented results for the duration of the trial in one of the two study scenarios(10;11). The review of economic evaluation studies based on trial end points showed that most of the primary modelling studies make the assumption of no continuing treatment effect and extrapolate from the separation of survival curves (6 out of 7) while majority of secondary modelling studies assume continuation of intervention and continuing treatment effect (11 out of 15 that have stated the assumption).

Studies modelling from trial end points use mainly the same source of primary data. The main characteristics and results of the randomised clinical trials used are presented in Table 2. All trials studied the impact of statins on CHD morbidity and mortality although slightly differently defined and measured. The trials' endpoints formed the basis of the models investigating the gain in life-years and the cost of the interventions. Although frequently using the same primary data, differences in the modelling assumptions and in the complementary data led to different results for the cost-effectiveness of statins. The results were also frequently generalised to populations other than those studied in the source trials.

Only four studies stated that a form of meta-analysis was used to synthesise final events from more than one randomised clinical trial(4;17;53;59) and two of these studies synthesise trials with similar design and populations(4;53).

The outcome analysed in the economic evaluations was predominantly the gain in life expectancy. The few studies adjusting for quality of life (10;11;16;21;63;73;77) used published analysis of the quality of life after a coronary heart event. No one of the major statin trials analysed the quality of life of patients on statin and placebo. Some shorter randomised clinical trials investigated impact of statins on quality of life and did not find any significant difference(34;52;55;67;68).

**Table 2 Major randomised clinical trials of statin interventions**

Trial Country	Intervention (Compared to placebo)	Length of follow-up (years)	Population Type prevention Sex/Age/baseline cholesterol/other	Impact on cholesterol	Impact on mortality/morbidity
4S(1) Scandinavian countries	Simvastatin 20-40 mg/day	5.4	Secondary prevention 4444 (2223 placebo) male, female/ TC5.5-8.0mmol/l/ post acute MI or unstable angina previous 6 months	TC-25%, LDL-35%, HDL+8%	CVmortality-42%, Total mortality-30% Coronary events-34% CVaccidents/TIA-37% Coronary revascularization-32% CHD hospitalisations-26% (AMI-37%, angina-22%, stroke/TIA-27%)
LIPID(2) Australia, New Zealand	Pravastatin 40 mg/day	6.1	Secondary prevention 9014 male, female/ 31-75yrs/ TC=4 to 7 mmol/l/post acute MI or unstable angina previous 3-36 months	TC-18% LDL -25% HDL+5%	CVmortality-24%, Total mortality-22% Major coronary events-24% AMI-29% Unstable angina-13% Cerebrovascular accidents-19% Coronary revascularizations-20% Hospitalisations for unstable angina-12% Hospital days-2.9% (0.6 days per patient)
CARE(66) US, Canada	Pravastatin 40 mg/day	5.0	Secondary prevention 4159 (3583 male, 576 female/ 21 to 75 yrs/TC<6.2mmol/l/LDL L-C=3.0 to 4.5mmol/l / AMI previous 3 to 20 months	TC-20% LDL -28% HDL+5%	CVmortality-20%, Total mortality-9% Major coronary events-24%, unstable angina-13%, cerebrovascular accidents-31% Coronary revascularizations-27% CHD hospitalizations-12%(AMI-37%, chest pain-22%, CABG/PTCA-34%, stroke/TIA-27%)
PLACI and PLACII(12;60) US	Pravastatin 40 mg/day	I: 2.4 yrs II: 3yrs	Secondary prevention I: 408 patients/mean age 60/LDL between 3.4 and 5 mmol/l II: 151 males, females/mean age 57 (50-75 yrs)/LDL 4.2 to 4.5mmol/l  Total: 559 (445 men and 114 women)	Not stated	CAD death ? Non-CAD death ? Fatal MI ? Nonfatal MI -55%
WOSCOPS(70) Scotland	Pravastatin 40 mg/day	4.9	Primary prevention 6595 men/45-64yrs/TC mean7mmol/l/LDL-C>4mmol/l	TC-20%, LDL -26%, HDL+5%	CVmortality-28%, Total mortality-22% Major coronary events-31% No diff in stroke found
AF/TexCAPS(13) Texas (US)	Lovastatin 40 mg/day	5.2	Primary prevention 6605 male, female/45-73 yrs/TC=4.65 to 6.83/LDL-C=3.36 to 4.91mmol/l/ HDL<1.16 (me), 1.22 (women) mmol/l/ triglycerides<4.52mmol/l	TC-20% LDL -25% Triglycerides-15%, HDL+6%	CVmortality ?, Total mortality ? First acute major coronary events (fatal or non fatal MI, unstable angina, sudden cardiac death) -37%, MI-32%, unstable angina-32%, cardiovascular events -25%, coronary events-33%, coronary revascularization procedures-33%

**Study scope**

The evidence from randomised controlled studies is often referred to as gold standard in terms of providing valid unbiased estimates. Unfortunately, these studies provide evidence only for the interventions and populations analysed and thus do not address all existing interventions and potential beneficiaries. The reviewed economic evaluations often addressed broader populations (i.e. young or older men; females) and interventions (different drug or drug doses) for which no reliable evidence existed. The detailed review is presented in Appendix 2.

Among the 52 reviewed studies, 39 addressed primary prevention (PP) populations (without documented coronary heart disease (CHD)) and 24 secondary prevention (SP) populations (with history of CHD). Only 17 studies analysed male populations only, while the rest 35 analysed both male and female populations. 18 studies include populations below the age of 40 and 12 studies populations above 65. Three studies analysed the cost-effectiveness of statins on diabetic patients(27;28;40). No cost-effectiveness analysis addressed hypertensive populations (diastolic blood pressure >90 mm Hg) directly although hypertension is frequently considered an additional risk factor and as such included in the presentation of results.

A number of statins were reported in the literature (i.e. lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin). While the large end point studies employ Simvastatin, Pravastatin and Lovastatin (see Table2) the cost-effectiveness analysis analysed a broader spectre of drugs and doses. Four studies analysed intervention with Atorvastatin, one Cerivastatin, twenty Paravastatin, four Fluvastatin, seventeen Lovastatin and twenty-six Simvastatin. The cost-effectiveness studies of statins that have not shown evidence for long-term impact on mortality and morbidity was modelled based on their impact on cholesterol level and extrapolation from cholesterol level to mortality and morbidity. Drug doses employed also vary greatly in the studies and the cost-effectiveness of different doses is also frequently modelled through their impact on cholesterol (see appendix 2). The cost-effectiveness studies generally show comparable results across variety of statins although a discussion for the power of different statins to decrease cholesterol level is ongoing. Cost-minimisation analyses are frequently employed in order to compare cost-effectiveness of statins achieving same cholesterol reduction (most of these studies were excluded from the review as they reported intermediate outcomes only).

The comparator in most of the studies was placebo, no intervention or low-cholesterol dietary advice. In practice it is unlikely that some guidance in terms of diet or lifestyle would not be provided complementary to the main intervention and a dietary advice is usually employed although not always stated. The randomised controlled trials usually incorporate a diet at both arms at the initial stage in order to account for appropriate usual care.

## **Study results**

The main study characteristics and results are presented in the review table in Appendix 2. Despite the significant number of published economic evaluation studies in the area, their comparability is impaired by different base case assumptions and parameters. The parameters that need to be taken into account include country of the study application,

discounting factors, price year and currency, cost perspective, populations analysed, interventions analysed, comparators, and study design.

The resource use was generally similarly addressed and mainly intervention costs and savings from prevented CHD were included in the analysis. Occasionally patient costs and future costs due to added years of life were included (i.e. cost of diabetes (27;28); added non-CHD costs (30;31;56;57)).

It would be generally invalid to compare economic evaluations across countries because different costs could introduce significant distortions in the final incremental cost-effectiveness ratios. The separate comparison of incremental benefits and costs could have a better comparability across countries but is often prevented by the poor reporting of study results.

The study results for the UK(7;8;11;16;17;22;27;50;58;59) were explored for similarities and trends. The nine UK studies were reviewed in respect of the intervention, population and results. All Incremental cost-effectiveness ratios were inflated to year 2000 based on HCHS inflation factors. In order to account for the impact of the baseline CHD risk(71) the study results were stratified according the population involved. Additional condition for comparability was the employment of same interventions. The results for two groups of populations (1) primary prevention (PP) of middle aged men with elevated total cholesterol treated with Pravastatin 40g/day and (2) secondary prevention (SP) of middle aged men with average total cholesterol treated with Simvastatin 20 to 40g/day were judged comparable and were presented on Fig 2. Although secondary prevention appears more cost-effective the study results show that the gap between the cost-effectiveness estimates for the two population groups decreases over time and the cost-effectiveness of primary prevention overlaps with the cost-effectiveness of secondary prevention in lower risk population groups.

The follow suggestive trends have been seen.

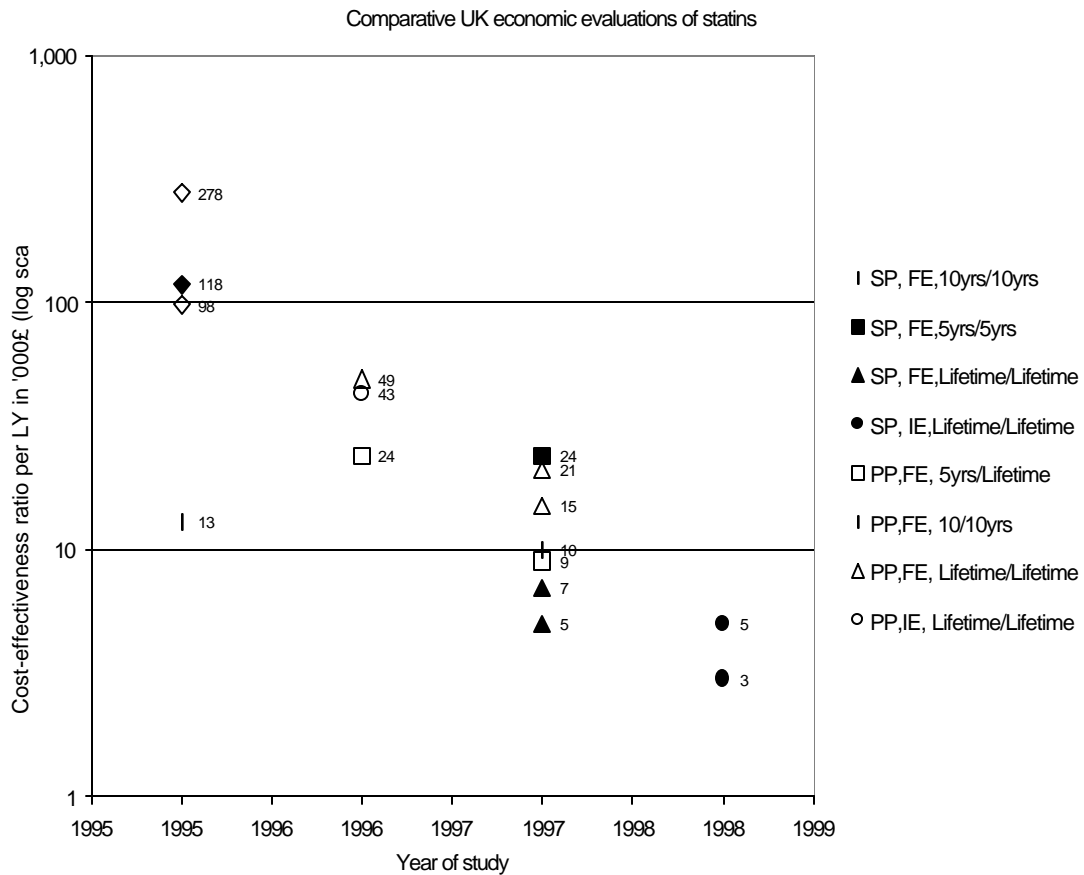
(i) The ICER was decreasing in time and more recent analysis report smaller cost-effectiveness ratios. This was observed in different patient populations. One reason behind this observation could be in changing price of statin or cost of treatment of major CHD events but other reasons could be evidence for larger impact of intervention or general move towards different modelling assumptions.

(ii) Slightly lower ICERs are reported from studies based on intermediate events (cholesterol level) in comparative cost-effectiveness studies. This could be due to the fact that prediction models based on a mix of risk factors are frequently richer in those factors than trials.

(iii) Studies with shorter time horizon show higher ICER(11;58) and this is justifiable as it impacts the estimate of effectiveness (life expectancy) as well as the resource use (averted CHD events).

(iv) Study time horizon has larger impact on cost-effectiveness than treatment duration (5-year treatment duration extrapolated to lifetime without continuing treatment benefit(7;8) compared to 10-year treatment duration over 10 year study horizon with assumed continuing benefit(58)).

**Fig. 2 ICER for primary and secondary prevention with statin (UK studies)**



If the general conclusions regarding cost-effectiveness of statins are considered, in the second half of 90s, the secondary prevention with statins of middle-aged men and primary prevention of middle-aged men with some additional risk factor(s) are presented as quite cost-effective. In this respect the cost effectiveness analysis of major trials prove to be highly influential.

## Discussion

This review of the cost-effectiveness of statin treatment highlights the difficulties encountered when attempting to provide an overview of the results of economic evaluations. Despite the large number of articles reviewed being based on limited primary evidence, many studies

show quite different results depending on their methodology and base case assumptions employed. From the comparative perspective our belief is that it remains problematic to compare study results directly when parameters such as costs, discounting factors, time horizon, duration of treatment, etc. are not the same between studies.

The design of studies can have an important impact on the final results to the extent that study design affects the choice of extrapolation assumptions, which in turn have a very important effect on the results. In particular, primary studies carried out alongside clinical trials tended not to assume treatment benefits beyond the follow-up of the trial (although in this review only one analyst presented within trial analyses in base case scenarios). By contrast, secondary modelling type studies tended to assume a longer treatment period, and therefore, a greater treatment effect. Although the assumption that people will benefit from longer cholesterol treatment is plausible there is no direct evidence as to the exact nature of benefit for longer treatment durations or after discontinuation of treatment. Uncertainty related to these extrapolation assumptions tended to be handled through simple sensitivity analysis.

In terms of extrapolation from intermediate to final endpoints, all studies assumed that the cholesterol reduction observed in clinical trials would reduce the risk of mortality to that seen by patients with lower cholesterol levels in cohort analyses. Of course, the evidence generated from cohort studies account for general risk factors but do not say anything directly about the statin treatment impact. However, it was rare to see this addressed in the studies' discussions or in sensitivity analyses.

The original motivation for this review was to address the question: can we really synthesize data from economic evaluations? In the area of economic evaluation of statins a common framework for data synthesis that incorporates the available evidence seems difficult to develop. The levels of evidence range from trial endpoints (intermediate and final) to cost-effectiveness analyses based usually on single trial endpoint(s) but employing different models. The major obstacle being the incorporation of parameters whose effect is difficult to disentangle (i.e. drug prices, inflation factors over time, extrapolation assumptions). An additional issue is the repetitive use of the same evidence.

The 'new approach' favoured by Nixon and colleagues involves summarising cost-effectiveness results in terms of areas in which the results fall on the cost-effectiveness plane. However, our review serves to highlight some of the problems of that approach(54). Firstly, the approach focuses on the final cost-effectiveness results only – all interventions that provide incremental health outcomes at incremental cost are classified in a single group.

In the case of UK results for the cost-effectiveness of statin therapy, all of the results (with a single exception in few subgroups) would fall in this group, despite significant variation in the cost-effectiveness ratios (see Figure 2). Secondly, there is no explicit framework for incorporating uncertainty in the estimated values – the approach appears to be based on simply working with point estimates. Finally, we observed that in cost-effectiveness studies, the same primary evidence is often used in the different studies and this should be accounted for in any evidence synthesis.

For these reasons we suspect that any approach to evidence synthesis based on the cost-effectiveness results themselves will be problematic. Two potential approaches remain: i) synthesis could occur in the cost and effectiveness outcomes separately (resource use, costs and effectiveness in LYs or QALYs), or ii) synthesis could occur at the level of intermediate/final events in a modelling process.

The area of systematic reviewing and meta-analysis has developed because of the need to synthesise evidence in clinical evaluation. Although traditional clinical meta-analysis has focused on synthesising results from studies (RCTs) with the same design, there has been a little work looking at ways of synthesising results from studies of different designs, which has been termed cross-design synthesis(15). This approach has even been implemented in the area of statin treatment in order to combine evidence from RCTs and observational studies(74). The problem for economic evaluation is that these clinical evaluation meta-analyses are often handling only one single parameter – for example, Sutton and colleagues(73) present their synthesis of RCTs and cohort studies for statin therapy in terms of an odds ratio for treatment – of course in economic evaluation we are interested in absolute risks and probabilities for all relevant for the resource use and effectiveness trial events.

The practical problems associated with implementing synthesis techniques at either the level of cost-effectiveness or for health outcomes costs separately, suggest that the best approach to evidence synthesis for an economic evaluation may be through modelling techniques where the parameters (such as odds ratios etc.) can be combined to estimate the outcomes of interest (QALYs, costs and cost-effectiveness). Indeed, Eddy and colleagues suggested just this sort of approach over ten years ago(18) which they termed the confidence profile method. Despite the production of software to aid implementation, the confidence profile method has not been widely used. However, with the increased power of personal computers and with more generally available software such as WinBUGS, there has been a recent revival of interest in this approach(72).



Of course, this sort of approach to evidence synthesis is very similar to the standard techniques of decision-analytic modelling that health economists have been using for many years. The difference is that evidence synthesis techniques have a strong focus on statistical methodology and on propagating uncertainty through the model in order to obtain the (Bayesian) distribution over the parameters of interest. However, probabilistic cost-effectiveness modelling shares much in common with these statistical techniques particularly when care is taken to appropriately specify the parameter distributions in the model and relate them to the available data. Indeed, a number of probabilistic cost-effectiveness models are adopting the use of Bayesian terminology to emphasise the robustness of the statistical approach taken(20;69).

The US Panel on cost-effectiveness analysis distinguish between parameter and modelling uncertainty(44). The use of simulation methods to propagate parameter uncertainty does not address the uncertainty in the model structure itself. Draper has argued, in terms of statistical models, that it is important to include uncertainty in the choice of model in order to fully represent uncertainty in the outcome of interest(14). This approach could be useful for exploring data synthesis of intermediate and end points events of primary studies as well as exploring the opportunity of allowing for different post trial scenarios.

## **Conclusion**

Having considered alternative approaches to synthesising the current evidence available on the cost-effectiveness of statins, we believe the best approach to be the construction of a cost-effectiveness model. Parameters of that model can then be estimated using standard evidence synthesis (meta-analytic) methods, where data from a number of studies is available. Uncertainty in the final outcomes of interest can be obtained by propagating parameter uncertainty through the model structure. Capturing structural uncertainty in the model itself is more problematic, although the model expansion methods can be employed.

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