Effectiveness calculation in economic analysis: the case of statins for cardiovascular disease prevention

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Methods: Methodological aspects were reviewed of seven primary studies (based on trial results) and 12 secondary modelling studies (extrapolated) on the cost effectiveness of statin treatment, published between 1995 and 2002. Estimates of life years gained were extracted and compared with estimates calculated using the Dutch male life table of 1996–2000.

Results: Of the seven primary modelling analyses, six showed all the essential data. They estimated that 3 to 5.6 years (average 4.6 years) of statin treatment resulted in 0.15 to 0.41 years (average 0.3 years) saved over a lifetime time horizon. In contrast none of the 12 secondary modelling studies provided transparent results. They assumed lifelong treatment, leading to life table estimations of 2.4 and 2.0 (undiscounted) years saved for 40 and 60 year olds, with peak savings at around the mean age of death: 75–80 years. With 5% discounting, these effects reduced to 0.4 and 0.8 years respectively.

Conclusion: Reporting of essential data and assumptions on statin treatment was poor for secondary modelling analyses and satisfactory for primary modelling studies. Secondary modeling studies made assumptions on long term effectiveness that were hard to justify with the available evidence, and that led to the majority of life years saved at high ages. Further standardisation in economic analyses is important to guarantee transparency and reproducibility of results.

Statins reduce the rate of coronary heart disease (CHD) by over 30% with limited side effects. However, costs of statins are substantial. Several costs effectiveness analyses (CEAs) have been performed to refine indications for statin use in the prevention of CHD with discrepant results. Cost effectiveness ratios are the ratio of the total costs of an intervention to the total health effects achieved by it (for example, years of life saved), when compared with a null-situation (for example, no intervention).

Years of life saved (YLS) can be derived by comparing the age specific mortality of treated and control cohorts. Given the mortality risks of the control cohort, the YLS by statin treatment are defined by the relative risk reduction. A transparent description of mortality by age in the control cohort is therefore important, together with either the relative risk reduction or the mortality by age in the treated cohort. The different methodologies used to calculate effectiveness estimates may be a source of the divergent results found among the various CEAs. However, the effect and the level of variation introduced by the different methodological alternatives in the outcomes remains unclear.

In an attempt to clarify the discrepant results, we reviewed published CEAs of statins. We aimed to identify the methods used to quantify the effectiveness of statin treatment and their influence on the magnitude of the effect estimates (YLS). We illustrated the different methodologies using a life table as standard tool.

Methods
Study selection
We searched for CEAs in English, Spanish, Dutch, or German on statins for the prevention (primary and/or secondary) of either CHD or cardiovascular disease. Reviews and meta-analyses were excluded. Studies needed to compare costs and effects of statin treatment with no statin treatment and present discounted or undiscounted cost per YLS as outcome.

Data extraction
We focused on the methods used to calculate the effects of mortality reduction attributable to statin treatment. We searched for data describing mortality in treated and control cohorts. We extracted information on the following variables: time of publication, source of risk for the untreated cohort, survivorship from the end of treatment, source of risk reduction for the treated cohort, treatment period (<10 years or >10 years), time horizon (trial duration or lifetime), and the outcome (YLS).

Abbreviations: CHD, coronary heart disease; YLS, years of life saved; CEA, cost effective analysis; LE, life expectancy
Primary modelling analyses were defined as six presented data on survivorship from the end assumptions in modelling treatment and time horizons. (A) to be constant (and identical to 8 at any mortality level the Franco, Steyerberg, Peeters, et al and a relative increase of mortality five years, treatment effects of statins taken from LaRossa the trial period. Here both treatment period and time horizon are extrapolated beyond effect (that is, same risk reduction as seen during the trial period). (C) The study extrapolates beyond the trial period but does not assume (treatment effect and time horizon limited to trial period). (B) Analysis based on treatment and effects seen during the trial period

**Figure 1** Assumptions in modelling treatment and time horizons. (A) Analysis based on treatment and effects seen during the trial period (treatment effect and time horizon limited to trial period). (B) The study extrapolates effects beyond the trial period but does not assume additional treatment effect (treatment period limited to trial period, time horizon extrapolated beyond trial period for lifetime). (C) The study extrapolates beyond the trial period and assumes additional treatment and effect (that is, same risk reduction as seen during the trial period). Here both treatment period and time horizon are extrapolated beyond the trial period. (*Trial period in the case of statins is generally around five years, treatment effects of statins taken from LaRossa et al.)*

Papers were classified by type of modelling: primary or secondary. Primary modelling analyses were defined as using all data directly collected from randomised controlled trials (RCTs). In secondary modelling analyses, mortality in the untreated cohort is either predicted (extrapolated) by risk functions or taken from other sources such as prospective cohorts. Mortality reduction was modelled by changes in risk factor levels (that is, LDL-cholesterol) or by application of relative risks of mortality or morbidity from published RCTs.

**Treatment period and time horizon**

The treatment period can be restricted to the trial period (generally around five years in the case of statins), or can be assumed to persist after the trial for limited or unlimited (lifelong) periods. The time horizon is the period of time considered when calculating the effects of treatment and can be limited to the trial period or extrapolated for additional limited or unlimited (lifetime) periods.

The combination of a limited treatment period and a limited time horizon is presented in figure 1A. Treatment and treatment effects are restricted to the trial period without additional extrapolation.

The scenario of combining a limited treatment period (restricted to the trial) with an unlimited (lifetime) time horizon is presented in figure 1B: effects seen during the trial period are extrapolated beyond this time but additional reductions in mortality risks beyond the period of medication are not assumed.

An alternative often seen in secondary analyses is to extrapolate both treatment period and time horizon beyond the trial period for lifetime: treatment is assumed to continue until extinction of the cohort or until very old ages (fig 1C).

**Life table comparison**

We used comparisons with the Dutch male life table of 1996–2000 to illustrate the effect of different assumptions of treatment duration and time horizon (fig 1A to 1C) on the effect estimates (YLS). The Dutch life table was used as a source of age specific mortality rates in the control cohort. While this life table does not have identical mortality to any of the statins trial control arms, its use served as a standardising tool to translate treatment effects into YLS. In the Gompertz function of mortality by age, mortality is predicted by a constant $\alpha$ and a relative increase of mortality by age of $\beta$. If we assume $\beta$ to be constant (and identical to the Dutch male mortality), any at mortality level the remaining life expectancy (LE) can be determined. The underlying concept is that of biological more than chronological age, biological age being determined by a certain observed mortality risk. Higher observed mortality is translated in shorter life expectancy by the life table. This simple assumption avoids the many tenuous extrapolations of an uncertain future, which are a large source of methodological variability in outcomes of cost effectiveness analyses. LE is the average number of years that a person of a given age is expected to remain alive. YLS are the LE of the treated minus the LE of the control cohort. Effects were calculated using two scenarios: limited treatment period (five year) and lifelong treatment period (both with lifetime time horizon).

Results were presented with 0% and 5% discounting. We used Excel spreadsheets to build the life tables.

**RESULTS**

**Description of the studies**

We included 19 studies: 7 primary modelling analyses and 12 secondary (table 1). Data on the mortality rate during the treatment period were presented for all primary analyses but only for two of the secondary analyses. Of the primary analyses, six presented data on survival from the end of treatment, in contrast with two of the secondary analyses. All primary analyses considered treatment periods below 10 years, while 11 of the 12 secondary analyses modelled the effects of lifelong statin treatment.

In primary analyses, YLS had generally two components: YLS saved during the trial, and YLS expected to be lived beyond the end of the trial (fig 1B). For example, the analyses of the 4S trial, which included people with CHD and hypercholesterolemia, showed that the treated cohort saved 0.067 life years per person during the trial and 0.312 after it.
This leads to 0.38 YLS/person from 15 years of treatment, or 136 years of treatment to save 10 life years. In six of seven primary evaluations, all relevant mortality information was presented. The seventh study described methods but did not present evaluations, all relevant mortality information was presented.

Of the 12 secondary analyses, none clearly described the mortality by age and treatment status.

**Life table comparisons**

Table 2 mimics the West of Scotland coronary prevention study (WOSCOPS). This is a large RCT (n = 6595) that studied the effects of statins among a male population free of CHD. In the treated cohort of WOSCOPS, all cause mortality was 22% lower than in the control arm. This relative risk reduction was applied to an untreated cohort (from the Dutch life table) for five years or lifelong.

### Table 2 Effects of allocation to statin treatment on male mortality risks using the results of the WOSCOPS* trial for the effects of statin treatment and mortality risks in Dutch men (1996–2000) for mortality risks in the absence of statin treatment: life table simulation

<table>
<thead>
<tr>
<th>Exact age</th>
<th>Untreated</th>
<th>Treated</th>
<th>Treatment period</th>
<th>Five years</th>
<th>Lifelong</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Five year</td>
<td>LE disc</td>
<td>Risk</td>
<td>YLS</td>
<td>YLS disc</td>
</tr>
<tr>
<td></td>
<td>risk of</td>
<td>5%</td>
<td>reduction</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>(years)</td>
<td>death†</td>
<td>LE</td>
<td>YLS</td>
<td>5%</td>
<td>YLS</td>
</tr>
<tr>
<td>40</td>
<td>0.9%</td>
<td>36</td>
<td>17</td>
<td>0.2%</td>
<td>2.4</td>
</tr>
<tr>
<td>50</td>
<td>2.5%</td>
<td>27</td>
<td>15</td>
<td>0.5%</td>
<td>2.3</td>
</tr>
<tr>
<td>60</td>
<td>7.2%</td>
<td>18</td>
<td>12</td>
<td>1.5%</td>
<td>2.0</td>
</tr>
<tr>
<td>70</td>
<td>20%</td>
<td>11</td>
<td>8.3</td>
<td>4.0%</td>
<td>1.7</td>
</tr>
<tr>
<td>80</td>
<td>46%</td>
<td>6.3</td>
<td>5.2</td>
<td>8.3%</td>
<td>1.2</td>
</tr>
</tbody>
</table>

LE, life expectancy; YLS, years of life saved; disc, discounted. *WOSCOPS trial (five year risk of death 4.17% at age 55, 22% reduction in all cause mortality) extrapolated to younger and older ages. The same risk reduction is calculated in four life table measures by two treatment periods: until the end of life (lifelong) and over five years both over a lifetime time horizon. 5% means that an annual discount rate of 5% is applied to the saved life years in the future cohort. The YLS apply to the survivors at age x. †Risk of dying between age x and x + 5. ‡Risk reduction in the treated cohort; the risk is 22% lower (WOSCOPS trial).
The YLS were higher the younger the treatment started (table 2). When we assumed that treatment started at age 40 and continued lifelong, a 22% reduction in all cause mortality saved 2.4 years. Most life years were however saved around the mean age of death in this population (76 years). After discounting by 5%, only 0.42 life years were saved (5.7 times less than the undiscounted values).

When only the savings of treating between age 40 and 45 were considered, combined with a lifetime time horizon (for example, fig 1B), a 22% reduction in all cause mortality saved 0.07 years.

In other words, 71 years of treatment would save one life year. An example of the effect obtained by treating a cohort aged 40–45 over a five year treatment period with benefits accumulated over a lifetime is shown in figure 2. An alternative would be to calculate this effect over a lifelong treatment period combined with a lifetime time horizon (fig 3).

Life table comparisons with primary modelling
Using the above method we compared the YLS estimates from each study with estimates derived from the Dutch life tables.

The estimate (YLS) of the 4S evaluators (0.38) was close to our life table estimate (0.41) (table 3), consistent with a slightly lower estimate of the YLS of survivors at the end of the trial compared with our estimate. The LIPID trial’s estimate was higher than ours (0.41 compared with 0.34 years), consistent with a LE at the end of trial that was 2.7 years higher than that of our life table (table 3). For the CARE trial, YLS were 0.22 compared with 0.15 years, again consistent with a lower LE of our life table. For the WOSCOPS trial, the estimated 0.25 YLS by treatment was higher than our estimate of 0.10 YLS. The WOSCOPS’ authors included estimates of an improved prognosis for the survivors without a CHD event, and this could explain the difference.

Finally, Ashraf et al12 presented all relevant data, but analysed
only 10 CHD deaths and six of other causes (data from the PLAC trial, not presented in table 3).

From the 12 secondary modelling analyses included, none clearly presented the modelled age specific mortality rates of treated and untreated cohorts. Therefore, we could not compare them with the life table estimates to illustrate their methodologies.

**DISCUSSION**

Within the scientific literature, the benefits of statin treatment in primary and secondary modelling analyses have been calculated with quite different assumptions about treatment period and treatment effect. Primary modelling analyses used mostly a treatment period equal to trial period and a lifetime time horizon while secondary modelling analyses assumed a lifelong treatment period and time horizon. Most primary modelling analyses considered the direct YLS during the trial, and combined these with YLS after the trial by the extra survivors who shared the LE of the control cohort (fig 1B). All secondary analyses extrapolated the treatment’s effects to periods of time far beyond the available evidence.

Overall we were confronted with a poor transparency in the presentation of essential data among secondary modelling cost effectiveness analyses of statins. This constituted an important impediment to the interpretation and evaluation of the selected studies.

Of the 19 evaluated studies, only six showed all the information on their age specific mortality rates. All six were primary analyses. A seventh primary analysis, the WOSCOPS study evaluation, was thorough but failed to show how prevented CHD affected survivorship after the trial period. This implied that a large part of the savings remained

Table 3  Trial characteristics, and years of life saved by treatment*: life table simulation and comparison using data on mortality risks taken from the Dutch male population

<table>
<thead>
<tr>
<th>Trials</th>
<th>4S</th>
<th>LIPID</th>
<th>CARE</th>
<th>WOSCOPS</th>
<th>AFCAPS/TexCAPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4444</td>
<td>9014</td>
<td>4159</td>
<td>6595</td>
<td>6605</td>
</tr>
<tr>
<td>Follow up (mean y)</td>
<td>5.4</td>
<td>6.1</td>
<td>5.0</td>
<td>4.9</td>
<td>5.2</td>
</tr>
<tr>
<td>Age (mean, y)</td>
<td>59</td>
<td>62</td>
<td>59</td>
<td>55</td>
<td>58</td>
</tr>
<tr>
<td>Men (%)</td>
<td>81</td>
<td>83</td>
<td>86</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td>History of MI (%)</td>
<td>79</td>
<td>64</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TC/HDL ratio</td>
<td>5.67</td>
<td>6.06</td>
<td>5.35</td>
<td>6.17</td>
<td>6.01</td>
</tr>
</tbody>
</table>

**Control arm**

| Five year risk of death (%) | 10.7 | 11.7 | 9.4  | 4.2 | 2.2 |
| Five year risk of CHD death (%) | 7.90 | 6.84 | 5.73 | 1.61 | 0.44 |
| Lived during trial (y) | 4.77 | 4.74 | 4.97 | 4.90 | 4.95 |
| Life expectancy (LE, y) | 15.7 | 15.1 | 16.7 | 22.6 | 28.1 |
| LE at end of trial (y) | 10.93 | 10.36 | 11.73 | 17.70 | 23.15 |

**Statin arm**

| Absolute risk reduction of all cause mortality (%) | 3.10 | 2.54 | 0.78 | 0.91 | –0.09 |
| Years saved during trial | 0.067 | 0.074 | 0.023 | 0.024 | 0.003 |
| Total years saved | 0.41 | 0.34 | 0.11 | 0.18 | Harm |
| Based on all cause mortality | 0.42 | 0.24 | 0.15 | 0.10 | 0.03 |
| Based on CHD mortality | 0.38 | 0.41 | 0.22 | 0.25 | 0.23 |
| Published estimates | 0.35 | 0.41 | 0.22 | 0.25 | 0.23 |

*The savings are calculated by two methods: using absolute reduction in all cause or in coronary heart disease mortality. †Years lived are based on the life table of Dutch men 1996–2000 (see text). At a five year risk of death of 10.7% (4S trial), Dutch men had a residual life expectancy of 15.7 years. ‡Years lived during the trial plus the absolute mortality reduction multiplied by the residual life expectancy at the end of the trial.

What is already known on the topic

- Statins reduce the rate of coronary heart disease by over 30% with limited side effects, but statins’ costs are substantial.
- Several cost effectiveness analyses have been performed to refine indications for statin use in the prevention of coronary heart disease with discrepant results.
- One potential source of the divergent results found in the various cost effectiveness analyses has been suggested to be the different methodologies used to calculate the effectiveness estimates. However, the effect and the level of variation introduced by the different methodological alternatives in the outcomes remains unclear.

What this paper adds

- Reporting of essential data was poor for secondary modelling cost effectiveness analyses and satisfactory for primary modelling cost effectiveness analyses on statins.
- Cost effectiveness analyses that used secondary modelling made assumptions on long term effectiveness that were hard to justify with the available evidence, and that led to the majority of life years saved at high ages.
- Primary modelling analyses had close links with underlying data from randomised controlled trials, reported better and made more reasonable assumptions; hence they should be viewed with more confidence than cost effectiveness analyses that use secondary modelling.
without a clear explanation. Of the six primary analyses that showed sufficient information, one study described a small population: resulting in very wide confidence limits. That left five studies for serious evaluation, which described the experience of the 4S, LIPID, and CARE trials. Among these, the 4S publications showed all the essential information most clearly. Additionally the results were consistent with our life table approach. Depending on the data and method used for estimating survival at the end of the trial, 11 to 13 years of statin treatment added one year of life.

From the 12 secondary modelling analyses included, none clearly presented the modelled age specific mortality rates of treated and untreated cohorts, leaving the reader with aggregate outcomes that could not be fully interpreted or reproduced. As health benefits are the primary aim of any health intervention, in future publications the modelled age specific event rates of the control and intervention cohort should be clearly shown. Most of the secondary analyses used lifelong treatment periods. Modelling treatment over lifelong periods requires assumptions on treatment effects over unobserved long periods and at old ages. The argument that considering lifelong treatment effect is “a more realistic assumption, as treatment is for life”28 calculates health benefits at an old age (>70 years) with limited evidence and at a time the studied drugs might be superseded by cheaper substitutes, or a polypill.29 To model the effect of a drug, it is not necessary to stretch the evidence far beyond observable time periods. As far as evidence is available, statins decrease the risk of CHD regardless of the duration they are taken (after a short lag time period).29 Risk reduction is around 30%, regardless if statins have been taken for two or five years. There is therefore no need to assume a lifelong treatment effect.

For our life tables, we used only data from Dutch men. We do not think this affects our conclusions as we used these data only to illustrate the different alternatives in methodologies and to increase comparability within the analysed studies. It is also possible that some relevant studies were not included in this analysis, but we do not think this would change our conclusions. We excluded three cost-utility analyses31–33 that did not present YLS, as our objective was to analyse the calculation methods of effectiveness and not of utilities. The outcome for cost-utility studies is years of life gained adjusted by quality weights (QALYs). YLS are solely derived from age specific mortality in treated and untreated cohorts. QALYs require estimates of incidence of disease stages, duration of these stages, and value judgments on the utility lost by decreased health in these stages. This limits the comparability.

In the particular scenario of statins for cardiovascular disease prevention, competing interests are important.3 This increases the necessity for robust methodology and transparent reporting. The advent of the internet lessens the space restrictions in paper journals. This may allow for the provision of detailed information in the world wide web, aiding the transparency in the reporting.

We found that reporting of essential data was poor for secondary modelling analyses and satisfactory for primary analyses on statins. Primary modelling analyses had close links with underlying data from randomised controlled trials, reported better and made more reasonable assumptions; hence they should be viewed with more confidence than secondary modelling studies. Better cost effectiveness analyses are rooted in the evidence of trials. The value of added survivorship in treated cohorts should be translated into YLS by transparent and interpretable methods (as seen in primary modelling analyses). Further standardisation in economical analyses is important to guarantee transparency and reproducibility of results.

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CONTRIBUTORSHIP STATEMENT

OHH, EWS, AP, and LB participated actively in all and each of the following aspects for this article: conception and design, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

GUARANTOR STATEMENT

OHH as guarantor of this paper accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Ethical approval was not needed, as this was a secondary data analysis.

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