EVIDENCE BASED PUBLIC HEALTH POLICY AND PRACTICE

Cost effectiveness of statins in coronary heart disease

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Introduction: Statin therapy reduces the rate of coronary heart disease, but high costs in combination with a large population eligible for treatment ask for priority setting. Although trials agree on the size of the benefit, economic analyses of statins report contradictory results. This article reviewed cost effectiveness analyses of statins and sought to synthesise cost effectiveness ratios for categories of risk of coronary heart disease and age.

Methods: The review searched for studies comparing statins with no treatment for the prevention of either cardiovascular or coronary heart disease in men and presenting cost per years of life saved as outcome. Estimates were extracted, standardised for calendar year and currency, and stratified by categories of risk, age, and funding source

Results: 24 studies were included (from 50 retrieved), yielding 216 cost effectiveness ratios. Estimated ratios increase with decreasing risk. After stratification by risk, heterogeneity of ratios is large varying from savings to $59 000 per life year saved in the highest risk category and from $6500 to $490 000 in the lowest category. The pooled estimates show values of $21571 per life year saved for a 10 year coronary heart disease risk of 20% and $16862 per life year saved for 10 year risk of 30%.

Conclusion: Statin therapy is cost effective for high levels of risk, but inconsistencies exist at lower levels. Although the cost effectiveness of statins depends mainly on absolute risk, important heterogeneity remains after adjusting for absolute risk. Economic analyses need to increase their transparency to reduce their vulnerability to bias and increase their reproducibility.

With the advent of statins, the controversy surrounding cardiovascular risk management has shifted from how to treat hypercholesterolaemia to the proportion of eligible people that may actually be treated because of financial constraints.[1] Statins reduce the rate of coronary heart disease (CHD) by more than 30%,[2–4] side effects are unusual, and they are well tolerated.[5] However, statins' high costs limit the scope of treatment: society wants the best returns for its investments in health.[6] This asks for priority setting aided by economical analyses, commonly cost effectiveness analyses (CEA).[7] As relative risk reduction is thought to be constant,[2 8 9] benefits are largely determined by absolute risk of CHD. The question is, because of costs, at which level of risk, treatment is cost effective. Different levels are used worldwide, ranging from 20%[10] to 30%[11] 10 year absolute risk of CHD.

Regardless of comparable health effects and drug costs, CEA of statins have reported contradictory results ranging from very low to very high cost effectiveness ratios (CERs). The reasons are unknown and subject to speculation about methodological issues and competing interests.

We reviewed CEA of statins and sought to identify sources of heterogeneity of CERs adjusted for categories of risk of CHD, age, and funding source.

METHODS

We performed a systematic review of the published statin CEA.

Inclusion criteria

We searched for CEA in English, Spanish, Dutch, or German on statins for the prevention of either CHD or cardiovascular disease (CVD) in adult male populations (>20 years). We selected more than one language to make our search criteria more comprehensive. Reviews and meta-analyses were excluded. Studies needed to compare cost effectiveness of statin therapy with no pharmacological treatment and present cost per years of life gained/saved (YLG, YLS) as outcome. Studies comparing statins with other statins or with other cholesterol lowering drugs were excluded.

Search strategy

We used the databases Medline, the British National Health Service Economic Evaluation Database (NHS EED), Database of Abstracts of Reviews of Effectiveness (DARE), and the Health Technology Assessment database (HTA). We searched for papers published between 1990 and July 2002 and used these terms for searching: Statins OR Hydroxymethylglutaryl-CoA-Reductase Inhibitors AND Cost-effectiveness.

Two independent investigators analysed the abstracts obtained from the databases. All studies that matched our inclusion criteria were retrieved, and their reference lists were checked manually to identify more studies. We contacted experts in the field to find unpublished or ongoing studies.

When the decision of inclusion could not be achieved by reading the abstracts, the papers were retrieved for analysis.

Study selection

Two independent investigators read each one of the articles retrieved and selected the studies to include based on the inclusion criteria. A third investigator was contacted to reach a decision in case of disagreement.

Data extraction

A data extraction form was elaborated based on prior knowledge and literature. Using the form, two independent investigators (which could be the same as the ones in the study selection process) collected the data from the articles.

Variables included in the form were: publication date, date and country used to calculate costs, annual drug costs, type of

Abbreviations: CHD, coronary heart disease; CEA, cost effectiveness analyses; CER, cost effective ratio; CVD, cardiovascular disease

Table 1 Description of the studies included in the review*

Paper	Publication year	Cost country	Age range (mean)	Modelling†	Prevention category‡	Treatment duration	Discount factor (%)	Funding source
Ashraf[17]	1996	United States	60	Both	Secondary	3,10 years	5	Pharmaceutical Company
Caro[18]	1997	United Kingdom	45–64 (55)	Primary	Primary	5 years	6	Pharmaceutical Company
Ganz[19]	2000	United States	75–84	Secondary	Secondary	Lifetime	3	University
Goldman[21]	1991	United States	35–84	Secondary	Both	Lifetime	5	Government
Goldman[20]	1993	United States	35–44	Secondary	Primary	Lifetime	5	Government
Grover[22]	1999	Canada	40–70	Secondary	Secondary	Lifetime	3	University
Grover[24]	2000	Canada	40–70	Secondary	Both	Lifetime	5	Pharmaceutical Company
Grover[23]	2001	Canada	40–70	Secondary	Both	Lifetime	3	Pharmaceutical Company
Hamilton[25]	1995	Canada	30–70	Secondary	Primary	Lifetime	5	Pharmaceutical Company
Hay[26]	1991	United States	35–55	Secondary	Primary	Lifetime	5	Pharmaceutical Company
Huse[27]	1998	United States	45–65	Secondary	Both	Lifetime	3	Pharmaceutical Company
Johannesson[28]	1997	Sweden	35–70	Secondary	Secondary	5 years	5	Pharmaceutical Company
Jonsson[39]	1996	Sweden	35–70 (59)	Primary	Secondary	5 years	5	Pharmaceutical Company
Jonsson[40]	1999	Sweden	35–70 (60)	Primary	Secondary	5 years	3	University
Martens[29]	1994	Canada	45	Secondary	Primary	Lifetime	5	Pharmaceutical Company
Muls[30]	1998	Belgium	60	Both	Secondary	3,10 years	5	Pharmaceutical Company
Perreault[31]	1998	Canada	44–56–57	Secondary	Primary	Lifetime	5	University
Pharoah[32]	1996	United Kingdom	45–64	Secondary	Both	10 years	5	None
Pickin[33]	1999	United Kingdom	55,58	Secondary	Both	5years, lifetime	6	University
Russell[34]	2001	Canada	45–65	Secondary	Both	Lifetime	5	Pharmaceutical Company
Szucs[36]	1998	Germany	45–65 (59)	Primary	Secondary	5 years	0	University
Szucs[35]	2000	Germany	45–65 (60)	Primary	Secondary	5 years	3	University
Riviere[38]	1997	Canada	35–70 (59)	Secondary	Secondary	5, 10, lifetime	5	Pharmaceutical Company
Van Hout[37]	2001	Netherlands	25–75	Secondary	Both	5years, lifetime	5	University

*In total 24 studies were included in the final analysis. †Primary: based on observations from a randomised trial. Secondary: based on expectations from a theoretical model. ‡Secondary prevention is among patients with clinical coronary heart disease or cardiovascular disease, primary prevention among apparently healthy persons.

model, category of prevention, mean or range of age at the start of treatment, annual level of absolute risk of CHD (fatal and non-fatal events) at the start of treatment, time horizon of treatment, method for effect calculation, economic perspective, discount factor, funding source, and final outcome (CERs).

Model type could be primary or secondary modelling. Primary modelling studies were conducted parallel to clinical trials. Secondary modelling studies used data from clinical trials or other sources to model the effect of statins. Studies were also divided in two categories of effect calculation: studies that used levels of CHD risk reduction to model the effect, or studies that used intermediate effects (for example, % cholesterol level reduction) for the modelling procedure.

The category of prevention was either primary, for populations free of either CHD or CVD, or secondary, for CHD or CVD patients.

Time horizon of treatment refers to the observed or assumed duration of treatment period. Treatment period can be restricted to the observed trial period (which in the case of statins is generally around five years), or can be assumed to last (that is, after the trial) for a limited or unlimited (lifelong) period. We classified time horizon of treatment in three categories: five years, 10 years, or >10 years/lifetime.

Discount factors are used to weight the value of future benefits and costs; four categories were used: 3%, 5%, 6%, or none.

Funding source of the studies was classified in two categories: funding provided by the industry and funding provided by others (academic or governmental institutions or none).

For each CER we wanted absolute risk of CHD of the study population before treatment. If not stated in the paper, we estimated risk by the D'Agostino CHD function [12] for primary and secondary prevention respectively, using these variables: levels of total cholesterol (or LDL), HDL cholesterol, smoking, blood pressure, diabetes history, and personal history of CHD.

Table 2 Distribution of CERs by category of absolute risk

	Categories of annual absolute risk (no)*				
Dispersion and centile values	<1% (33)	1%–<2% (33)	2%–<3% (13)	3%–4% (42)	>4% (95)
Centile 10	24505	10205	12951	7987	5449
Median	48559	26933	23060	15048	10607
Centile 90	255893	73124	46273	48701	21545

CERs, cost effectiveness ratios ($ per year of life saved).

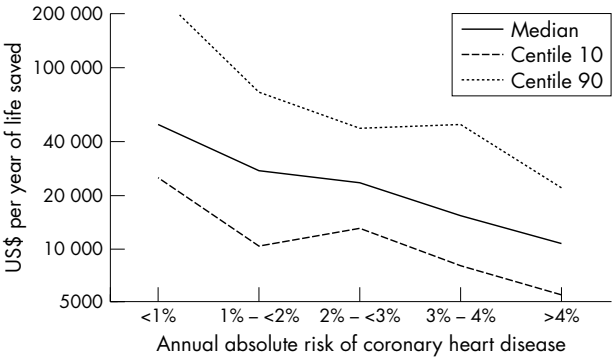

Figure 1 Cost effectiveness of statins per categories of absolute risk. Centiles and median refer to the distribution of published cost effectiveness ratio per category of absolute risk.

Final outcomes

The CERs were stratified by categories of risk, age groups, and funding source, and standardised.

To standardise we used only ratios reported as cost per YLG or YLS that were calculated using net costs and with future costs and benefits weighted with the same discount factor. As the CERs were reported using different currencies and dates, we standardised by calendar year and currency. Firstly, to correct for inflation, we converted all currencies into the same date: 30 December 2001, using the correspondent consumer price index (CPI). Afterwards all currencies were converted into US dollars of the date 30 December 2001. Data on CPI and conversions were taken from different sources: Federal Reserve Bank of Indianapolis USA, Bank of Canada, The European Union (publication: statistics in focus, economy and finance: prices and purchasing power parities, theme 2-48/2002), and the University of Exeter England.

We considered CERs under \$20 000/YLS as ''cost effective'', over \$40 000/YLS as ''expensive'', and in between as ''moderate''.[13–16]

After standardisation, CERs were stratified by categories of risk of CHD, by age groups at the start of treatment and by funding source.

The categories of annual risk of CHD at the start of treatment were: <1%, 1%–<2%, 2%–<3%, 3%–4%, and >4%.

Age groups used were: <45 years, 45–65 years, and >65 years.

Outcomes were compared by whether the study was funded by pharmaceutical companies or by others.

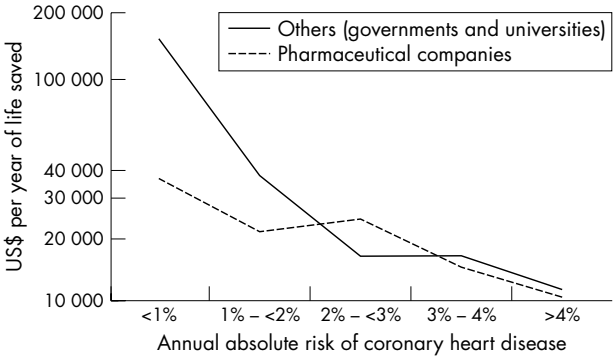

Figure 2 Funding source in cost effectiveness of statins per categories of absolute risk. Medians refer to the distribution of published cost effectiveness ratio per category of absolute risk.

Once stratified, the CERs were plotted using spreadsheets. For each category of risk the distribution of the outcomes was calculated (median, quartiles, and centiles) and compared.

Statistical analysis

Data were analysed using a linear mixed effect model. The log of the CER was taken as continuous response value, because errors were assumed to become larger with larger CERs. The studies were put at the first level and CERs at the second level. The result of this design is that the power of characteristics of the study is limited to the number of studies and that the power of predictors that differ within the studies is increased by the extraction of the variance between studies from the random error. We included 11 variables in the analysis: absolute risk (continuous), age (<45, 45–65, and >65), treatment duration (<5years, 5–10 years, and >10 years (lifetime)), country used as source of costs (USA, Canada, and Europe), type of model (primary and secondary), effect calculation (direct reduction of risk and indirect risk reduction through lipid lowering), category of prevention (primary and secondary), perspective (societal and third party payer), funding source (pharmaceutical companies and others), year of publication (<1996 and ⩾1996), and discount factor (<5%, ⩾5%). Drug cost was not included as an explanatory variable because of its high correlation with the CER. First we performed a univariate analysis to find overall predictors, and then an analysis of interactions with risk. This last analysis shows the effect modification by variables over changing risk.

Variables were considered significant at a two sided p value <0.05.

We used S-PLUS (version 6.0 for Windows) for the analyses.

RESULTS

Study identification and selection

We found 308 references using the databases: 235 with Medline and 73 with the NHS EED, DARE, and HTA databases. From the 308 references, 186 were rejected because they were not CEA. Of the 122 abstracts selected, 50 studies were retrieved. By checking reference lists we found four new references, but they did not match our inclusion criteria. Finally 24 studies were selected for the analysis.[17–40]

Reasons for exclusion were: seven studies were reviews or meta-analyses,[41–47] seven compared statins with statins or with other lipid lowering drugs,[48–54] three were cost-utility analyses,[55–57] three compared strategies of cardiovascular risk management,[58–60] three did not use as outcome cost/YLS,[61–63] two were descriptive methodological papers,[64 65] and one study was excluded because it was not possible to determine absolute risk before treatment.[66]

Descriptive of the studies

All the studies compared statin therapy with no treatment of CHD or CVD risk and were conducted in developed countries.

Mean annual drug cost was US\$ 7687 (ranged from 399 to 1670). Pharmaceutical companies funded 13 studies. Only one study presented the estimated CERs without any discount factor, the rest used predominantly 5% (table 1).

Final outcomes

The outcome selected was cost per YLS standardised by calendar year and currency.

From the 24 studies selected we identified 216 CERs.

The ratios reported ranged over an enormous range: from savings to \$489 000/YLS (table 2). However there were no negative CERs (suggesting that the statins were worse than the comparator) in any of the studies selected.

Table 3 Multilevel linear regression analyses (outcome: CERs)

Variables	Univariate analysis Effect in % (95% CI)	Interaction effects with absolute risk of CHD* Effect in % (95% CI)
Absolute risk of CHD	−21.8 (−27.6, −15.6)†	–
Age in years		†
<45	Reference	−53.3 (−62.2, −42.4)†
45–65	23 (−20, 91)	−26.4 (−32.1, −20.2)†
>65	76 (0, 211)	−24.3 (−36.6, −9.8)†
Treatment duration		NS
<5 years	Reference	
5 to 10 years	−22 (−69, 103)	
Lifetime (>10 years)	−42 (−73, 24)	
Cost country		†
USA	Reference	−27.9 (−35.6, −19.3)†
Canada	165 (−59, 1594)	−4.4 (−16, 8.8)
Europe	207 (−48, 1764)	−31 (−40.7, −19.9)†
Effect modelled		NS
Intermediate effects	Reference	
Risk reduction	69 (−58, 581)	
Type of modelling‡		NS
Primary	Reference	
Secondary	−27 (−71, 87)	
Prevention Categories§	†	†
Primary	Reference	−31.5 (−40.6, −21.1)
Secondary	−62 (−74, −45)	−5.6 (−16.8, 7)
Economical perspective		NS
Societal	Reference	
Third party payer	−53 (−89, 96)	
Funding source		†
Pharmaceutical companies	Reference	−13.9 (−22, −5)
Others	−44 (−86, 129)	−31.3 (−38.8, −23)
Publication year		†
<1996	Reference	−40.2 (−49, −29.8)
⩾1996	147 (−55, 1255)	−16.5 (−23.3, −9.2)
Discount factor		†
>=5%	Reference	−28.9 (−35.1, −22.2)

CERs, cost effectiveness ratios; CI, confidence interval; NS, not significant effect; CHD, coronary heart disease. *Effects on the cost effectiveness ratios, per 1% rise in absolute risk of coronary heart disease. The original (univariate) effect of 1% increase in absolute risk (21.8 % decrease in CERs) is compared in each variable category with account for potential interactions. †p Value <0.05. ‡Primary: based on findings from a randomised trial. Secondary: based on expectations from a theoretical model. §Secondary prevention is among patients with clinical cardiovascular disease, primary prevention among apparently healthy persons.

Outcomes were first stratified by categories of risk at the start of treatment as absolute risk is an important determinant of the cost and benefits of statin therapy. We found a strong inverse relation between absolute risk at baseline and the CER (fig 1).

Even though there was an external consistency between the studies, the variability among the ratios extracted was high, even after standardisation and stratification. In all categories of risk there were cost effective, moderate, and expensive ratios (table 2).

For levels of annual absolute risk over 4% most of the CERs agreed in showing statins as a cost effective option, at least 90% of the ratios were not expensive. For the lowest level of risk (<1%) the agreement of the studies was also clear, but in showing statin therapy as an expensive option. For the rest of the levels (1% to 4%) there was no clear agreement.

Stratified by risk, the difference between the 10th and 90th centile of the CERs was still fourfold to sevenfold.

A comparison between the age groups was not possible as estimates for younger (<45) and older ages (>65) were few.

Funding source

Estimated CERs from studies funded by others were generally more expensive than estimates from studies funded by pharmaceutical companies. This difference is striking at lower levels of risk (<2%), corresponding to primary prevention (fig 2).

Multilevel linear regression

Our aim was evaluate the degree to which explanatory variables account for the observed variability in CERs between the studies. In the univariate analysis (second column, table 3) only absolute risk and category of prevention are significant. For levels of 2% and 3% annual risk of CHD the corresponding average CERs were $21571/YLS and $16 862/YLS. As annual absolute risk increases by 1% the CER is expected to decrease by 21.8%.

Compared with primary prevention, secondary prevention represents a decrease of 62% in the CER: category of prevention is highly correlated with absolute risk.

The third column of table 3 shows the interaction effects between absolute risk and the other explanatory variables. Here we compared the original (univariate) effect of 1% increase in absolute risk (21.8 % decrease in CERs) in each variable category. For age, cost country, category of prevention, funding source, year of publication, and discount factor the effect of absolute risk in the CER differed significantly between categories. As a result of the multilevel analysis each CER is compared with other CER within the same study, which gives more discriminating power to find interactions.

Lower (more negative) effects imply steeper decreases of cost effectiveness by increasing absolute risk; therefore the impact of absolute risk on the CER is larger. In secondary prevention, the gradient of absolute risk is less important, as it is always high. At lower ages (<45 years), which also constitutes generally populations at lower levels of risk, increases in the level absolute risk has a higher impact than in older populations with higher levels of risk. Studies funded by pharmaceutical companies tended to report lower CERs for the same levels of absolute risk (fig 2) and were also less responsive to the effect of absolute risk (table 3). Studies published before 1996, generally responded more

dramatically to the effect of absolute risk as they generally used populations at lower levels of risk that were classified according to their individual risk factors, and not based on comprehensive CHD risk. High discount rates increase the effect of absolute risk at start of treatment: increases of absolute risk further in time/age are devalued more by higher discount rates.

DISCUSSION

In randomised trials, meta-analysis pool empirical results, reducing the level of random error and bias. In CEA, systematic reviews may identify agreement and disagreement. As prognosis is such an important predictor of absolute effects, the model used standardises for known determinants of health outcomes. Cost effectiveness of statin treatment is strongly related to absolute risk of CHD. Our pooled estimates show values of $21 571/YLS for an annual CHD risk of 2% and $16 862/YLS for annual risk of 3%. Most studies agree that statin treatment is cost effective for high risk patients (annual absolute risk >4%) but not cost effective for low risk patients (annual risk <1%). For medium risk patients (annual absolute risk 1 to 4%) the decision of whether treatment is cost effective depends on the choice of the study. After adjusting for levels of absolute risk, large heterogeneity in the estimated CERs remained. Most of the remaining variability can be explained by interactions between absolute risk and age, cost country, category of prevention, funding source, year of publication, and discount factor. We were not able to identify further methodological differences, assumptions, or model design that caused the remaining heterogeneity. Variability in the risk reduction with statins underlying each of the studies could not explain the variability in the CERs estimates, as there is general concordance among studies with respect to effect size, and we standardised for absolute risk. The role of costs in the CER was evaluated standardising or adjusting for the year costs, year of publication, country of costs, drug costs, economic perspective, and currency used.

Diverse levels of survival and prevalences of risk can explain the different effects of absolute risk by age groups. For age group <45, a population at generally low levels of risk, high risks at start of treatment represent low CERs. In contrast, age group >65 with generally high levels of risk, benefits are limited by a shorter life expectancy and the relative effect of absolute risk on the CERs is lower. However, the effect of age is difficult to disentangle, as it is included in absolute risk. Age and absolute risk are highly correlated, but risk (corrected for age) is negatively correlated with CER and age (corrected for risk) is positively related with CER.

The different effects of absolute risk by cost country could be caused by methodological differences, gaps in interventions' prices, different practice patterns specific to each country, and the characteristics of the populations studied. It could be inferred from the observed differences between countries that the generalisability of CERs to additional geographical areas is limited and the estimates might be specific to the country or area used in the original analyses.

Studies funded by pharmaceutical companies generally showed more cost effective CERs. This might be because of the interests that pharmaceutical companies may have in expanding treatment thresholds to lower levels of absolute risks. We found no clear differences in the methods used, in the populations' characteristics, or in the levels of risk. The differences were striking at low levels of risk, representing large eligible populations. It is tempting to suggest competing interests as an explanation, although we could not prove this.

The possibility of studies that could have been missed exists, but the likelihood that these would change our conclusions is low. The outcome for cost utility studies is years of life gained adjusted by quality weights (QALYs) mortality in treated and untreated cohorts. QALYs add value judgements on the utility lost by decreased health in different disease stages. The different sources of weight values lead to extra potential sources of heterogeneity, which are often not well described in the articles, and interpretation of that heterogeneity is extremely difficult. Therefore, we excluded three cost utility analyses that did not present YLS, the sole outcome of this pooling YLS are solely derived from age specific study.

The primary objective of this study was to evaluate levels of heterogeneity and predictors on CEA of statins; we decided to include only studies reporting results for male populations. Studies of female populations are rarer and more difficult to interpret, as women at the same age run lower heart disease risks. While the absolute CERs will differ by sex, we do not expect the levels of heterogeneity to do so. Of the studies included in this study, 14 separately reported CERs for women. All of them consistently show higher CERs (compared with men).

Not all the studies used absolute risk for their analyses; therefore risk factor combinations were translated into absolute risk of CHD. This approach was not validated and some might have been misclassified. Residual confounding particularly in the first risk group exists (there are great relative differences possible in the group <1%). However, the variability is seen in all risk groups and misclassification will be limited (people at lower levels of risk factors will be at lower levels of risk).

Other methods exist to standardise CER to a same cost year, but this will not change our results and conclusions.

In conclusion, this review confirms how the cost effectiveness of statins treatment in the prevention of CHD is related to the absolute risk of CHD, but shows that within risk strata

What this paper adds

- Statin therapy is cost effective for high levels of risk, but inconsistencies exist at lower levels. Although the cost effectiveness of statins depends mainly on absolute risk, important heterogeneity remains after adjusting for absolute risk.
- The most probable explanation for this ample heterogeneity is different methodology in the CEA. However, the impact of funding source found suggests the potential for some estimates to be biased.
- Economic analyses need to increase their transparency to reduce their vulnerability to bias and facilitate their evaluation.

Policy implications

- Economic analyses need to increase their transparency to reduce their vulnerability to bias and facilitate their evaluation. New policies to standardise these types of analyses are mandatory.
- Statin therapy is a cost effective intervention to treat populations at high risk of cardiovascular disease (>4%/year) and it is not cost effective for populations at low risk (<1%/year). For populations with moderate risk (1 to 4%/year) the available evidence is contradictory and new transparent evaluations are needed.

there still exists large variability in cost effectiveness estimates. Nearly all studies agree that treatment at high levels of risk is cost effective and at low levels is expensive. But in practice, it is not difficult to find CERs that fit any decision for the population at large with intermediate annual risk of CHD (1% to 4%). The most probable explanation for these differences is different methodology in the CEA, and the impact of funding source suggests the potential for some estimates to be biased. It was very difficult, even impossible to pinpoint all the divergent model assumptions that caused the variability.

Further standardisation of methodology for economic analyses and greater transparency in the presentation of results would aid in the evaluation of potential sources of bias, as well as facilitate the evaluation of reproducibility.

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CONTRIBUTORS

Oscar H Franco, Anna Peeters, Caspar Looman, and Luc Bonneux; 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. Oscar H Franco as guarantor of this paper accepts full responsibility for the integrity of the data and the accuracy of the data analysis, had full access to all the data in the study, and controlled the decision to publish.

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Ethical approval was not required as this was a secondary data analysis.

REFERENCES

1 **Raithatha N**, Smith RD. Paying for statins. *BMJ* 2004;**328**:400–2.
2 **LaRosa JC**, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999;**282**:2340–6.
3 **Law MR**, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;**326**:1423.
4 **Wei L**, Ebrahim S, Bartlett C et al. Statin use in the secondary prevention of coronary heart disease in primary care: cohort study and comparison of inclusion and outcome with patients in randomised trials. *BMJ* 2005;**330**:821.
5 **Knopp RH**. Drug treatment of lipid disorders. *N Engl J Med* 1999;**341**:498–511.
6 **Creese A**. Global trends in health care reform. *World Health Forum* 1994;**15**:317–22.
7 **Drummond M**, Brandt A, Luce B, *et al*. Standardizing methodologies for economic evaluation in health care. Practice, problems, and potential. *Int J Technol Assess Health Care* 1993;**9**:26–36.
8 **Shepherd J**, Cobbe SM, Ford I, *et al*. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;**333**:1301–7.
9 **The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group**. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;**339**:1349–57.
10 **Expert Panel on Detection Evaluation, and Treatment of High Blood Cholesterol in Adults**. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) full report 2002. http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf.
11 **NHS Executive**. *Standing medical advisory committee on use of statins*. London: Department of Health, 1997. http://www.dh.gov.uk/assetRoot/04/01/13/48/04011348.pdf.
12 **D'Agostino RB Sr, Grundy S, Sullivan LM, et al**. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA* 2001;**286**:180–7.
13 **McKenney JM**, Kinosian B. Economic benefits of aggressive lipid lowering: a managed care perspective. *Am J Manag Care* 1998;**4**:65–74.
14 **Laupacis A**, Feeny D, Detsky AS, *et al*. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *Can Med Assoc J* 1992;**146**:473–81.
15 **Tengs TO**, Adams ME, Pliskin JS, *et al*. Five-hundred life-saving interventions and their cost-effectiveness. *Risk Anal* 1995;**15**:369–90.
16 **Redaelli A**, Cranor CW, Okano GJ, *et al*. Screening, prevention and socioeconomic costs associated with the treatment of colorectal cancer. *Pharmacoeconomics* 2003;**21**:1213–38.
17 **Ashraf T**, Hay JW, Pitt B, *et al*. Cost-effectiveness of pravastatin in secondary prevention of coronary artery disease. *Am J Cardiol* 1996;**78**:409–14.
18 **Caro J**, Klittich W, McGuire A, *et al*. The West of Scotland coronary prevention study: economic benefit analysis of primary prevention with pravastatin. *BMJ* 1997;**315**:1577–82.
19 **Ganz DA**, Kuntz KM, Jacobson GA, *et al*. Cost-effectiveness of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor therapy in older patients with myocardial infarction. *Ann Intern Med* 2000;**132**:780–7.
20 **Goldman L**, Goldman PA, Williams LW, *et al*. Cost-effectiveness considerations in the treatment of heterozygous familial hypercholesterolemia with medications. *Am J Cardiol* 1993;**72**:75–9D.
21 **Goldman L**, Weinstein MC, Goldman PA, *et al*. Cost-effectiveness of HMG-CoA reductase inhibition for primary and secondary prevention of coronary heart disease. *JAMA* 1991;**265**:1145–51.
22 **Grover SA**, Coupal L, Paquet S, *et al*. Cost-effectiveness of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors in the secondary prevention of cardiovascular disease: forecasting the incremental benefits of preventing coronary and cerebrovascular events. *Arch Intern Med* 1999;**159**:593–600.
23 **Grover SA**, Coupal L, Zowall H, *et al*. How cost-effective is the treatment of dyslipidemia in patients with diabetes but without cardiovascular disease? *Diabetes Care* 2001;**24**:45–50.
24 **Grover SA**, Coupal L, Zowall H, *et al*. Cost-effectiveness of treating hyperlipidemia in the presence of diabetes : who should be treated? *Circulation* 2000;**102**:722–7.
25 **Hamilton VH**, Racicot FE, Zowall H, *et al*. The cost-effectiveness of HMG-CoA reductase inhibitors to prevent coronary heart disease. Estimating the benefits of increasing HDL-C. *JAMA* 1995;**273**:1032–8.
26 **Hay JW**, Wittels EH, Gotto AM Jr. An economic evaluation of lovastatin for cholesterol lowering and coronary artery disease reduction. *Am J Cardiol* 1991;**67**:789–96.
27 **Huse DM**, Russell MW, Miller JD, *et al*. Cost-effectiveness of statins. *Am J Cardiol* 1998;**82**:1357–63.
28 **Johannesson M**, Jonsson B, Kjekshus J, *et al*. Cost effectiveness of simvastatin treatment to lower cholesterol levels in patients with coronary heart disease. Scandinavian Simvastatin Survival Study Group. *N Engl J Med* 1997;**336**:332–6.
29 **Martens LL**, Guibert R. Cost-effectiveness analysis of lipid-modifying therapy in Canada: comparison of HMG-CoA reductase inhibitors in the primary prevention of coronary heart disease. *Clin Ther* 1994;**16**:1052–62.
30 **Muls E**, Van Ganse E, Closon MC. Cost-effectiveness of pravastatin in secondary prevention of coronary heart disease: comparison between Belgium and the United States of a projected risk model. *Atherosclerosis* 1998;**137**(suppl):S111–16.
31 **Perreault S**, Hamilton VH, Lavoie F, *et al*. Treating hyperlipidemia for the primary prevention of coronary disease. Are higher dosages of lovastatin cost-effective? *Arch Intern Med* 1998;**158**:375–81.
32 **Pharoah PD**, Hollingworth W. Cost effectiveness of lowering cholesterol concentration with statins in patients with and without pre-existing coronary heart disease: life table method applied to health authority population. *BMJ* 1996;**312**:1443–8.
33 **Pickin DM**, McCabe CJ, Ramsay LE, *et al*. Cost effectiveness of HMG-CoA reductase inhibitor (statin) treatment related to the risk of coronary heart disease and cost of drug treatment. *Heart* 1999;**82**:325–32.
34 **Russell MW**, Huse DM, Miller JD, *et al*. Cost effectiveness of HMG-CoA reductase inhibition in Canada. *Can J Clin Pharmacol* 2001;**8**:9–16.
35 **Szucs TD**, Berger K, Marz W, *et al*. [Cost effectiveness of pravastatin in secondary coronary prevention in patients with myocardial infarct or unstable angina in Germany. An analysis on the basis of the LIPID trial] Kosteneffektivitat von Pravastatin in der koronaren Sekundarpravention bei Patienten mit Myokardinfarkt oder instabiler Angina pectoris in Deutschland. Eine Analyse auf der Grundlage der LIPID-Studie. *Herz* 2000;**25**:487–94.
36 **Szucs TD**, Guggenberger G, Berger K, *et al*. [Pharmacoeconomic evaluation of pravastatin in the secondary prevention of coronary heart disease in patients with average cholesterol levels. An analysis for Germany based on the CARE study] Pharmakookonomische Bewertung von Pravastatin in der Sekundarpravention der koronaren Herzkrankheit bei Patienten mit durchschnittlichen Cholesterinwerten. Eine Analyse fur Deutschland auf der Grundlage der CARE-Studie. *Herz* 1998;**23**:319–29.

37 **van Hout BA**, Simoons ML. Cost-effectiveness of HMG coenzyme reductase inhibitors; whom to treat? *Eur Heart J* 2001;**22**:751–61.
38 **Riviere M**, Wang S, Leclerc C, *et al*. Cost-effectiveness of simvastatin in the secondary prevention of coronary artery disease in Canada. *Can Med Assoc J* 1997;**156**:991–7.
39 **Jonsson B**, Johannesson M, Kjekshus J, *et al*. Cost-effectiveness of cholesterol lowering. Results from the Scandinavian simvastatin survival study (4S). *Eur Heart J* 1996;**17**:1001–7.
40 **Jonsson B**, Cook JR, Pedersen TR. The cost-effectiveness of lipid lowering in patients with diabetes: results from the 4S trial. *Diabetologia* 1999;**42**:1293–301.
41 **Troche CJ**, Tacke J, Hinzpeter B, *et al*. Cost-effectiveness of primary and secondary prevention in cardiovascular diseases. *Eur Heart J* 1998;**19**(suppl C):C59–65.
42 **Jacobson TA**, Schein JR, Williamson A, *et al*. Maximizing the cost-effectiveness of lipid-lowering therapy. *Arch Intern Med* 1998;**158**:1977–89.
43 **Thompson D**, Oster G. Cost-effectiveness of drug therapy for hypercholesterolaemia: a review of the literature. *Pharmacoeconomics* 1992;**2**:34–42.
44 **Hay JW**, Yu WM, Ashraf T. Pharmacoeconomics of lipid-lowering agents for primary and secondary prevention of coronary artery disease. *Pharmacoeconomics* 1999;**15**:47–74.
45 **Wendland G**, Klever-Deichert G, Lauterbach K. [Cost effectiveness of lipid lowering therapy] Kosteneffektivitat der lipidsenkenden Therapie. *Herz* 2001;**26**:552–60.
46 **Shepherd J**. Economics of lipid lowering in primary prevention: lessons from the West of Scotland coronary revention study. *Am J Cardiol* 2001;**87**:19–22B.
47 **Jacobson TA**. Cost-effectiveness of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor therapy in the managed care era. *Am J Cardiol* 1996;**78**:32–41.
48 **Smart AJ**, Walters L. Pharmaco-economic assessment of the HMG-CoA reductase inhibitors. *S Afr Med J* 1994;**84**:834–7.
49 **Tarraga Lopez PJ**, Celada Rodriguez A, Cerdan Oliver M, *et al*. [Cost-effectiveness of atorvastatin against simvastatin as hypolipemic treatment in hypercholesterolemic patients in primary care] Analisis coste-efectividad de atorvastatina frente a simvastatina como tratamiento hipolipemiante en pacientes hipercolesterolemicos en atencion primaria. *Aten Primaria* 2001;**27**:18–24.
50 **Plans Rubio P**, Rovira Forns J. [Cost-effectiveness of pharmacologic treatments for the reduction of blood lipids] Estudio coste-efectividad de los tratamientos farmacologicos hipolipemiantes. *Med Clin (Barc)* 1995;**105**:327–33.
51 **Elliot W**, Weir D. Comparative cost-effectiveness of HMG-CoA reductase inhibitors in secondary prevention of acute myocardial infarction. *Am J Health Syst Pharm* 1999;**56**:1726–32.
52 **Cobos A**, Jovell AJ, Garcia-Altes A, *et al*. Which statin is most efficient for the treatment of hypercholesterolemia? A cost-effectiveness analysis. *Clin Ther* 1999;**21**:1924–36.
53 **Attanasio E**, Russo P, Allen SE. Cost-minimization analysis of simvastatin versus atorvastatin for maintenance therapy in patients with coronary or peripheral vascular disease. *Clin Ther* 2001;**23**:276–83.
54 **Perreault S**, Hamilton VH, Lavoie F, *et al*. A head-to-head comparison of the cost effectiveness of HMG-CoA reductase inhibitors and fibrates in different types of primary hyperlipidemia. *Cardiovasc Drugs Ther* 1996;**10**:787–94.
55 **Chau J**, Cheung BM, McGhee SM, *et al*. Cost-effectiveness analysis of applying the cholesterol and recurrent events (CARE) study protocol in Hong Kong. *Hong Kong Med J* 2001;**7**:360–8.
56 **Tsevat J**, Kuntz KM, Orav EJ, *et al*. Cost-effectiveness of pravastatin therapy for survivors of myocardial infarction with average cholesterol levels. *Am Heart J* 2001;**141**:727–34.
57 **Prosser LA**, Stinnett AA, Goldman PA, *et al*. Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics. *Ann Intern Med* 2000;**132**:769–79.
58 **Goldman L**. Cost-effectiveness perspectives in coronary heart disease. *Am Heart J* 1990;**119**:733–9.
59 **Field K**, Thorogood M, Silagy C, *et al*. Strategies for reducing coronary risk factors in primary care: which is most cost effective? *BMJ* 1995;**310**:1109–12.
60 **Assmann G**, Schulte H. Primary prevention of coronary heart disease in the Federal Republic of Germany. Analysis of cost-effectiveness. *Drugs* 1990;**40**(suppl 1):33–7.
61 **Schulman KA**, Kinosian B, Jacobson TA, *et al*. Reducing high blood cholesterol level with drugs. Cost-effectiveness of pharmacologic management. *JAMA* 1990;**264**:3025–33.
62 **Perreault S**, Levinton C, Le Lorier J. Efficacy and cost of HMG-CoA reductase inhibitors in the treatment of patients with primary hyperlipidemia. *Can J Clin Pharmacol* 2000;**7**:144–54.
63 **Spearman ME**, Summers K, Moore V, *et al*. Cost-effectiveness of initial therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors to treat hypercholesterolemia in a primary care setting of a managed-care organization. *Clin Ther* 1997;**19**:582–602.
64 **Cucherat M**, Boissel JP. A mathematical model for the determination of the optimum value of the treatment threshold for a continuous risk factor. *Eur J Epidemiol* 1998;**14**:23–9.
65 **Morris S**. A comparison of economic modelling and clinical trials in the economic evaluation of cholesterol-modifying pharmacotherapy. *Health Econ* 1997;**6**:589–601.
66 **Lim SS**, Vos T, Peeters A, *et al*. Cost-effectiveness of prescribing statins according to pharmaceutical benefits scheme criteria. *Med J Aust* 2001;**175**:459–64.

APHORISM OF THE MONTH

"There is a hidden healthcare system with clear definitions and roles. Eighty-five percent of healthcare takes place in a big pool without the 'benefit' of 'medical clergy'."

Lowell Levin