Cost-effectiveness of ezetimibe coadministration in statin-treated patients not at cholesterol goal: application to Germany, Spain and Norway


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

Health technology
The use of ezetimibe co-administration in statin-treated patients who have failed to reach their lipid goal, for the primary and secondary prevention of coronary heart disease (CHD). The alternative health technologies serving as comparators included maintenance of current dose of statin, and titration of statin to the highest per diem dose approved or until the lipid goal was achieved.

Type of intervention
Primary and secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of statin-treated patients who had failed to reach national target cholesterol levels with their currently prescribed statin. The national target levels were less than 100 mg/dL low-density lipoprotein cholesterol (LDL-C) in Germany and Spain, and less than 5.0 mmol/L total cholesterol (TC) in Norway. Two sub-groups of patients were examined, patients with CHD (prior CHD) in Germany, Spain and Norway, and diabetic patients without CHD (diabetic non-CHD) in Spain and Norway. Individual patient risk factor profiles were created on the basis of actual data obtained from patients in the three countries examined.

Setting
The setting of the study appears to have been outpatient secondary care. The analysis referred to health care services in Germany, Spain and Norway.

Dates to which data relate
The effectiveness evidence was derived from studies published between 1991 and 2004. The years to which the sources of the cost data referred were not reported, and nor was the price year.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of completed studies.

Modelling
A decision-analytic Markov model was developed to compare the projected lifetime cost and benefit of ezetimibe co-administration with a statin versus statin alone treatment strategies. The model included several health states associated with CHD events (e.g. angina and myocardial infarction) and a final state of death, caused by a CHD event or other, non-CHD related causes. Transition probabilities between health states depended on the patients’ lipid levels. A 1-year
time lag was assumed between treatment changes and the effect on CHD event rates. The cycle length of the model was one year. The time horizon was apparently the patients' lifetime.

The key assumptions used in the model were as follows.

Patients were assumed to be compliant with the treatment strategies for their lifetime.

The annual CHD risk can be predicted using Framingham risk equations.

Post-treatment risk (and risk reduction) can be predicted using the Framingham risk equations with updated risk factor levels for TC (or LDL-C) following a treatment change.

Lipid lowering due to statin titration or co-administration of ezetimibe impacts CHD risk starting in the year following the treatment change.

**Outcomes assessed in the review**

The outcomes assessed were:

- the reductions in LDL-C and TC levels achieved with either ezetimibe co-administration or statin titration in patients not at goal with statin-alone therapy;
- the annual risk of fatal and nonfatal CHD-related events depending on the patients' lipid levels; and
- the risk of death from non-CHD-related causes.

In addition, the characteristics of the hypothetical patient population used in the model (individual patient risk factor profiles) were determined from the review of the literature.

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

Not reported.

**Sources searched to identify primary studies**

Not reported.

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

Not reported.

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

Not reported.

**Number of primary studies included**

Approximately 3 primary studies were included in the review.

**Methods of combining primary studies**

The primary studies were apparently not combined since their results referred to different outcome measures.

**Investigation of differences between primary studies**

An investigation of differences was not applicable as the primary studies investigated different types of outcomes.
Results of the review
The mean reductions in LDL-C and TC achieved with ezetimibe co-administered with atorvastatin in patients not at goal with statin-alone therapy were 21.8 to 27.1% (LDL-C) and 14.5 to 20.0% (TC), respectively, depending on atorvastatin dose (10 to 80 mg).

The mean reductions in LDL-C and TC achieved with ezetimibe co-administered with simvastatin for patients not at goal with statin-alone were 23.8 to 29.4% (LDL-C) and 16.3 to 20.2% (TC) respectively, depending on simvastatin dose (10 to 80 mg).

The mean reductions in LDL-C and TC achieved with atorvastatin titration were 7.4 to 8.8% (LDL-C) and 5.7 to 5.9% (TC), respectively, depending on atorvastatin doses before and after titration.

The mean reductions in LDL-C and TC achieved with simvastatin titration were 9.8 to 11.6% (LDL-C) and 6.5 to 7.1% (TC), respectively, depending on simvastatin doses before and after titration. Standard deviations, median values and interquartile ranges of lipid level percentage reductions were also provided.

The annual risks of fatal and nonfatal CHD-related events based on patient lipid levels were not reported. Mortality rates due to non-CHD-related causes were also not reported. Characteristics of the hypothetical patient population were presented. These included age, gender, lipid levels, systolic blood pressure, the proportion of patients with diabetes mellitus (for the prior CHD sub-group) and the proportion of smokers.

Methods used to derive estimates of effectiveness
Due to a lack of clinical evidence, the authors made an assumption about the distribution of lipid changes.

Estimates of effectiveness and key assumptions
It was assumed that the distribution of lipid changes in patients treated with simvastatin who titrated from 10 to 20 mg would be the same as that for patients who titrated from 20 to 40 mg.

Measure of benefits used in the economic analysis
The measure of benefits used was the number of life-years gained (LYG) by adopting each of the strategies assessed. Future benefits were discounted at an annual rate of 3%.

Direct costs
The direct costs included medical costs only. These consisted of therapy costs (drug costs and costs of physician visits including a lipid test), and costs associated with acute care of fatal and nonfatal CHD-related events (e.g. angina, myocardial infarction and CHD death). Long-term maintenance costs associated with CHD events were not included in the analysis. The quantities and the costs were analysed separately for the cost of therapy. The drug costs were based on national prices and, in the case of Germany, they included Value Added Tax (VAT) in order to be consistent with the perspective adopted.

The first-year costs associated with CHD events were derived from local estimates. More specifically, unpublished data on 14,000 hospitalisations in Germany, Disease Related Group (DRG)-based costs in Spain, and national sources reporting DRG costs and other published studies in Norway. Second-year costs associated with CHD events were mainly based on assumptions. The total costs were derived using modelling. Discounting was applied at an annual rate of 3% as the costs were incurred during the patients' lifetime. The price year was not reported.

Statistical analysis of costs
The costs were treated deterministically. No statistical analysis of the costs was undertaken.
Indirect Costs
The indirect costs were not included in the analysis.

Currency
Euros (Euro). Norwegian kroners (NOK) were converted to Euros at an exchange rate of Euro 1 = NOK8.75.

Sensitivity analysis
One-way sensitivity analyses were performed to assess the robustness of the results to the uncertainty of the input parameters and assumptions used in the model. The model parameters examined were the annual CHD-related event risks, the time lag between treatment changes and the effect on transition probabilities associated with CHD events, the daily costs of atorvastatin and simvastatin and the discount rate. Also investigated was a scenario of 5-year duration of ezetimibe co-administration (rather than over lifetime, as assumed in the base-case analysis). The values used in the sensitivity analysis were based on authors’ assumptions.

Estimated benefits used in the economic analysis
The remaining life expectancy for the various sub-populations of patients above the target lipid levels when initial statin doses were maintained (no further statin titration) were:

- for prior CHD, Germany 14.49 years, Spain 16.61 years and Norway 18.04 years;
- for diabetic non-CHD, Spain 19.94 years and Norway 24.06 years;

The number of LYG by adopting "observed titration rate" was:

- for prior CHD, Germany 0.03, Spain 0.15 and Norway 0.03;
- for diabetic non-CHD, Spain 0.11 and Norway 0.02.

The number of LYG by adopting "titration to goal" was:

- for prior CHD, Germany 0.51, Spain 0.60 and Norway 0.45;
- for diabetic non-CHD, Spain 0.50 and Norway 0.40.

The number of LYG by ezetimibe co-administration was:

- for prior CHD, Germany 0.80, Spain 0.88 and Norway 0.88;
- for diabetic non-CHD, Spain 0.65 and Norway 0.75.

The benefits were estimated over the patients’ lifetime and were discounted at an annual rate of 3%.

Cost results
The total costs associated with each of the alternative interventions examined were not reported.

Synthesis of costs and benefits
The costs and benefits were combined in the form of incremental cost-effectiveness ratios (ICERs), expressing the incremental costs per additional LYG by switching practice from each of the statin-only treatment strategies (maintenance or titration) to ezetimibe co-administration.

The ICERs of ezetimibe co-administration versus no further statin titration were:
for prior CHD, Germany Euro 14,057/LYG, Spain Euro 17,029/LYG and Norway Euro 11,765/LYG;
for diabetic non-CHD, Spain Euro 28,591/LYG and Norway Euro 19,013/LYG.

The ICERs of ezetimibe co-administration versus "observed titration rate" were:
for prior CHD, Germany Euro 14,240/LYG, Spain Euro 17,760/LYG and Norway Euro 11,798/LYG;
for diabetic non-CHD, Spain Euro 29,499/LYG and Norway Euro 19,077/LYG.

The ICERs of ezetimibe co-administration versus "titration to goal" were:
for prior CHD, Germany Euro 7,215/LYG, Spain Euro 25,949/LYG and Norway Euro 14,079/LYG;
for diabetic non-CHD, Spain Euro 47,561/LYG and Norway Euro 23,024/LYG.

The results were relatively sensitive to decreases in the annual risk of CHD-related events. A reduction of 10% and 20% in all CHD-related event risks resulted in ICER increases of around 10% and 20 to 25% respectively, depending on the patient sub-group. Nevertheless, the ICERs remained under Euro 22,000/LYG in the prior CHD patients and under Euro 37,000/LYG in the diabetic non-CHD patients.

The scenario of co-administering ezetimibe only for 5 years (and not over lifetime) led to increases of 15 to 18% for prior CHD patients and of 42 to 49% for diabetic non-CHD patients. Increasing the time lag to benefit had little effect on the results (increases in ICERs of between 5 and 10%), whereas reductions in statin daily costs had virtually no effect on the relative cost-effectiveness of the strategies compared. The ICERs were also sensitive to different discount rates. Using a discount rate of 6% resulted in increases in ICERs of 21 to 35%, while applying no discounting led to reductions in ICERs of 19 to 28%.

Authors' conclusions
Compared with the three alternative statin-alone strategies (maintenance or titration of statin dose), ezetimibe co-administration appears to have been cost-effective for both patients with coronary heart disease (CHD) and diabetic, non-CHD patients who had failed to reach their lipid goal with their current statin therapy in Germany, Norway and Spain.

CRD COMMENTARY - Selection of comparators
The comparators of the analysis (maintenance or titration of statin dose) represented alternative strategies observed in routine clinical practice in Germany, Spain and Norway. The strategy of titrating all patients was more aggressive than practice observed within the countries examined, but it was selected as it provided an upper bound as to the potential benefit and cost of a statin-only strategy. You should consider whether any of the statin-only strategies serving as comparators reflect widely used practice in your own setting.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken. The authors used data from the available studies selectively. Although this is a common practice with models, it does not always ensure that the best data available are used in the model. One cannot be sure that all the relevant literature was identified, although the estimates of effectiveness appear to have been derived credibly from the studies identified. The effectiveness rates from the primary studies were not combined since they referred to different types of outcomes. Thus it was not relevant to consider potential differences between the primary studies.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. The Markov model used was not described in detail. However, in principle it was appropriate for this purpose as it enabled the calculation of lifetime benefits, by incorporating CHD-related health
states with transition probabilities depending on the patients' lipid levels, as modified by the treatment strategies examined.

**Validity of estimate of costs**
It was stated that the study adopted a health insurance (sickness funds) perspective in the analysis for Germany, and a government payer perspective in the analyses for Norway and Spain. All the categories of costs relevant to the perspectives adopted were included in the analysis. Long-term maintenance costs associated with CHD events were not included in the analysis. However, the authors stated that it was unlikely that such an omission would have a major impact on the results. The costs and the quantities were analysed separately in terms of therapy costs and this, in part, increases the reproducibility of the results. A sensitivity analysis was conducted only in the case of statin costs, with ranges based on authors' assumptions. The authors performed appropriate currency conversions for Norwegian costs. Discounting was applied, which was appropriate since the costs were incurred during the patients' lifetime. The price year was not reported, and this hinders the reproducibility of the results.

**Other issues**
The authors made comparisons of their findings (in particular those associated with projected benefits) with the results of other studies. The issue of generalisability to other settings was not addressed. Nonetheless, the study provided separate analyses for three countries and potential differences in the results were illustrated. The cost-effectiveness results were adequately reported, although the cost results were not provided separately. The conclusions about the cost-effectiveness of ezetimibe co-administration were somewhat arbitrary, as the ICERs were not evaluated against an accepted cost-effectiveness threshold expressing current willingness-to-pay for other health care interventions. Nevertheless, the authors' conclusions reflected the scope of the analysis.

**Implications of the study**
It might be inferred, from the authors' conclusions, that ezetimibe co-administration in patients already treated with a statin, who failed to reach their lipid goal, might be considered an alternative strategy on cost-effectiveness grounds.

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