Projected cost-effectiveness of ezetimibe/simvastatin compared with doubling the statin dose in the United Kingdom: findings from the INFORCE study
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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.

CRD summary
This study examined the cost-effectiveness of switching to a combination of ezetimibe and simvastatin, compared with doubling the statin dose, for patients with acute coronary syndrome, who had been on a stable (suboptimal) dose of a statin for at least six weeks. Three statin dose potencies were considered: low, medium, and high. The authors concluded that switching to ezetimibe/simvastatin was cost-effective from a health service perspective. The study was well designed and the authors’ conclusions appear to be robust.

Type of economic evaluation
Cost-utility analysis

Study objective
This study examined the cost-effectiveness of switching to combined ezetimibe and simvastatin (ezetimibe/simvastatin) compared with doubling the sub-maximal statin dose, for patients with acute coronary syndrome (ACS) who had taken a stable (suboptimal) dose of a statin for at least six weeks.

Interventions
The two interventions were 10mg ezetimibe plus 40mg simvastatin versus remaining on a statin at double the original dose. The original statin doses were at three levels low potency (fluvastatin 40mg, pravastatin 10mg or 20mg, or simvastatin 10mg), medium potency (atorvastatin 10mg or simvastatin 20mg), and high potency (atorvastatin 20mg or 40mg, rosvastatin 10mg or 20mg, or simvastatin 40mg).

Location/setting
UK/primary care.

Methods
Analytical approach:
The economic evaluation was based on a Markov model with a lifetime horizon. The authors stated that the analysis was conducted from the perspective of the payer (the UK Department of Health).

Effectiveness data:
The bulk of the clinical evidence came from the INFORCE study, a multicentre, multi-country, randomised, controlled trial (RCT) with a 12-week time horizon and a sample of 384 patients who had received a suboptimal statin dose and who were either switched to ezetimibe/simvastatin or had their statin dose doubled. The primary endpoint was the reduction in lipid levels with these two options. These data were used in the Markov model to project the long-term risk of coronary heart disease (CHD), using Framingham risk equations. The death rates not related to ACS, were from the UK Office for National Statistics.

Monetary benefit and utility valuations:
The utility values were from a published pharmacoeconomic model.

Measure of benefit:
Quality-adjusted life-years (QALYs) were the summary benefit measure and they were discounted at an annual rate of 3.5%.
Cost data:
The economic analysis included the costs of prescriptions for statins and ezetimibe and the annual event costs associated with non-fatal myocardial infarction, stable angina pectoris, unstable angina, and fatal CHD. The drug costs were from the Department of Health, while the disease-related costs were from two previous economic evaluations. All costs were in UK pounds sterling (£) and a 3.5% annual discount rate was applied. The price year was 2008 for cardiovascular disease costs and 2009 for other costs.

Analysis of uncertainty:
A statistical analysis was undertaken to account for baseline differences between the treatment groups in the clinical trial. Bootstrapping was also carried out for the expected total costs, QALYs, and incremental cost-utility ratios. A sensitivity analysis was conducted on the projected costs and benefits, assuming that the acquisition price for generic atorvastatin was equivalent to that for generic simvastatin.

Results
The switch to ezetimibe/simvastatin led to an additional cost of £2,524 and a gain of 0.218 QALYs, resulting in an incremental cost per QALY gained of £11,571. The incremental cost per QALY gained was £13,552 in the subgroup on a low-potency dose, £11,930 in the subgroup on a medium-potency dose, and £10,148 in the subgroup on a high-potency dose.

Assuming the cost of generic simvastatin for atorvastatin, the incremental cost per QALY gained with ezetimibe/simvastatin rose to £17,616. The bootstrapping analysis showed that 95% of simulations were between £8,181 and £18,600 per QALY.

Authors' conclusions
The authors concluded that switching to ezetimibe/simvastatin was a cost-effective strategy from the perspective of the health service.

CRD commentary
Interventions:
The comparators appear to have been appropriately selected and are likely to be relevant in other health care settings.

Effectiveness/benefits:
The clinical data came from a well-conducted RCT and its methods should ensure the validity of the clinical inputs. Its international and multicentre nature also enhances its external validity. More details of the trial were published elsewhere (Reckless, et al. 2008, see 'Other Publications of Related Interest' below for bibliographic details). The authors noted that the study groups were not well balanced at baseline, but the potential impact of confounding factors was taken into account using statistical analysis. The long-term disease progression was modelled using standard UK equations. Little information on the utility valuations was provided, which reduces the possibility of judging the validity of the data. QALYs appear to have been a valid benefit measure for this patient population and will allow comparisons to be made with the projected benefits of other health care interventions.

Costs:
The cost categories were consistent with the perspective of the health service. The unit costs and resource quantities were reported for the drugs. Other costs were presented as total categories and were from published studies, the methods of which were not reported. One of these publications was submitted to the National Institute for Health and Clinical Excellence (NICE) and its methods presumably followed the conventional framework for economic evaluation. The impact of variations in assumptions on the unit costs or patterns of resource consumption was not investigated, except for the cost of atorvastatin. A unique price year was not used and this was acknowledged as a potential limitation.

Analysis and results:
The results were clearly reported for the whole sample and for subgroups with different potencies of statin dose. An incremental approach was appropriately used to synthesise the costs and benefits. The issue of uncertainty was adequately investigated by using bootstrapping methods to calculate the average values in the context of skewed data.
The key details of the model structure and its pathways were reported. The authors noted some limitations of their analysis and they compared their study with other published analyses, highlighting potential differences.

Concluding remarks:
The study was well designed, and the authors’ conclusions appear to be robust.

Funding
Supported by Merck & Co, Inc.

Bibliographic details

PubMedID
20561328

DOI
10.1111/j.1524-4733.2010.00742.x

Original Paper URL

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Acute Coronary Syndrome /drug therapy /economics; Aged; Anticholesteremic Agents /administration & dosage /economics; Azetidines /administration & dosage /economics; Cost-Benefit Analysis; Drug Therapy, Combination /economics; Ezetimibe; Female; Great Britain; Humans; Hydroxymethylglutaryl-CoA Reductase Inhibitors /administration & dosage /economics; Hypercholesterolemia /drug therapy /economics; Male; Markov Chains; Middle Aged; Models, Economic; Randomized Controlled Trials as Topic; Simvastatin /administration & dosage /economics

AccessionNumber
22010001709

Date bibliographic record published
24/11/2010

Date abstract record published
12/01/2011