Secondary prevention after PCI: the cost-effectiveness of statin therapy in the Netherlands

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Background. Little is known about the cost-effectiveness of secondary prevention after percutaneous coronary intervention (PCI). The aim of this study was to estimate the cost-effectiveness of statin therapy.

Methods. A cost-effectiveness analysis was performed using data from the Lescol Intervention Prevention Study (LIPS). In the LIPS trial, patients with normal-to-moderate hypercholesterolaemia who had undergone a first PCI were randomised to receive either fluvastatin 40 mg twice-daily plus dietary counselling or dietary counselling alone. A Markov model was used to estimate the incremental costs per quality-adjusted life year (QALY) and life year gained (LYG). Costs were based on prices and reimbursed charges, utility data were drawn from literature. Monte Carlo simulations and multivariate analysis were used to assess uncertainty.

Results. Routine statin treatment costs an additional €734 (SD €686) per patient over ten years compared with controls. It resulted in an additional 0.078 (0.047) QALYs or 0.082 (0.041) LYG. The incremental costs per QALY and LYG were €9312 (€14,648) and €8954 (€16,617) respectively. Anticipating a willingness to pay of €20,000 per QALY, there is a 75.1% chance that fluvastatin treatment is cost-effective.

Conclusion. Statin therapy with fluvastatin is economically efficient with regard to reducing heart disease in the Netherlands when given routinely to all patients following PCI. *(Neth Heart J* 2004;12:331-6.)

Key words: cardiac events, cost-effectiveness, fluvastatin, secondary prevention, statins

Coronary heart disease (CHD) is a common cause of death in the Netherlands and approximately 4.2% of the population suffers from this condition.[1,2] Percutaneous coronary intervention (PCI) has become a routine and effective procedure to remove occlusions from coronary arteries. The number of PCIs in the Netherlands has faced an increase over the past few years to a total of 25,037 procedures in 2002.[3] Although PCI has shown to be an effective therapy to achieve short-term improvements in ischaemic symptoms, patients continue to have high rates of postprocedure cardiovascular events.[4]

Concurrent with the use of interventional cardiology procedures, the use of lipid-lowering medications, such as statins, has increased. A landmark study showed significant reductions with statins in all-cause mortality and coronary death rates of 12 and 18% respectively.[5] Other studies have confirmed the preventive effect of statins.[6,7]

Only a few clinical trials have examined the effectiveness of routinely initiating statin therapy after a successful PCI. The Lescol Intervention Prevention Study (LIPS) investigated the benefits of long-term treatment with fluvastatin in patients immediately following a first PCI.[8] In this multinational double-blind placebo-controlled trial, patients (n=1677) with normal to moderate hypercholesterolaemia (average baseline total cholesterol 5.2 mmol/l) were randomised to receive fluvastatin 40 mg twice-daily plus dietary counselling or dietary counselling only (control group). Primary endpoint was a first major adverse cardiac event or MACE, defined as cardiac death, a nonfatal myocardial infarction or reintervention procedures (PCI or coronary artery bypass graft (CABG)). The relative risk reduction of MACE in the fluvastatin group was 22% (95% CI 5-36%).

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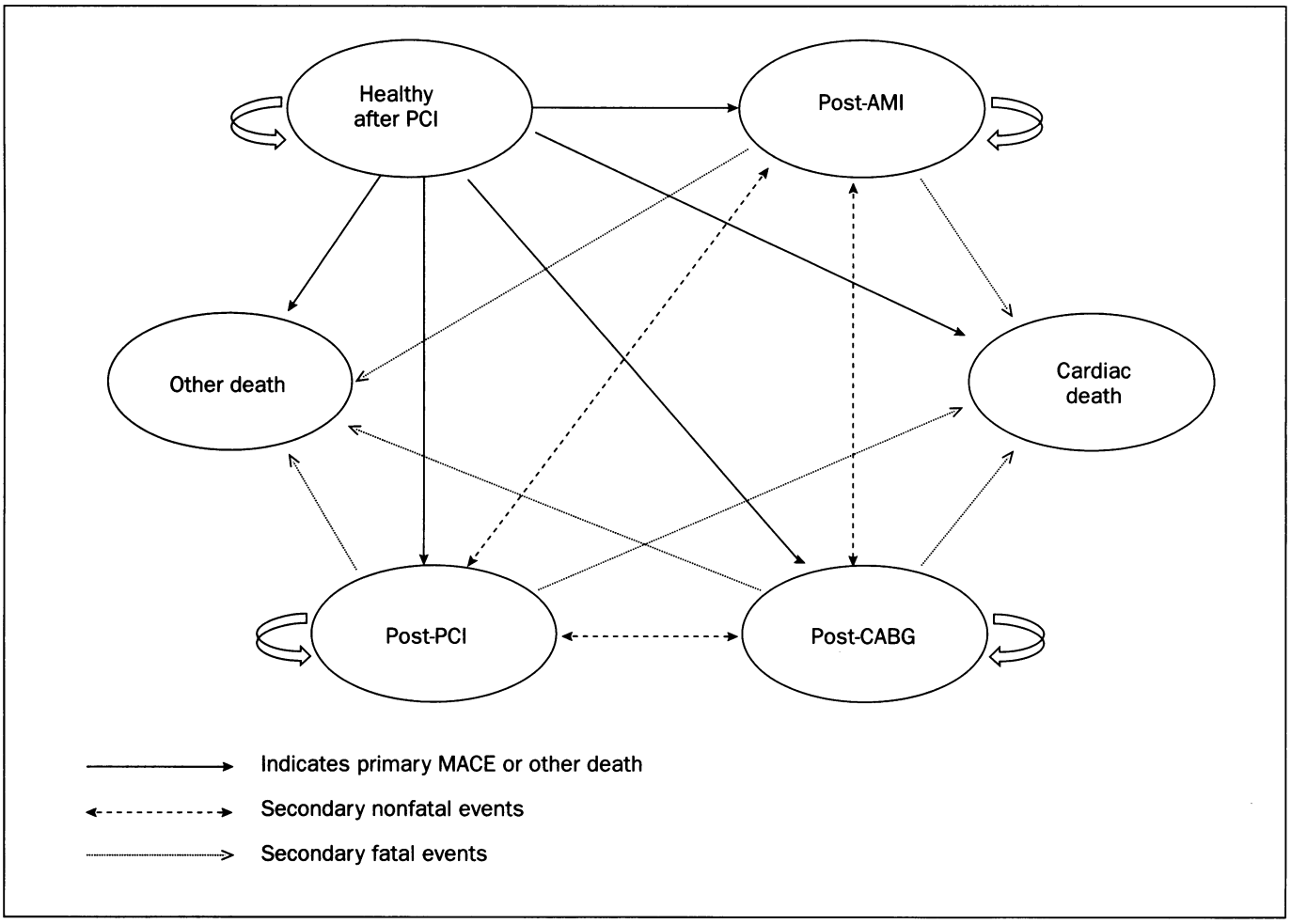

Figure 1. Health states and transitions in the Markov model.

These results established that fluvastatin, used for patients who have undergone a first PCI, is an effective strategy in reducing cardiac events.

Treatment guidelines have been developed in the Netherlands for both primary and secondary prevention of CHD.[9] In its recommendations, the CBO consensus is driven by the need to make cost-effective choices in treatment.

The aim of this study is to assess the costs, benefits and finally the incremental cost-effectiveness of secondary prevention, that is, routinely adding the statin fluvastatin after a first successful PCI. A secondary aim is to assess whether the cost per quality-adjusted life year gained is below the threshold, that is, the society's willingness to pay for a life year gained as laid down in the CBO consensus.

Methods

Markov model

The cost-effectiveness analysis is based on a Markov model developed in the UK.[10] The model consists of six health states and possible transitions among these health states and was developed to simulate the occurrence of cardiac events (MACE) in the LIPS trial (Software: DataPro).[11] The health states and possible transitions in the model are depicted in figure 1.

Patients who remain alive can pass through any number of defined health states in the model. A patient will remain in a particular health state until another event occurs. The transition from one health state to another was determined by monthly transition probabilities. These probabilities were directly derived from the LIPS trial. Since being in a certain health state incurs healthcare costs on the one hand, and may impact quality of life on the other, both costs and quality-adjusted survival were assigned to the particular health state. The model distinguishes between one-off costs and effects due to the occurrence of an event and costs and effects due to living in a certain health state. The model allowed withdrawals and uptake of other lipid-lowering drugs to occur, as observed in the LIPS trial. To account for uncertainty, transition probabilities,

costs and effects were described by distributions and were analysed using state-of-the-art Monte Carlo simulation.

Costs

Unit costs in this study were based on prices and reimbursed charges (€2002). Inpatient costs and standard deviations were obtained by PHARMO (Utrecht), based on the Dutch National Medical Registration (LMR). It covers all procedures and admissions in 2002 and includes the charges for hospital procedures (by ICD-9-CM code), admissions and specialist fees. The price of fluvastatin is taken from the List Price (Taxe) and for the costs of other statins used in the trial, a weighted-average cost of statins was calculated based on market share in the Netherlands. A reliable source for the cost of (non)cardiac death was not available: we assumed a cost of €1000 per fatality.

Effectiveness: health outcomes

The outcomes modelled were quality-adjusted life years (QALYs) and life years gained (LYG). A monthly utility or quality of life weight was assigned for each health state. These weights were derived from published studies.[12-14] To calculate QALYs, the utility weights were multiplied by the duration in each health state. Patients experiencing an event (AMI, PCI or CABG) were assigned disutility weights to take into account the one-off decrease in their health status due to the event. For PCI and CABG events, disutility weights included decreased utility from angina in the two months prior to intervention, decreased utility in the months of intervention and for CABG also decreased utility 2.5 months post-CABG. Patients experiencing an acute myocardial infarction (AMI) were assumed to have twice the disutility of angina, lasting for three months. Post-AMI patients were also assumed to have lower utility than post-PCI or post-CABG patients, irrespective of subsequent interventions.

Assumptions

The cost-effectiveness was estimated over a period of ten years. Cost and effects were discounted at 4% per annum to correct for time preferences, in accordance with Dutch guidelines.[15] Routine outpatient follow-up visits were assumed to take place once every three months in the first year and every six months thereafter. The LIPS study was powered to detect significant differences in the first MACE between the fluvastatin and control group. Since the trial was not powered to detect significant differences for a subsequent MACE, no valid inferences could be drawn concerning the rates for a subsequent MACE. It was assumed that following the first MACE, subsequent AMI, PCI, CABG, and cardiac death rates were the same for both fluvastatin and control groups (i.e. a conservative estimation of treatment effect). A yearly uptake of statin therapy in the control group of 8% was included in the model, as was observed in LIPS. For the fluvastatin group, the model accounted for patient withdrawal and the use of other lipid-lowering drugs for patients in whom fluvastatin was not sufficiently effective as observed in LIPS.

Uncertainty and analysis

To reflect parameter uncertainty in the model, transition probabilities, costs and effects were not entered as point estimates but as a distribution of possible estimates. Distribution parameters were calculated from the observed means and standard deviations. Transition probabilities were assumed to follow beta distributions, as they are constrained on the interval zero-one.[16] Similarly, utility and disutility weights were assumed to follow beta distributions, with means and standard

Table 1. Event rates from the LIPS trial up to month 48.

	Fluvastatin (n=844)	Placebo (n=833)
Acute myocardial infarction		
- Before 28 months	0.028	0.028
- After 28 months	0.008	0.014
AMI outcomes		
- Remain healthy	0.202	0.202
- CABG	0.132	0.132
- PCI	0.618	0.618
- Cardiac death	0.033	0.033
PCI		
- Before 18 months	0.150	0.150
- After 18 months	0.023	0.050
PCI outcomes		
- Remain healthy	0.887	0.887
- AMI	0.000	0.000
- CABG	0.066	0.066
- Cardiac death	0.033	0.033
CABG		
- Before 3 months	0.008	0.008
- After 3 months	0.031	0.035
CABG outcomes		
- Remain healthy	0.905	0.905
- PCI	0.095	0.095
- Cardiac death	0.000	0.000
Cardiac Death		
- Before 3 months	0.005	0.005
- After 3 months	0.011	0.022
Other deaths	0.029	0.029
Drug withdrawal rate	0.037	N/A
Drug crossover rate	0.048	N/A
Lipid uptake	N/A	0.081

N/A=not applicable.
AMI=acute myocardial infarction, CABG=coronary artery bypass graft, PCI=percutaneous coronary intervention.

Table 2. Cost and utility per health state.

Health state	Cost of state[1]	Cost of event[2] (SD)	State utility[1] (SD)	Event utility[2] (SD)
Remain healthy after first PCI	Costs for statin treatment and follow-up[3]	0	0.86[5] (0.16)	0
PCI	Costs for statin treatment and follow-up	€9811[4] (€3231)	0.86[5] (0.16)	-0.0426[6,7] (0.042)
AMI	Costs for statin treatment and follow-up	€5821[4] (€5796)	0.78[5] (0.16)	-0.083[9] (0.014)
CABG	Costs for statin treatment and follow-up	€17,514[4] (€6775)	0.86[5] (0.16)	-0.059[6-8] (0.059)
Death	0	€1000	0	0

1 Cost or utility incurred as a result of living in a certain health state.
2 One-off cost or disutility incurred in case of a cardiac event.
3 Cost of fluvastatin (€27.08 per month), other lipid-lowering drugs (€35.26 per month) and outpatient follow-up (€73.40 per visit).
4 Average cost in the Netherlands based on LMR discharge records.
5 Based on literature.
6 Two months of disutility from angina whilst waiting for procedure (utility weight angina=0.703 scaled by the baseline utility weights in the ARTS trial; i.e. 0.86/0.87x0.703=0.695).
7 One month of disutility in month of procedure (utility weight=0.68 for CABG, 0.69 for PCI).
8 Recovery lasts for 2.5 months (months 2 to 4.5 utility weight=0.78).
9 AMI was assumed to be twice as bad as angina and to last for three months (disutility of angina per month: (0.860-0.695)/12=0.014 disutility weight AMI=0.014x2=0.028, for three months=0.0825).

deviations drawn from published studies.[12-14] Because cost data tend to be skewed to the right (i.e. a few patients tend to incur high costs) gamma distributions bounded between zero and infinity were used for these parameters.[16]

Monte Carlo simulation was conducted to analyse parameter uncertainty by drawing 10,000 samples from the distributions described above and subsequently running the Markov model. Results were expressed in incremental cost per QALY and per life year gained (LYG). A multivariate analysis was conducted by regressing all parameters with distributions assigned on the net health benefits using ordinary least squares. A one-way sensitivity analysis was then conducted around the parameters that were statistically significant, as well as around the discount rate. For this analysis variables were changed by a constant + or - 10% and the percentage change in final outcome (ICER) was calculated. To assess whether routine treatment with fluvastatin after PCI meets the required standard of efficiency as laid down in the CBO consensus, an acceptability curve was plotted. This plot shows the chance of an intervention being cost-effective, given a society's willingness-to-pay for a unit of effect, usually a QALY.[17] The willingness-to-pay in the CBO consensus was €18,000 per life year gained in 1998. A conservative estimate of society's willingness to pay of €20,000 per QALY in 2002 was used as cut-off in this study.

Results

The event rates observed in the LIPS study are shown in table 1. These rates were converted into monthly transition probabilities.

The costs and quality of life weights (utility) per heath state are presented in table 2. A CABG is the most costly event (€17,514) and the impact on quality of life is the largest for an AMI, that is, its disutility associated with the event (-0.083) as well as living in the post-AMI health state (0.78).

A graphical representation of running 10,000 Monte Carlo simulations, including a 95% confidence limit (ellipse) is depicted in figure 2. More QALYs were obtained in 96.0% of the simulations and greater costs

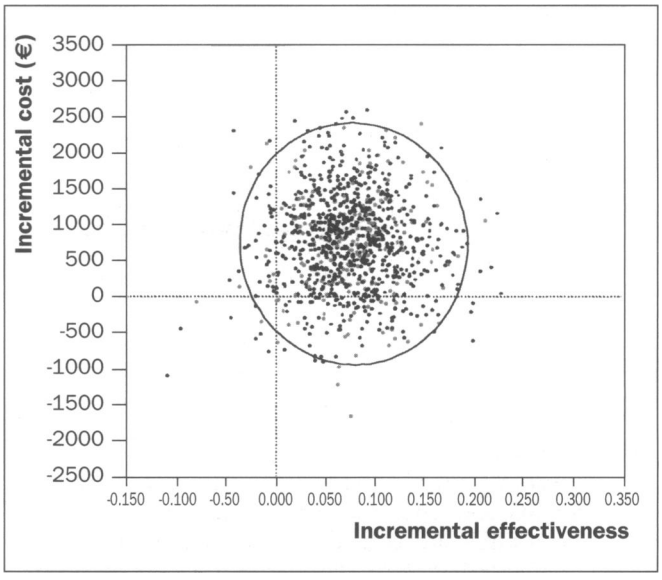

Figure 2. Scatter plot and 95% confidence limits for fluvastatin 80 mg/day.

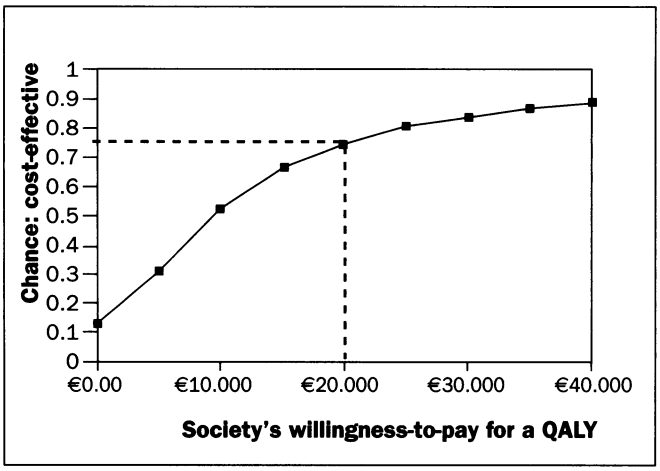

Figure 3. Acceptability curve for routine statin treatment after PCI: the chance that treatment is cost-effective, given society's willingness to pay for a QALY.

incurred in 86.1%. The chance of greater costs and worse outcomes was 3.1% (i.e. the upper left quadrant where fluvastatin is dominated) whereas the chance that fluvastatin is dominant was 13.0% (i.e. lower right quadrant). The average total discounted costs in the fluvastatin group were €8487 (SD €1197) per patient per ten years and €7752 (€1326) per patient in the control group. The net incremental cost was €734 (€686) per patient using fluvastatin per ten years. The number of life years gained through fluvastatin was 0.105 (0.054). Correction for quality of life and time preferences resulted in an average 6.685 (1.027) and 6.607 (1.005) discounted QALYs for fluvastatin and control patients respectively, resulting in an incremental effectiveness of 0.078 (0.047) QALYs. The incremental costs per QALY and LYG for fluvastatin were €9312 (€14,648) and €8954 (€16,617) respectively.

Given a society's willingness to pay €20,000 per QALY, the likelihood that secondary prevention with fluvastatin is a cost-effective intervention is 75.1%, as shown in figure 3.

The regression analysis of the net health benefits identified 16 factors as having significant effects on the results. These factors were the rates of primary MACE in the fluvastatin and control group, the costs of MACE and fluvastatin and the utility weights of the health states post-PCI, post-AMI and post-CABG. The one-way sensitivity analysis revealed that the cost of fluvastatin and the discount rate had the largest effect on the ICER; a 10% decrease in the cost of fluvastatin resulted in a 30.7% decrease in the ICER and increasing the cost by 10% increased the ICER by 31.7%. However, neither the cost of fluvastatin nor the discount rate are factors associated with high levels of uncertainty. The sensitivity analysis for other variables revealed that the model results were fairly robust.

Discussion

The LIPS study established that fluvastatin, used for patients who have undergone a first PCI, is an effective strategy for reducing cardiac events. A Markov model, based on the LIPS endpoints and event rates, was subsequently used to estimate the costs and effects associated with routinely adding fluvastatin after a first PCI. Based on Dutch cost data and utilities, drawn from literature, fluvastatin therapy was considered cost-effective, for it produced a QALY at an average cost of €9312 and a life year, uncorrected for its quality, at an average cost of €8954. Taking into account a society's willingness-to-pay of €20,000 for a QALY, the chance of statin therapy with fluvastatin being cost-effective is 75%.

The validity of any model relies heavily on the data used, on the appropriateness of the assumptions made and on the proper analytical techniques used. The LIPS model was based the actual four-year follow-up data from the trial. Its population (n=1677) consisted of patients from Europe (15% Dutch), Canada and Brazil and, therefore, the results are more likely to be applicable to the Netherlands than say a trial undertaken in the US where intervention rates are generally higher. In addition, the cost-effectiveness estimates obtained in this study using ten-year and 25-year horizons were broadly comparable with other published studies on statins.[18-20] The inpatient cost estimates were based on the LMR data that cover virtually 100% of procedures and admissions in the Netherlands. Based on this source, highly reliable average cost estimates and standard deviations could be extracted. The only uncertain cost parameter used in the model was the costs associated with (cardiac) death. Sensitivity analysis, however, revealed that the cost per QALY was not sensitive to changes in the cost of (cardiac) death (less than 1% impact).

The assumptions made in this study can be characterised as conservative. Following the primary MACE, we assumed the rates of subsequent interventions and outcomes were equal in the fluvastatin and control groups. This assumption was made because the LIPS trial was not powered to detect differences between groups following the primary endpoint (i.e. the numbers observed for the outcomes following primary MACE were small). This assumption is likely to understate the true effectiveness of fluvastatin because it is likely that those treated with statins might have lower rates of AMI, subsequent interventions and cardiac death following the primary MACE. Therefore, the cost per QALY estimated here might be higher than if data were drawn from a larger trial.

The outcomes of the four-year LIPS trial have been projected to ten years. The average age of a patient undergoing a first PCI in the Netherlands is approximately 60 years and given that patients have a compromised or shortened life expectancy,[3] the ten-year time frame was seen as a reasonable period for the benefits and costs of treatment with statins to be accrued.

To account for uncertainty around the ICER, produced by the model, state-of-the-art modelling techniques were used. Since data on the variance of several input parameters were available, second order or parameter uncertainty was introduced to the model by means of Monte Carlo simulation (DataPro). By drawing 10,000 samples from these distributions, a scatterplot of possible point estimates could be drawn, including a 95% confidence interval. This confidence interval can be regarded as a probability interval or posterior distribution (Bayesian analysis). Bayesian analysis has the appealing property that it can give a probability that a hypothesis is true or false, in contrast to more widely used frequentist statistics. This is visualised in the acceptability curve that answers the intuitively natural question of a physician or policy maker: 'What is the chance of this intervention being cost-effective?'. Furthermore, extensive one-way sensitivity analysis (and multivariate analysis) was performed to assess the robustness of the model.

Increasing demand and limited budgets for care will ultimately result in making choices. Cost-effectiveness analysis is just one way of making informed choices in healthcare, but one of increasing importance. While there is a clear need for information concerning the cost-to-benefit ratio of (costly) interventions, well-performed country-specific economic evaluations are scarce in the Netherlands. Fluvastatin is the only statin which has proved to be effective and also cost-effective in preventing MACE in new PCI patients; other statins lack this evidence. This makes fluvastatin a viable and economically efficient pharmaceutical to reduce heart disease in the Netherlands when given routinely to all patients following PCI. ■

Acknowledgements

We are indebted to Martien Panneman from the PHARMO Institute in the Netherlands (Utrecht) for the provision of inpatient cost data. This study was funded by research grants from Novartis Pharmaceuticals UK Ltd and Novartis Pharma, the Netherlands.

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