Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis

Pignone M, Earnshaw S, Tice J A, Pletcher M J

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 study examined the use of aspirin, statins, and a combination of aspirin and statins for the primary prevention of coronary heart disease (CHD).

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of male patients aged 45 years without a history of cardiovascular disease, with various levels of 10-year risk for CHD (2.5%, 5%, 7.5%, 10%, 15% and 25%).

Setting
The setting was primary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were taken from published studies dating from 1993 to 2004. The cost data were taken from a number of sources dating from 1998 to 2003. All costs were converted to 2003 US dollars.

Source of effectiveness data
The effectiveness data were obtained from a review of published studies.

Modelling
A Markov state-transition model was developed to simulate cohorts of initially healthy middle aged men with no history of cardiovascular events and with various levels of 10-year risk for CHD. The Markov model included a healthy state, five other health states (angina, myocardial infarction, or stroke as an initial cardiovascular event, and gastrointestinal bleeding or myopathy as adverse effects from therapy) and one "dead" state. A lifetime horizon was adopted for the model. The duration of each cycle was 1 year. The model was based on various assumptions around efficacy, transition probabilities and costs, which were all reported in the study. However, they are too numerous to be reported in this abstract.

Two approaches to model the effect of aspirin on stroke were used. In the base-case analysis, haemorrhagic stroke and ischaemic stroke were included together in one estimate of the effect of aspirin on total stroke. In an alternate scenario, haemorrhagic stroke and ischaemic stroke were modelled as separate health states.
Outcomes assessed in the review
The outcomes assessed in the review were:

- the relative risk (RR) of primary prevention of myocardial infarction, stroke, angina and death from CHD;
- the annual risk of adverse events (myopathy from statins, death resulting from myopathy, gastrointestinal bleeding from aspirin and death from gastrointestinal bleeding);
- the increase in RR of death after myocardial infarction, stroke and angina; and
- the RR for all-cause mortality with secondary prevention for statins and aspirin.

Study designs and other criteria for inclusion in the review
The authors reported that randomised controlled trials and meta-analyses were used to assess the outcomes.

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
Sixteen primary studies were included in the review.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
The annual risk of myopathy from statins was 0.001% (range: 0.0005 to 0.05).

The annual risk of death from myopathy was 0.00001% (range: 0.000001 to 0.0001).

The annual risk of gastrointestinal bleeding was 0.0007% (range: 0.0004 to 0.01).

The annual risk of death from gastrointestinal bleeding was 0.00001% (range: 0.000001 to 0.0001).

The increase in RR for death after myocardial infarction was 3.7% (range: 3 to 4.7).

The increase in RR for death after angina was 3.0% (range: 2.1 to 4.2).

The increase in RR for death after stroke was 2.3% (range: 1.6 to 4.6).
The RR for all-cause mortality with secondary prevention was 0.79% (range: 0.72 to 0.86) for statins and 0.85% (range: 0.80 to 0.90) for aspirin.

**Methods used to derive estimates of effectiveness**
Where the data were limited, conservative assumptions were made. Baseline risks for initial cardiovascular events were drawn from Framingham risk equations and then translated into annual event-related transition probabilities by assuming an exponential distribution.

**Estimates of effectiveness and key assumptions**
The efficacy of the combined use of aspirin and statins was assumed to be independent on the basis of data from secondary prevention trials.

The RR of primary prevention for myocardial infarction was 0.7% (range: 0.62 to 0.79) for statins and aspirin.

The RR of primary prevention for stroke was 0.85% (range: 0.57 to 1.28) for statins and 1.06% (range: 0.91 to 1.24) for aspirin.

The RR of primary prevention for angina was 0.68% (range: 0.49 to 0.95) for statins and 1% (range: 0.80 to 1.20) for aspirin.

The RR of primary prevention for death from CHD was 0.71% (range: 0.56 to 0.91) for statins and 0.87% (range: 0.70 to 1.09) for aspirin.

Adherence to treatment was assumed to be 100% in the absence of adverse events.

**Measure of benefits used in the economic analysis**
The benefit measure used was the quality-adjusted life-years (QALYs). These were drawn from the literature and were estimated using the time trade-off techniques described in the original studies. Where no data were available, estimates were used and examined in sensitivity analysis.

**Direct costs**
Discounting was carried out at an annual rate of 3%. The costs were derived from data from published literature and national databases, and were expressed in 2003 dollars. Hospital charges were converted to costs using the 1999 cost-to-charge ratio derived from the Medicare provider analysis and review of short stay hospitals. The medical Consumer Price Index was then used to inflate these costs to 2003 dollars. The drug costs were obtained from the 2003 Red Book average wholesale prices.

**Statistical analysis of costs**
No statistical analysis was undertaken.

**Indirect Costs**
Indirect costs were not used in the model.

**Currency**
US dollars ($).

**Sensitivity analysis**
A one-way sensitivity analysis was undertaken on baseline assumptions and parameter estimates, including the effect of different levels of 10-year risk for CHD, different starting ages, main efficacy, adverse events, costs and utility estimates. The ranges were derived from the literature. A probabilistic sensitivity analysis was undertaken on RRs for myocardial infarction, stroke or death from CHD, other adverse events, costs and utilities. A normal distribution was assumed for adverse events and a triangular distribution was used for utilities.

**Estimated benefits used in the economic analysis**

Compared with no treatment, aspirin treatment for 10 years in 45-year-old men with a 10-year risk for CHD of 7.5% increased mean QALYs (17.16 versus 17.20).

Compared with aspirin alone, combination therapy for 10 years in 45-year-old men with a 10-year risk for CHD of 7.5% resulted in an increase of 35 quality-adjusted days gained.

For the alternate haemorrhagic stroke model, compared with no treatment, aspirin treatment for 10 years in 45-year-old men with 10-year risk for CHD of 7.5% increased mean QALYs (17.177 versus 17.150).

For the alternate hemorrhagic stroke model, compared with aspirin alone, combination therapy for 10 years in 45-year-old men with a 10-year risk for CHD of 7.5% resulted in an increase of 35 quality-adjusted days gained.

**Cost results**

In the base-case analysis, the cost for aspirin therapy alone was $6,694 compared with $6,909 for no therapy.

In the alternate model, the cost for aspirin therapy alone was $6,888 compared with $6,880 for no therapy.

**Synthesis of costs and benefits**

The costs and benefits were combined to give an incremental cost per QALY gained. This was not applicable for aspirin alone versus no therapy as the treatment was both less costly and more effective.

For combination therapy versus aspirin alone, the cost per QALY was $56,200 in the base-case and $57,100 in the alternate model.

The sensitivity analysis showed that excess risk for haemorrhagic stroke and gastrointestinal bleeding with aspirin, risk for CHD, the cost of statins, and the disutility of taking medication had important effects on the cost-utility ratios.

**Authors’ conclusions**

The initial use of aspirin for 10 years was both more effective and less costly than no treatment for the primary prevention of coronary heart disease (CHD) events in middle-aged men with a 10-year risk for CHD of 7.5% or greater. The addition of a statin to aspirin therapy gave a cost per quality-adjusted life-year (QALY) gained of $56,200. The results of the analysis were sensitive to the costs of statins: when the annual cost of statin was less than $633, its addition to aspirin therapy resulted in a cost per QALY of less than $50,000 for men with a 10-year risk of 7.5%.

**CRD COMMENTARY - Selection of comparators**

The rationale for the comparators was clear. National treatment guidelines recommend aspirin and statin drugs individually for the primary prevention of CHD events in men who are at increased risk.

**Validity of estimate of measure of effectiveness**

The paper did not state whether a systematic review was undertaken. Although this is common practice with models, it does not always ensure that the best data available are used in the model. The effectiveness data were taken from existing meta-analyses or RRs from individual trials. It was not stated how the results of these trials were combined to give estimates of benefits. In addition, the impact of differences between the studies identified was not taken into account.
account when estimating effectiveness. The authors made assumptions for some estimates of effectiveness, but did not provide any justification for the choice of assumptions. Sensitivity analyses were conducted to improve both the internal validity of the study and the generalisability of the results.

**Validity of estimate of measure of benefit**
The economic benefit was measured through QALYs, which were estimated using a decision model. The model took the health states that the patients could enter and the probability of moving between states into consideration. The utility weights were taken from published literature.

**Validity of estimate of costs**
The authors presented their results from the perspective of a third-party payer. The source of the cost data was appropriately reported. Since the costs were incurred during a long period, discounting was relevant and was appropriately reported. The price year was also reported, which should assist with any future reflation exercises. As only hospital charges were available, the authors estimated costs using an appropriate cost-to-charge ratio. Although the costs were treated deterministically, extensive sensitivity analyses were conducted. Such analyses improve both the internal validity and the generalisability of the study by demonstrating the robustness of the results to changes in the base-case estimates. In addition, cost estimates were compared with recent medical literature.

**Other issues**
The authors made appropriate comparisons with other published studies. Generalisability to other settings was not addressed. The authors’ conclusions reflected the scope of the analysis. The authors acknowledged the limitations of their study. For instance, several of the parameters that were used in the model had only limited empirical supporting data and were therefore subject to error. However, an extensive sensitivity analysis was conducted around these parameters. In addition, the model did not capture all of the possible beneficial or harmful effects of each drug and did not investigate incomplete adherence for either aspirin or statin use.

**Implications of the study**
The authors suggested that, for middle-aged men with a 10-year risk for CHD of 7.5% or greater, aspirin should be recommended; for men at or below these risk levels, aspirin should not be routinely recommended. The authors did not provide explicit recommendations concerning the need for further research.

**Source of funding**
Supported by Bayer and the Centers for Disease Control and Prevention.

**Bibliographic details**

**PubMedID**
16520473

**Other publications of related interest**


Naglie IG, Detsky AS. Treatment of chronic nonvalvular atrial fibrillation in the elderly: a decision analysis. Med Decis