Analysis of aspirin-associated risks in healthy individuals

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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.

Health technology
The study examined the use aspirin 325 mg daily in healthy individuals.

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of healthy individuals of 50 years of age.

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

Dates to which data relate
The effectiveness data and some resource use data were derived from studies published between 1989 and 2002. The price year was 2000.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies and authors’ opinions.

Modelling
A Markov model based on first-order Monte Carlo simulations was constructed to determine the risk of complications and the costs associated with aspirin use in healthy men aged 50 years. The model simulated healthy individuals and followed them until death. Individuals could remain in the healthy state or develop complications (intermediate or major cerebral vascular bleeding, upper gastrointestinal or genitourinary bleed) related to aspirin use. Both disabling and non-disabling cerebral vascular bleeding was considered. Participants could die from these complications or from all other causes. If a complication occurred, individuals stopped aspirin therapy and complications no longer occurred. The cohort of patients taking aspirin was compared with a cohort of individuals not taking it. A simplified graphical representation of the model was provided.

Outcomes assessed in the review
The outcomes estimated from the literature were:

the excess or increased rates of total noncerebral bleeds (major bleeds and intermediate bleeds) that were attributable to
aspirin,
depth from noncerebral complications,
total haemorrhagic cerebral vascular accident (CVA), and
depth from CVA.

Also estimated were utility reductions associated with major bleed and CVA, and the quality of life weight associated with disabling CVA, non-disabling CVA and noncerebral bleed.

**Study designs and other criteria for inclusion in the review**
A review of the published literature was performed to identify relevant studies. Details of the design of the studies were not reported, with the exception of one meta-analysis and a clinical trial. All-cause mortality came from US Life Tables.

**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**
Some data came from a meta-analysis, which should ensure high internal validity.

**Number of primary studies included**
Ten primary studies provided evidence.

**Methods of combining primary studies**
Not stated.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The excess or increased rates attributable to aspirin per 100,000 individuals was:

- 220 (Range: 22 to 2,200) for total noncerebral bleeds,
- 40 (Range: 4 to 400) for major noncerebral bleeds,
- 180 (Range: 18 to 1,800) for intermediate noncerebral bleeds,
- 4.4 (Range: 0.44 to 44) for death from noncerebral complications,
- 20 (Range: 2 to 200) for total haemorrhagic CVA,
- 11 (Range: 1.1 to 110) for disabling CVA.
9 (Range: 0.9 to 90) for nondisabling CVA, and
6 (Range: 0.6 to 60) for death from CVA.

The utility reduction was 1 week from major bleed and 1 month from CVA. The quality of life factor was 50% for disabling CVA, 75% for non-disabling CVA, and 97% for noncerebral bleed.

Methods used to derive estimates of effectiveness
The authors made some assumptions to derive some clinical estimates.

Estimates of effectiveness and key assumptions
The model assumed that the acute post-complication quality of life was 70% of that before a procedure for one day following an intermediate noncerebral bleed, one week following a major noncerebral bleed, and 4 weeks following a stroke. The utility reduction due to intermediate bleed was 1 day.

Measure of benefits used in the economic analysis
The main model output was the quality-adjusted life-years (QALYs). These were derived by combining utility weights and survival obtained from the literature. Information on the methods used to estimate the utility values was not reported, but some were taken from the literature and others were based on authors' assumptions. An annual discount rate of 3% was used. Other model outputs were life expectancy, complication rates and complication-related deaths.

Direct costs
The analysis was performed from a societal perspective. The direct medical costs were for aspirin, intermediate bleed, major bleed and CVA. The unit costs were not presented separately from the quantities of resources used for all items. Resource use was estimated on the basis of published data, while the costs were estimated using average wholesale prices for drugs and published studies for the remaining categories. Discounting was relevant, as the costs were incurred over a long period of time, and an annual rate of 3% was applied. All the costs were inflated to 2000 values using the medical care component of the Consumer Price Index.

Statistical analysis of costs
Statistical analyses of the costs were not carried out in the base-case.

Indirect Costs
The indirect costs (i.e. productivity losses associated with workdays missed due to aspirin-related complications) were included in the analysis carried out from a societal perspective. The unit costs and the quantities of resources used were not presented separately, but the cost of a day's wage was reported. The value of a day's wage was based on the US median income, while the source of workdays missed was not reported. As in the analysis of the direct costs, an annual discount rate of 3% was applied and the price year was 2000.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were carried out to assess the impact of variations in some model inputs on the total costs and benefits. In particular, alternative analyses were run with different starting ages, gender distributions, rates of complications, use of a proton-pump inhibitor (PPI), costs, and length of follow-up.
**Estimated benefits used in the economic analysis**
The estimated QALYs were 15.55 in the cohort of healthy individuals not taking aspirin and 15.52 in the cohort of individuals taking aspirin.

Life expectancy was 27 years for healthy individuals not taking aspirin and 26.96 years for healthy individuals taking aspirin.

The overall complication rate due to aspirin therapy was 6.79% (4.94% for intermediate non-cerebral bleed, 1.31% for major noncerebral bleed, and 0.54% for total haemorrhagic CVAs). In other words, for any 15 healthy 50-year-old men started on aspirin therapy, one will have a complication. Thus, the number-needed-to-treat (NNT) to cause a single complication was 15.

The death rate was 0.18% (0.05% for noncerebral bleed deaths and 0.13% for CVA deaths).

The NNT to cause death was 556, that is, for every 556 individuals one will die from a complication related to aspirin.

The sensitivity analysis produced some interesting results. Starting aspirin at an earlier age reduced the QALYs in comparison with no therapy. Women had similar QALYs to men. The use of PPIs showed a modest increase in QALYs (increase of 0.01 QALYs over the time horizon of the model). A shorter duration of aspirin therapy resulted in fewer complications and a smaller effect on the overall QALYs.

**Cost results**
The total costs per patient were $0 for individuals not taking aspirin and $460 for individuals taking aspirin.

The results of the sensitivity analysis on total costs were as follows. Starting aspirin at an earlier age increased the costs. Similar costs were observed among women. The use of PPIs increased the costs (incremental costs of $18,400 over an individual's lifetime). Changes in the cost of aspirin led to variations in the total costs that were greater than those observed when varying the costs of complications (due to the small number of complications).

**Synthesis of costs and benefits**
No incremental cost-effectiveness ratio was calculated for aspirin versus no aspirin, given that the aspirin strategy was dominated (more costly and loss of QALYs).

An incremental cost-effectiveness ratio was calculated for the use of PPIs plus aspirin versus aspirin alone. This resulted in $1.8 million per QALY gained.

**Authors' conclusions**
Aspirin therapy for the primary prevention of cardiovascular and oncologic events in healthy individuals led to a small reduction in quality-adjusted life-years (QALYs) at an overall low cost per person in the USA. However, the authors highlighted that this analysis only took complications and negative aspects of the aspirin therapy into consideration, and not the positive effects such as prevention of cardiovascular disease or cancer. Thus, these results should be compared with the benefits associated with aspirin for the primary prevention of these diseases in healthy individuals.

**CRD COMMENTARY - Selection of comparators**
The selection of the comparator (i.e. no therapy) was appropriate as it represented the standard pattern of care for patients with no documented cardiovascular disease. You should decide whether this is a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The clinical evidence came from a review of the literature, the methods and conduct of which were not reported. For example, no information was provided on the design and other characteristics of most primary studies. Inclusion and
exclusion criteria were not reported. The method used to pool the primary estimates was not reported, and the issue of homogeneity across the primary studies was not addressed. However, some data came from a meta-analysis of primary studies, which should increase the internal validity of these clinical inputs. The impact of changes in the clinical data was investigated in the sensitivity analysis.

**Validity of estimate of measure of benefit**

The use of QALYs as the summary benefit measure was appropriate as they capture the effect of the interventions on quality of life and survival. Discounting was applied to life expectancy, in accordance with guidelines for economic evaluations. Disease-specific benefit measures were also considered.

**Validity of estimate of costs**

The analysis of the costs was appropriate as it was performed from a societal perspective. Thus, both the direct and indirect costs were included. The categories of costs included in the analysis were reported, but the costs were not broken down and most were presented as macro-categories. Data on the unit costs and resource consumption were not reported clearly, which may limit the possibility of replicating the analysis in other settings. The source of the data was reported. Details of the cost calculations were not provided since most costs had been estimated in previous studies. Statistical analyses of the costs were not performed, but the impact of altering the cost estimates was investigated in the sensitivity analysis. The price year was reported, which will facilitate reflation exercises in other time periods.

**Other issues**

The authors did not compare their findings with those from other studies. The issue of the generalisability of the study results to other settings was not explicitly addressed, although extensive sensitivity analyses were carried out by considering alternative scenarios in the decision model. The results of the main analysis and those of the sensitivity analyses were satisfactorily reported. The authors noted that an uncertain aspect of the analysis was the heterogeneity of the patient population eligible for aspirin therapy.

**Implications of the study**

The study results suggest that complications associated with aspirin therapy in healthy individuals would have a minor effect on QALYs and life expectancy and would not substantially increase the societal costs.

**Source of funding**

None stated.

**Bibliographic details**


**PubMedID**

15590881

**DOI**

10.1345/aph.1E115

**Other publications of related interest**


Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Aged; Anti-Inflammatory Agents, Non-Steroidal /adverse effects /economics; Aspirin /adverse effects /economics; Decision Support Techniques; Female; Humans; Male; Middle Aged; Models, Statistical; Monte Carlo Method; Quality-Adjusted Life Years; Risk Assessment; Sensitivity and Specificity

AccessionNumber
22005000115

Date bibliographic record published
30/06/2006

Date abstract record published
30/06/2006