Which patients should receive aspirin for primary prevention of cardiovascular disease: an economic evaluation
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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 evaluated the use of low-dose aspirin (75 to 325 mg) in the primary prevention of cardiovascular disease (CVD).

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients aged 50 to 60 years at differing risk of CVD.

Setting
The setting appears to have been primary care. The economic study was performed in the UK, Germany, Italy and Spain.

Dates to which data relate
The effectiveness data were derived from studies published between 1996 and 2003. The costs and resource use data came from an economic evaluation (Lamotte et al. 2006, see 'Other Publications of Related Interest' below for bibliographic details). The price year was 2003.

Source of effectiveness data
The effectiveness evidence was derived from a review of published studies, and some estimates of effectiveness based on opinion.

Modelling
A Markov model was used to estimate the cost-effectiveness of low-dose aspirin in the primary prevention of CVD. Cycles of 1 year were used, and a total time horizon of 10 years was considered. The health states considered in the model were 'no history of CVD' (no known coronary heart disease (CHD), peripheral arterial disease or cerebrovascular disease), history of stroke, history of myocardial infarction (MI), history of CVD, and death. All individuals started the model without a history of CVD. Each year, each individual had a risk of CVD, stroke, or dying from another cause. Independently from these risks, each individual had a risk of gastrointestinal bleeding. A uniform distribution of events during the year was assumed (half-cycle corrections were used). To represent more accurately the real-life situation, it was assumed that the risk of a fatal or nonfatal CVD event increased as time passed and the 10-year risk of fatal CVD, rather than the fixed annual risk, was used. The structure of the model was common for the four countries in which the
economic evaluation was performed, but country-specific data were used to calculate the cost-effectiveness ratios.

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

the efficacy of aspirin in the primary and secondary prevention of CVD;

the relationship between fatal and nonfatal CHD and stroke;

the risk of dying from other causes; and

the utility values associated with the model health states.

Study designs and other criteria for inclusion in the review
The efficacy of aspirin in the primary prevention of CVD was obtained from 2 meta-analyses, both based on the same 5 large trials. The efficacy data for aspirin in the secondary prevention of CVD was obtained from the CAPRIE trial. The SCORE equation was used to estimate the risk of cardiovascular events.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not explicitly reported. All the effectiveness data, with the exception of utility values, were derived from randomised controlled trials.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Four studies were included in the review.

Methods of combining primary studies
A narrative approach was used to combine the primary studies.

Investigation of differences between primary studies
Not reported.

Results of the review
The annual risks in the first year, assuming a baseline 10-year risk of fatal CVD of 5%, were:

for CHD, 0.68 with aspirin and 0.93 without aspirin;

for fatal CHD, 0.21 with aspirin and 0.24 without aspirin;

for stroke, 0.51 with aspirin and 0.50 without aspirin;

for fatal stroke, 0.09 with aspirin and 0.07 without aspirin;
for survival after a stroke, 0.43 with aspirin and 0.44 without aspirin;
for haemorrhagic stroke, 0.07 with aspirin and 0.06 without aspirin;
for ischaemic stroke, 0.36 with aspirin and 0.37 without aspirin;
for gastrointestinal bleeding, 0.31 with aspirin and 0.18 without aspirin.

The annual risks in the tenth year, assuming a baseline 10-year risk of fatal CVD of 5%, were:
for CHD, 1.69 with aspirin and 2.33 without aspirin;
for fatal CHD, 0.52 with aspirin and 0.60 without aspirin;
for stroke, 1.28 with aspirin and 1.26 without aspirin;
for fatal stroke, 0.22 with aspirin and 0.17 without aspirin;
for survival after a stroke, 1.06 with aspirin and 1.09 without aspirin;
for haemorrhagic stroke, 0.18 with aspirin and 0.16 without aspirin;
for ischaemic stroke, 0.89 with aspirin and 0.93 without aspirin;
for gastrointestinal bleeding, 0.31 with aspirin and 0.18 without aspirin.

The secondary prevention annual risks with aspirin were:
for nonfatal stroke, 0.58 to 5.39;
for nonfatal MI, 0.62 to 260;
for intracranial haemorrhage, 0.26;
for vascular death, 1.66 to 2.06;
for fatal and nonfatal gastrointestinal bleeds, 1.40.

The risks of dying from other causes were country-, age- and gender-specific.

The mean time trade-off score was 0.88 (95% confidence interval, CI: 0.84 to 0.93) for post-MI patients and 0.68 (95% CI: 0.53 to 0.83) for post-stroke patients.

If an acute event (MI or stroke) occurred, a utility of 0 was applied for 1 week.

Extracranial haemorrhage decreased utility for 2 weeks (utility of 0.5 was applied for 2 weeks).

Methods used to derive estimates of effectiveness
The authors made some assumptions to support the data used in the decision model.

Estimates of effectiveness and key assumptions
The authors assumed four different baseline 10-year risks levels of fatal CVD (2, 3, 4 and 5%) to estimate which patients should receive aspirin for the primary prevention of CVD. It was also assumed that all patients, independent of the starting treatment, were treated after an event with aspirin. These assumptions were based on the literature. Therefore, all the key estimates of effectiveness have been reported in the 'Results of the Review' section.
Measure of benefits used in the economic analysis
The summary benefit measure used was the quality-adjusted life-years (QALYs). These were derived using the model. The utility weights were obtained from the literature. Country-specific annual discount rates were applied (3.5% in the UK, 5% in Germany, and 3% in Spain and Italy).

Direct costs
The analysis included the costs of aspirin treatment, cardiovascular events (MI, ischaemic or haemorrhagic stroke, fatal MI and fatal stroke), gastrointestinal bleeds, and the annual in-hospital follow-up costs (nonfatal stroke, nonfatal MI and nonfatal MI plus nonfatal stroke). With the exception of the cost of aspirin, the costs were presented as macro-categories. When available, the 95% CIs for costs were used in the model (Spain and the UK). Country-specific annual discount rates were applied (3.5% in the UK, 5% in Germany, and 3% in Spain and Italy). Further details of the methodology used to estimate the costs were reported elsewhere (Lamotte et al. 2006).

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included.

Currency
Euros (EUR).

Sensitivity analysis
The model was run for four different baseline 10-year risks of fatal CVD (2, 3, 4 and 5%). These took into account the fact that the UK and Germany were high-risk countries and that Spain and Italy were low-risk countries. Thus, in total, eight scenarios were studied. In addition, a Monte Carlo simulation was performed with 1,000 replications, assuming a normal distribution for all variables. Finally, the impact of a higher risk of gastrointestinal bleeding was assessed by more than doubling the baseline risk of bleeding found in the literature (the baseline value of 0.18% was increased to 0.40%).

Estimated benefits used in the economic analysis
At a 5% risk of fatal CVD, the estimated QALYs for patients treated with aspirin were 7.73 in the UK, 7.39 in Germany, 7.96 in Italy and 7.94 in Spain. The corresponding figures for the 'no aspirin' group were 7.71 for the UK, 7.37 for Germany, 7.94 for Italy and 7.92 for Spain.

The estimated QALYs for the 4, 3 and 2% risks of fatal CVD were reported in full in the paper.

Cost results
In the UK, the costs with aspirin ranged from EUR 473 (at a 2% risk of fatal CVD) to EUR 829 (at a 5% risk of fatal CVD), whereas the costs without aspirin ranged from EUR 525 (at a 2% risk of fatal CVD) to EUR 963 (at a 5% risk of fatal CVD).

The cost results for Germany, Italy and Spain were presented in full in the paper.

Synthesis of costs and benefits
Incremental cost-utility ratios were calculated to combine the costs and benefits in the absence of dominance.
For those patients with a 10-year risk of fatal CVD of 2% or higher, treatment with aspirin resulted in lower total costs and more QALYs gained in the UK, Germany and Spain. In Italy, savings started at a 10-year risk of 3%. At a 10-year risk of 2%, the incremental cost per QALY gained was EUR 1,030. The lower degree of dominance in Italy was due to the high cost of gastrointestinal bleeding in that country.

The Monte Carlo analysis showed that aspirin was dominant (cost-saving and more effective) in more than 90% of patients at a 10-year risk of 4 and 5% in the four countries. This decreased to 89% (3% risk) and 86% (2% risk) in the UK, Germany and Spain, and to 60% (3% risk) and 24% (2% risk) in Italy. The impact on the results of doubling the annual risk of gastrointestinal bleeding was not significant in the UK, Germany and Spain. In Italy, if the annual risk of gastrointestinal bleeding was doubled, the cost-effectiveness ratio increased to EUR 14,040 per QALY gained.

Authors' conclusions
Even in patients at low risk of a cardiovascular event, the level of risk could be further reduced by using low-dose aspirin treatment. Moreover, cost-savings could be achieved with low-dose aspirin for the primary prevention of cardiovascular disease (CVD) in patients with a 10-year risk of fatal CVD as low as 2%.

CRD COMMENTARY - Selection of comparators
The rationale for the selection of the comparator was clear. No treatment was selected in order to assess the active value of aspirin in the primary prevention of CVD. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came mainly from published sources, which included meta-analyses and clinical trials. These represent robust sources of data, although only limited details on the primary studies were provided. In addition, the methods used to extract and combine the primary studies were not reported. The authors made some assumptions based on the literature. However, the eight baseline scenarios evaluated, along with the sensitivity analyses conducted, increase the external validity of the effectiveness estimations.

Validity of estimate of measure of benefit
The use of QALYs as the summary measure of benefit was appropriate as QALYs capture the impact of aspirin treatment on both quality of life and survival. They also permit comparisons to be made with the results of other studies. Country-specific discount rates were applied.

Validity of estimate of costs
It seems that the costs considered were consistent with the perspective adopted. The price year was reported and appropriate discounting was carried out. However, no detailed information on the methodology used to calculate the costs was reported because the costs were obtained from another economic evaluation. The lack of detail means that it is impossible to make any meaningful comment about the quality of the initial costing.

Other issues
The authors compared their findings with those of other studies and similar conclusions were found. The issue of generalisability was not explicitly addressed, but sensitivity analyses were performed. The conclusions of the analysis appear to be quite robust and the authors reported their results in detail, in particular the results of the Monte Carlo simulation.

Implications of the study
The results of the study suggest that low-dose aspirin treatment becomes cost-saving in the primary prevention of CVD, even at a very low 10-year risk of fatal CVD.
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Other publications of related interest

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