The cost-effectiveness of aspirin versus cyclooxygenase-2-selective inhibitors for colorectal carcinoma chemoprevention 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 use of aspirin versus cyclooxygenase-2-selective inhibitors (coxibs) as primary chemoprevention for colorectal carcinoma (CRC).

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of healthy men aged 50 years.

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

Dates to which data relate
The effectiveness evidence was derived from studies published between 1989 and 2003. The cost data were derived from literature published in 1990 and 2003. Year 2000 prices were used.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of completed studies.

Modelling
A Markov decision analytic model was developed to compare coxibs with aspirin as primary chemoprevention for CRC mainly, although the results may have potential application to any other malignancies inhibited by coxibs and aspirin. A hypothetical cohort of healthy men aged 50 years initiated treatment with either 325 mg enteric-coated aspirin daily, or 400 mg celecoxib twice daily. The model considered potential complications associated with coxibs or aspirin, as well as the cardioprotective benefit of aspirin. Complications were bleed, ulcer and myocardial ischaemia (MI). Minor bleeds (e.g. nose bleeds) and strokes were not included in the model. Celecoxib therapy did not include an increased risk of cardiovascular events. In the case of complications, individuals were assumed to discontinue therapy, losing any of the prophylactic benefits associated with treatment. The model did not include potential cancer benefits of either therapy, as it was assumed that if there were to be any potential cancer benefits, aspirin and coxibs would be equally effective and the benefits would cancel each other out. Individuals in the cohort were at risk of death from complications, as well as age- and gender-related mortality. The model was run in monthly cycles for a 10-year time horizon.
Outcomes assessed in the review
The outcomes assessed were:

the annual rates of aspirin and coxibs complications,

the proportion of bleeds characterised as intermediate or major,

the rate of ulcer perforation,

the risk of MI following the use of aspirin or coxibs, and

mortality rates from bleed, ulcers and MI.

Quality of life weights were also derived from the literature. Utilities were then further adjusted to reflect recuperation from complications, based on authors' assumptions.

Study designs and other criteria for inclusion in the review
The rate of MI following the use of aspirin was derived from a published meta-analysis (Sanmuganathan et al., see Other Publications of Related Interest). Symptomatic ulcers rates were derived from a randomised clinical trial (Physicians( Health Study Research Group, see Other Publications of Related Interest). The designs of the primary studies included for the other estimates were not reported.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

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

Number of primary studies included
Approximately 5 primary studies were included in the review.

Methods of combining primary studies
The results of the primary studies were not combined.

Investigation of differences between primary studies
Not applicable.

Results of the review
The annual rates of complications associated with aspirin and coxibs were, respectively, 2.55 (aspirin) and 2.14 (coxibs) for bleed and 0.30 and 1.04 for ulcers. Out of all bleeds, 18.0% were characterised as intermediate and 82.0% as major.

The bleeding rates for aspirin represented rates for all bleeds, excluding cerebral bleeds.

The rate of ulcer perforation was 1.0%.
The probability of MI was 0.37 following the use of aspirin and 0.52 following the use of coxibs.

The mortality rate was 2.0% from bleed and 0.2% from ulcer.

For MI, the 30-day mortality rate was 7.1% and the 3-year mortality rate was 17.3%.

Quality of life weights assigned to different health states were 0.97 for noncerebral bleed, 0.91 for ulcer and 0.88 for post-MI.

Methods used to derive estimates of effectiveness
Authors’ assumptions were used to supplement the effectiveness evidence to populate the model.

Estimates of effectiveness and key assumptions
It was assumed that aspirin and coxibs were equally effective in the primary chemoprevention of CRC.

The authors assumed that the acute postcomplication quality of life was 70% of the precomplication quality of life for a total of 1 day after an intermediate bleed, 1 week after a major noncerebral bleed, 2.6 days after an ulcer, and 5 days after an MI.

Measure of benefits used in the economic analysis
The measure of benefit used was the number of quality-adjusted life-years (QALYs) after applying each of the health technologies assessed. In addition, the rate of excess complications (relative to comparator) and the total mortality rates (comprised of all-cause mortality and complication-associated excess mortality) were estimated. Years of life were weighted according to age- and gender-adjusted population values found in published literature.

Direct costs
The direct costs consisted of health service costs. These included drug costs and the costs of treating complications, reflecting both inpatient and outpatient care. The quantities and the unit costs were not analysed separately. The drug unit costs were taken from the Drug Topics Red Book, 2000. The costs of treating complications were derived from studies published between 1990 and 2003. The total costs were derived using modelling. The costs were discounted at an annual rate of 3% since they were incurred during a 10-year period. All the costs were converted to 2000 prices using the medical care component of the Consumer Price Index.

Statistical analysis of costs
The costs were treated deterministically. No statistical analysis of the costs was undertaken.

Indirect Costs
The indirect costs consisted of wages lost as a result of missed days from work, during the recuperation period after a complication. The costs and the quantities were analysed separately. Estimates for the recuperation period were based on assumptions. Average wages reflected the US median income as reported in the US Census Bureau, 2000. Since all costs were reported in 2000 values, there was no need to convert indirect cost prices. Discounting was applied at an annual rate of 3%, as the costs were incurred during a 10-year period.

Currency
US dollars ($).

Sensitivity analysis
A sensitivity analysis was undertaken to examine how varying the model parameter estimates affected the results. The parameters examined in one-way sensitivity analyses included the age of individuals at the beginning of chemoprevention, length of follow-up, drug costs and discount rate. The ranges of values used were based on authors’ assumptions. In addition, a threshold analysis was carried out to determine the values of excess complication rates and the cost of coxib at which the results changed.

**Estimated benefits used in the economic analysis**
Aspirin resulted in 7.60 QALYs per patient, while coxib resulted in 7.57 QALYs per patient. Aspirin provided 0.03 more QALYs than coxib.

The total excess complication rates were 3.539% for aspirin and 7.416% for coxib.

The total mortality rates were 8.702% for aspirin and 8.875% for coxib.

The total excess complication and total mortality rates were found to be higher in the coxib group than in aspirin group by 3.877% (complications) and 0.173% (mortality), respectively.

The benefits were estimated over a time horizon of 10 years and were discounted at an annual rate of 3%.

**Cost results**
The average total cost per patient was $181 in the aspirin group and $23,403 in the coxib group. Thus, coxib demonstrated an additional cost equal to $23,222 per patient, on average.

The costs were incurred during a 10-year period and were discounted at an annual rate of 3%.

The costs of complications due to the interventions examined were included in the analysis.

**Synthesis of costs and benefits**
It was not necessary to combine the costs and benefits in a single cost-effectiveness ratio since aspirin dominated coxibs (i.e. it was both more effective and less costly). This result was robust to any changes in variables investigated in the one-way sensitivity analysis.

The threshold analysis showed that the results were not sensitive to the relative excess MI rate of coxibs and the cost of coxibs. Even when these values were assumed to be 0, aspirin still dominated coxibs. Coxibs became more effective than aspirin when the relative ulcer rate between them was reduced by 93%, or when the relative combined MI and ulcer rate was reduced by 60%.

In terms of aspirin parameters, if the rate of noncerebral bleeding increased more than 5.5 times, then coxibs became more effective therapy.

**Authors' conclusions**
Assuming equal efficacy in the prevention of colorectal cancer (CRC) over a 10-year period, aspirin was both more effective and less costly than therapy with cyclooxygenase-2-selective inhibitors (coxibs) when used for primary chemoprevention of CRC.

**CRD COMMENTARY - Selection of comparators**
The choice of the comparator (aspirin) used in the analysis was implicitly justified since it had been found to provide chemopreventive cancer benefits, and had been already recommended as chemopreventive therapy for CHD. You should consider whether the comparator is widely used for this purpose in your own setting.
Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken. They appeared to use data from the available studies selectively. Since the methods used to find and select the primary studies and to extract the data were unclear, it is difficult to assess the validity of the estimates. There may be relevant studies that were not included. Key assumptions were used in the model structure. Not all of the authors' assumptions were justified with reference to the medical literature. These facts introduced uncertainty into the effectiveness results obtained.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. The Markov decision analytic model used was appropriate for this purpose, as it included all potential benefits and complications associated with the interventions considered. However, the assumptions made by the authors to reflect recuperation from complications were not justified with reference to the medical literature.

Validity of estimate of costs
The authors stated that the study adopted a societal perspective. All the categories of cost relevant to this perspective were included in the analysis. However, the estimation of indirect costs was limited to productivity losses during the recuperation period after a complication, and did not account for wage losses due to CHD or CRC in the long term. Nevertheless, the omission of productivity losses due to CRC does not affect the results, as both interventions were assumed to be equally effective in CRC primary chemoprevention. The costs and the quantities were mostly derived from published literature and, therefore, were not reported separately. This might hinder the generalisability of the results. A sensitivity analysis of the costs was undertaken only in the case of drug costs. The ranges used were wide enough to capture any potential sensitivity of the results to the drug costs. Discounting was appropriately undertaken since the costs were incurred during a 10-year period. The date to which the prices referred was reported, which increases the reproducibility of the results.

Other issues
The authors made appropriate comparisons of their results with those of other studies that had assessed the effectiveness of aspirin versus no therapy, or the cost-effectiveness of coxibs versus naproxen, although no other analysis comparing the effectiveness or cost-effectiveness between aspirin and coxibs had been performed by the time of this study. The issue of generalisability to other settings was partially addressed using sensitivity analyses. The authors reported several limitations of their study, owing to a lack of appropriate data. First, the exclusion of any potential cancer prevention benefit from either aspirin or coxib therapy. Second, the relatively short time horizon of the model. Finally, there was no assessment of the potential impact of population heterogeneity on the results. The authors presented their results in full and their conclusions reflected the scope of the analysis.

Implications of the study
The authors suggested that aspirin should be chosen over coxibs for chemoprevention in healthy individuals, assuming equal efficacy in cancer prevention. However, they highlighted the need for additional studies to determine the efficacy of both aspirin and coxibs in preventing tumours, in order to confirm the equivalency assumption made for their analysis.

Source of funding
None stated.

Bibliographic details

PubMedID
Other publications of related interest


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Subject indexing assigned by NLM

MeSH
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