Blood pressure destabilization and related healthcare utilization among hypertensive patients using nonspecific NSAIDs and COX-2-specific inhibitors

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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 authors compared patients treated with celecoxib, rofecoxib, ibuprofen, diclofenac, or naproxen. The latter three treatments are nonsteroidal anti-inflammatory drugs (NSAIDS). No further details of the drugs (producer), or the doses used, were reported. Celecoxib was the comparator.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with stable hypertension who had recently begun therapy with celecoxib, rofecoxib, ibuprofen, diclofenac, or naproxen. Eligible patients were those who had not filled a prescription for a non-specific NSAID or COX-2-specific inhibitor within the preceding 180 days. Patients were then eligible if they had stable hypertension for at least 3 consecutive months out of the 4 months preceding the study, and had continuously enrolled in the LifeLink database for 12 months prior to the study.

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

Dates to which data relate
Effectiveness data were collected for patients beginning therapy between 1st January 1999 and 30th September 2000, and patients were followed for 90 days. Therefore, the study ended in approximately December 2000. Resource use was estimated for the same period of time. No price year was stated.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
Costing was carried out on the same sample of patients as that used in the effectiveness study.

Study sample
The authors did not report the use of power calculations in determining sample size: these are used to rule out the influence of chance on their results. The patient sample was selected by reviewing the LifeLink database for users of
celecoxib, rofecoxib, ibuprofen, naproxen and diclofenac between the dates relevant for the trial. The initial sample was appropriate for the study question as it included patients receiving the treatment drugs of interest.

The study investigators identified 53,510 patients. For the study on blood pressure destabilisation incidence rates, three groups were defined from these 53,510 patients. There were 20,915 patients in the celecoxib group, 12,952 in the rofecoxib group and 21,529 in the nonspecific NSAIDs (ibuprofen, naproxen and diclofenac) group.

**Study design**
The effectiveness analysis, which formed part of the cost analysis, was based on a retrospective cohort study. Data were derived from the LifeLink database over the period 1 January 1999 to 30 September 2000.

**Analysis of effectiveness**
Analysis was based on actual treatment received. The primary health outcome was the incidence rate of patients with at least one inpatient blood pressure destabilisation event among the different drug groups. Events qualified as a destabilisation event if there was either an increase in the daily dose of antihypertensive medication or an initiation of a new antihypertensive medication.

The authors reported that they evaluated the history of each patient to look for any confounding factors and found that patients prescribed COX-2-specific inhibitors had a higher prevalence of cardiovascular risk factors than patients prescribed non-specific NSAIDs. They also reported significant differences in demography. Adjustments were made for age, gender, and higher prevalence of cardiovascular disease using multivariate analyses and direct adjustment methods.

**Effectiveness results**
The number of patients with BP events was 5,740 for the celecoxib group, 3,460 for the rofecoxib group and 2,175 for the non-specific NSAIDs group.

The days of exposure were 2,527,114 for the celecoxib group, 1,322,883 for the rofecoxib group and 879,717 for the non-specific NSAIDs group.

The adjusted rate ratio (and associated confidence interval) was 1.00 for the celecoxib group, 1.17 (CI: 1.12 - 1.22) for the rofecoxib group and 1.17 (CI: 1.10 - 1.23) for the non-specific NSAIDs group.

The adjusted rate per 1000 pt-d was 2.27 for the celecoxib group, 2.66 for the rofecoxib group and 2.65 for the non-specific NSAIDs group.

The adjusted p value was <0.001 for the rofecoxib group and <0.001 for the non-specific NSAIDs group.

**Clinical conclusions**
The authors did not draw clinical conclusions independently from cost conclusions.

**Measure of benefits used in the economic analysis**
There was no summary measure of benefits. Therefore, effectively, a cost-consequences analysis was conducted.

**Direct costs**
Two cost analyses were performed. One investigated the incremental cost for an inpatient blood pressure destabilisation event. The second investigated the incremental attributable cost per patient per day for each drug use group.

The first analysis was based on a case-control study. From the effectiveness analysis it was determined that 11,375 patients had at least one outpatient claim for a BP stabilisation event. This was the case group. The control group was
defined by matching patients with an event to patients without an event on a 1-to-1 basis, according to drug, age in 10-year intervals, gender, history of CVD, and history of diabetes. The controls were randomly selected and matched to the treatment patients as explained above. The method of random selection was not described. The analysis was based on insurance claims data and therefore it was effectively a multi centre trial. Patients were followed for 90 days with no loss to follow-up reported. Costs were estimated for two follow-up periods; 30 days following the BP event, and 31 to 90 days following the event.

The second analysis combined the drug group incidence rates and the incremental cost of an event to derive the incremental cost per day per drug group relative to the celecoxib group. There was no mention of including the drug costs themselves.

As costs were estimated for a period of less than two years, discounting was not required in this study. Costs were estimated as the total cost from all claims incurred during the relevant time period, and were categorised according to outpatient, inpatient, outpatient pharmacy, and outpatient laboratory. Unit costs were not reported separately. A price year for the study was not stated.

**Statistical analysis of costs**

Poisson multiple regression models were used to compare incidence rates across groups after adjustments were made for confounding variables.

**Indirect Costs**

No indirect costs were included.

**Currency**

US dollars ($).

**Sensitivity analysis**

No sensitivity analysis was reported.

**Estimated benefits used in the economic analysis**

Please refer to the effectiveness results reported earlier.

**Cost results**

During the 0 - 30-day period the direct adjusted geometric mean cost was $358.50 (95% CI: $350.21 - $366.99) for patients in the case group and $113.78 (95% CI: $109.39 - $118.359) for patients in the control group.

During the 31 - 90-day period the direct adjusted geometric mean cost was $421.79 (95% CI: $407.88 - $436.19) for patients in the case group and $207.52 (95% CI: $198.93 - $216.47) for patients in the control group.

The incremental cost for those with BP destabilization compared to those without was $244.72 in the first 30 days and $214.27 between 31 and 90 days.

The total incremental cost over the full period of observation for those with BP destabilization compared to those without was $458.99.

The total incremental cost of outpatient blood pressure destabilisation related to rofecoxib compared to celecoxib was $0.18 and the total increment cost related to nonspecific NSAIDs compared to celecoxib was $0.17.

**Synthesis of costs and benefits**
Consistent with the cost-consequences definition of this study, costs and benefits were not combined.

**Authors’ conclusions**
The authors concluded that patients with BP destabilisation events were significantly more likely to have claims for inpatient and outpatient visits, outpatient pharmacy costs and outpatient laboratory costs. In addition they concluded that compared with celecoxib there are additional monetary and physical costs associated with BP stabilization when using rofecoxib and non-specific NSAIDs. Finally, the authors claimed that both inpatient and outpatient BP stabilization were more strongly associated with rofecoxib than with celecoxib.

**CRD COMMENTARY - Selection of comparators**
The study aimed to assess the cost of BP destabilisation in patients treated with rofecoxib, ibuprofen, diclofenac, or naproxen, relative to those treated with celecoxib. It was not clear why celecoxib was treated as a reference point. The comparators where chosen as they were alternative treatments with various advantages and disadvantages that were well discussed by the authors.

**Validity of estimate of measure of effectiveness**
Despite their aim the authors grouped together the three NSAID drug treatments and presented results for patients receiving celecoxib, rofecoxib, and NSAIDs. The authors justified this by saying that the NSAIDs had similar incidence rates. Given the specific aim of the study, the authors should have presented the results separately. The analysis was based on a retrospective cohort study. As a consequence of this choice of study design there is a possibility of selection bias. Confounding was accounted for in the best way possible, through multivariate regression analysis.

**Validity of estimate of measure of benefit**
The authors did not derive a summary measure of benefit that was combined with costs and therefore the study was categorized as a cost-consequences analysis.

**Validity of estimate of costs**
The authors used the perspective of the insurer and seemed to estimate all costs relevant to this perspective by calculating the total costs of claims. The authors did not report a confidence interval for the incremental cost of an outpatient BP stabilization event and therefore it is not possible to assess whether this cost differed significantly from zero. However, as the incremental costs was $458.99, small omissions in cost seem unlikely to affect the principle conclusions of this study. Some quantities were reported separately from costs. The costs could have been presented more clearly for each drug group and it would have been useful to see the specific drug costs and not just the consequent costs from a BP destabilisation event.

**Other issues**
The authors made appropriate comparisons of their findings with results published previously, pointing out both similarities and differences, and the reasons for any differences observed. In addition there is a valuable discussion of some of the limitations of the study including the use of claims data, which impose a difficulty when trying to establish a causal relationship, and a possible underestimation of costs. The authors considered the issue of the generalisability of their results and specifically mentioned problems in generalising to elderly populations who were not well represented in the claims data. The authors mentioned in their discussion the “ultimate costs to the patient in terms of development or exacerbation of a serious medical condition”. It is not apparent why they did not discuss this earlier and make some attempt to value these costs in their study. One of the conclusions was that both inpatient and outpatient BP stabilization were more strongly associated with rofecoxib than with celecoxib. This conclusion was not apparent from the results presented in the study.

**Implications of the study**
The authors stressed the importance of considering the costs of managing adverse consequences from drug therapy as well as the personal consequences to the patient when assessing the cost of a medication. They did not suggest any areas for further research.

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None stated.

**Bibliographic details**

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**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

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