Preventing non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: are older strategies more cost-effective in the general population?

R. A. Elliott, L. Hooper, K. Payne, T. J. Brown, C. Roberts and D. Symmons

Objectives. To assess the relative cost-effectiveness of five gastroprotective strategies for patients in the general population not judged to be at high gastrointestinal (GI) risk requiring regular traditional (t) non-steroidal anti-inflammatory drugs (NSAIDs) for over 3 weeks: tNSAID/H2 receptor antagonists (H2RAs); tNSAID/proton pump inhibitors (PPIs); tNSAID/misoprostol; COX-2 preferential NSAIDs or COX-2-specific NSAIDs (COXIBs).

Methods. A systematic review of outcomes and UK cost data were combined in an incremental economic analysis. Incremental cost-effectiveness ratios were generated for quality-adjusted life years (QALYs) gained.

Results. Cost–utility analysis showed a tNSAID with a H2RA is safer and less costly than tNSAIDs alone, and equally effective and less costly than COXIBs. tNSAID/misoprostol was also dominated by tNSAID/H2RA due to withdrawal caused by side-effects reducing overall health status. The incremental increase in QALYs gained by using COXIBs instead of tNSAID/H2RA would cost £670 000 per QALY gained. The incremental increase in QALYs gained by using tNSAID/PPI instead of COXIBs would cost £26 000 per QALY gained. If the decision-maker will pay up to £140 000 per extra QALY, the optimal strategy is tNSAID/H2RA. If the decision-maker will pay over this the optimal strategy is tNSAID/PPI.

Conclusion. The economic analysis suggests that there may be a case for prescribing H2RAs in all patients requiring NSAIDs. Our recommendations are tentative due to the quality of the data available and the assumptions we have had to make in our model, and it is possible that other strategies may be preferred in patients with higher baseline GI risk.

Key words: Health economics, Outcomes, COX-2-specific inhibitors, Health resource utilization, NSAIDs, Preventive strategies, Gastrointestinal events, Drug utilization.

Traditional non-steroidal anti-inflammatory drugs (tNSAIDs) may cause gastrointestinal (GI) toxicity that results in significant morbidity and mortality [1]. Clinicians may protect against NSAID-induced GI toxicity by co-prescribing gastroprotective agents (GPA) such as H2-receptor antagonists (H2RAs), proton pump inhibitors (PPIs) or misoprostol, or using preferential COX-2 inhibitors (etodolac, meloxicam, nabumetone and nimesulide) or specific COX-2 inhibitors (COXIBs) (celecoxib, etoricoxib).

Our systematic reviews of randomized controlled trials (RCTs) [2] assessed the effectiveness of these strategies for long-term use. We separated preferential COX-2 inhibitors from tNSAIDs and COXIBs because they are marketed as ‘safe’ NSAIDs. Each strategy except tNSAID plus H2RAs, where there were few event data, showed significant protection against symptomatic ulcers. Each strategy except preferential COX-2 inhibitors, where there were few event data, showed significant protection against endoscopic ulcers. Misoprostol was associated with a high drop-out level, but reduced incidence of serious GI events. The evidence was limited by a shortage of trials on H2RAs and PPIs, and of head-to-head comparisons between the strategies. There were insufficient data on serious events (such as death) or other outcomes (such as cardiovascular events) to make comparisons. The review was not able to identify an optimal GPA strategy for decision-makers based on the clinical indicators reported.

Newer medicines generally have a higher acquisition cost than older medicines. Claims of increased effectiveness and safety in newer medicines may prematurely reduce the use of older, effective medicines with a proven safety record. Reductions in costs associated with management of GI toxicity are often claimed to offset costs of COX-2 inhibitors. We found over 40 economic analyses of NSAIDs and GPAs published between 1989 and 2005, mostly comparing preferential COX-2 inhibitors, COXIBs or misoprostol with NSAIDs. The 10 head-to-head economic analyses found were modelling studies, synthesizing clinical and cost data from a range of sources, none from the UK. Despite the limitations of models, in the absence of alternatives they allow decision-makers to consider, explicitly, the costs and outcomes.
associated with their decisions. A recent US modelling analysis suggests that a tNSAID plus PPI is a preferred strategy over COXIBs [3]. There were no head-to-head economic evaluations of all five strategies. We performed an economic analysis to establish which strategies are cost-effective interventions to prevent NSAID-induced GI toxicity in a general population not judged to be at high risk.

Methods
A systematic review and meta-analysis of outcomes [2] was combined with up-to-date UK resource use and unit costs in an incremental economic analysis. Due to lack of primary data we had to carry out a modelling study. To prevent addition of yet another NSAID/GPA model [4], we based our study approach on models used by Maetzel et al. [5] and Moore et al. [6]. Combining data from different sources assumes that the source populations are comparable, which is a limitation of all models. We have presented our model explicitly, with a clear explanation of data sources and any assumptions made.

Strategies compared in the economic analysis
The economic analysis compared tNSAID alone, tNSAID + PPI, tNSAID + H₂RA, tNSAID + misoprostol and COX-2 preferential inhibitor + COXIB. Agents and doses used are summarized in Table 1. In common with National Institute for Clinical Excellence (NICE) guidelines, tNSAIDs, COX-2 preferential inhibitors and COXIBs were assumed to have equal analgesic efficacy in a group of patients, although it is recognized that there is inter-patient variability in efficacy [7]. The most commonly prescribed drugs in each class were selected and a class effect was assumed for H₂RAs and PPIs with regards to gastroprotective efficacy. In the meta-analysis we only included studies that used the therapeutic doses of GPAs required for efficacy (such as 300 mg ranitidine per day) [2]. Diclofenac and ibuprofen are the two most commonly prescribed NSAIDs in the UK [8]. This analysis assumed equivalent safety for equivalent doses of ibuprofen and diclofenac [9, 10]. Risk of adverse GI outcomes from tNSAIDs and COX-2 preferential inhibitors increases with dose [11, 12]. In this study, it was assumed that a dose in the middle of the prescribed range for each agent was used, in line with the defined daily dose (DDD) for that drug [13].

Patient population
The meta-analysis included patients with chronic arthritis (primarily rheumatoid arthritis and osteoarthritis) who require regular NSAIDs for more than 3 weeks, with and without risk factors for adverse GI events. The review included 112 RCTs (74,666 participants). Two-thirds of patients were women, baseline GI risk was not known in 62/112 studies and 101/112 studies reported a mean age below 65 yr of age. Only 138 deaths and 248 serious GI events were reported.

Cost and benefits identified in the economic analysis
Figure 1 represents the decision-analytic model (‘decision tree’). Tables 1 and 2 summarize the clinical and cost data.

Data extraction
Clinical data. Outcome data are reported in the systematic review as relative risk, with 95% confidence intervals (CIs), for gastroprotective strategies (arms 2 to 6) vs tNSAIDs (arm 1) [2]. Due to insufficient head-to-head comparisons, indirect comparisons were used. Lack of comparative non-GI outcomes meant that we assessed GI outcomes only (no GI adverse event, GI discomfort, uncomplicated ulcer and serious GI complication). Symptomatic ulcers, serious GI events and death rates were reported rarely and/or unreliably. These outcomes were recorded particularly poorly in earlier studies, which principally recorded endoscopic ulcers. It is likely that such patients were withdrawn, rather than being allowed to progress to symptomatic ulcers or GI complications. To be able to compare all strategies we had to use the parameter ‘endoscopic ulcers’ (see Table 1) and assume a proportion of those ulcers will become symptomatic.

The MUCOSA study estimated that 85% of endoscopic ulcers remained silent [5]. Therefore, P[Symptomatic ulcer, given endoscopic ulcer] in this analysis was assumed to be 15% of P[endoscopic ulcer]. This probability was assigned a range (0–30%) and distribution in the analysis.

Recently, rofecoxib, a COXIB, has been suggested to have reduced cardiovascular safety compared with naproxen [14], which led to its voluntary worldwide withdrawal. The cardiovascular safety of other COXIBs is now under investigation to examine whether this is a ‘class effect’. Celecoxib and valdecoxib studies have not demonstrated increased risk of thrombosis [15–17], but long-term studies are needed. In contradiction to recent events, alternative hypotheses suggest that COX-2 enzyme inhibition may actually reduce the risk of cardiac events [18–21]. In a climate of such uncertainty, drug manufacturers must assess cardiovascular safety urgently. We used celecoxib in our study and, due to the substantive uncertainty around relative cardiovascular safety, assumed equivalent cardiac outcomes between arms.

Treatment pathways, such as proportion and management of patients requiring hospital admission, occurring due to these outcomes were obtained primarily from two sources, which provided the most comprehensive follow-up of treatment pathways [5, 6] (see Table 2). The most up-to-date UK information on gastric bleed death rate (17.3%) was used [1].

We assumed that minor and major adverse events occur independently of one another. Evidence suggests little correlation between abdominal symptoms and the presence of NSAID-induced gastric lesions [22, 23]. Furthermore, the clinical course of major events such as duodenal ulcer haemorrhage is not significantly different in patients with and without minor events such as dyspepsia [24]. Intolerance to misoprostol leads to many patients withdrawing from treatment. This was dealt with explicitly in the analysis.

We assumed that GI discomfort rates reported in RCTs in the meta-analyses related to persistent, not transient, GI discomfort, requiring patients to return to their GP. Most patients...
who experience GI discomfort do so within the first 2 weeks of initiating therapy [25]. We assumed that patients with persistent GI discomfort will not remain on the same therapy but will be changed to the most commonly prescribed alternative, a tNSAID plus PPI [26]. We assumed that patients already on a tNSAID plus PPI would be switched to a COXIB.

Quality-adjusted life years (QALYs) were the outcome measure used in the analysis. To calculate QALYs we incorporated validated utilities for the health states experienced along each treatment pathway in the model (see Table 3). We used published estimates for time spent in each health state and calculated the utility lost (‘disutility’) associated with each treatment pathway. Where a published range was not available, we assigned wide ranges to each health state and a distribution to reflect uncertainty around that parameter in the analysis.

Due to the lack of clinical data, we assumed that adverse event rates and associated costs remain constant over a 6-month period, which was used as the time horizon.

![Decision analytic model for economic analysis of tNSAIDs vs tNSAIDs + GPAs vs COX-2 preferential inhibitors or COXIBs.](image)

**Table 2. Treatment pathways [5]**

<table>
<thead>
<tr>
<th>Proportions of patients undergoing</th>
<th>tNSAID (%)</th>
<th>tNSAID + GPA or COX-2 preferential inhibitor or COXIB (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation after GI discomfort</td>
<td>2.20</td>
<td>1.76</td>
</tr>
<tr>
<td>In-patient management of GI discomfort</td>
<td>24.0</td>
<td>39.0</td>
</tr>
<tr>
<td>Out-patient management of GI discomfort</td>
<td>76.0</td>
<td>61.0</td>
</tr>
<tr>
<td>Out-patient endoscopy of GI discomfort</td>
<td>35.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Out-patient no endoscopy of GI discomfort</td>
<td>65.0</td>
<td>85.0</td>
</tr>
<tr>
<td>Endoscopy, given ulcer</td>
<td>27.0</td>
<td>27.0</td>
</tr>
<tr>
<td>In-patient management of complication</td>
<td>67.0</td>
<td>56.0</td>
</tr>
<tr>
<td>Out-patient management of complication</td>
<td>33.0</td>
<td>44.0</td>
</tr>
<tr>
<td>In-patient surgical intervention</td>
<td>39.0</td>
<td>29.0</td>
</tr>
<tr>
<td>In-patient medical intervention</td>
<td>61.0</td>
<td>71.0</td>
</tr>
</tbody>
</table>
expressed as ‘expected cost per patient’. 

This cost is the ‘expected cost’, usually calculated how much the total cost would be for a cohort of patients how much each pathway cost for one patient, we were able to how many patients would go along each pathway. As we knew six strategies, we knew from the probabilities for that strategy was assigned a range and gamma distribution in the analysis.

We assumed that if a cohort of patients was assigned to one of the six strategies (see Table 5). Each cost variable for each of the 12 possible treatment pathways for each of the six strategies (see Table 5). Each cost variable was assigned a range and gamma distribution in the analysis. We assumed that if a cohort of patients was assigned to one of the six strategies, we knew from the probabilities for that strategy how many patients would go along each pathway. As we knew how much each pathway cost for one patient, we were able to calculate how much the total cost would be for a cohort of patients for each of the six strategies. This cost is the ‘expected cost’, usually expressed as ‘expected cost per patient’.

Resource use data. The perspective of the analysis was the UK National Health Service (NHS). Costs were calculated for the 2003 price year. No detailed resource use data were collected in RCTs in the meta-analysis. We used recent, relevant, patient-based and disaggregated cost data (see Table 4).

Cost data were attached to the 12 possible treatment pathways for each of the six strategies (see Table 5). Each cost variable was assigned a range and gamma distribution in the analysis. We assumed that if a cohort of patients was assigned to one of the six strategies, we knew from the probabilities for that strategy how many patients would go along each pathway. As we knew how much each pathway cost for one patient, we were able to calculate how much the total cost would be for a cohort of patients for each of the six strategies. This cost is the ‘expected cost’, usually expressed as ‘expected cost per patient’. (probability, cost, QALY). This allowed us to generate 95% CIs (see Table 6). The probabilistic analysis summed the results of multiple analyses (iterations). Each iteration sampled the values for the variables at random from the specified distributions. The main areas of uncertainty in the model were estimates of effectiveness of each strategy. The sampling method used was Monte Carlo, expected value. The simulation software used was @RISK, as an add on to Microsoft Office Excel v.7.0 [27]. The number of iterations for each simulation to generate reliable statistics was determined by the software, which halted the simulation when convergence at less than 1.5% in percentile values, mean and standard deviation was achieved.

Cost-effectiveness analysis

Expected costs and outcomes were generated for each of the six arms for outcome measures derived directly from the meta-analysis and for QALYs. We generated incremental cost-effectiveness ratios (ICERs), a series of cost-effectiveness acceptability curves (CEACs) and a cost-effectiveness acceptability frontier (CEAF) to reflect uncertainty in costs, effects and the maximum willingness to pay for a decision-maker.

<table>
<thead>
<tr>
<th>Treatment pathway</th>
<th>Utility of GI adverse event health state</th>
<th>Duration of GI adverse event health state/days</th>
<th>QALYs lost over 6 months</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>No GI adverse event</td>
<td>1.00</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GI discomfort, switch therapy: moderate dyspepsia before seeking help</td>
<td>0.91 [34]</td>
<td>10 [25]</td>
<td>0.005</td>
<td>0–0.064</td>
</tr>
<tr>
<td>GI discomfort, in-patient medical management: severe dyspepsia before seeking help</td>
<td>0.87 [34]</td>
<td>10 [25]</td>
<td>0.0318</td>
<td>0–0.058</td>
</tr>
<tr>
<td>in-patient days with endoscopy</td>
<td>0.5675 [35]</td>
<td>2 [35]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe dyspepsia after therapy</td>
<td>0.87 [34]</td>
<td>12 [36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate dyspepsia after therapy</td>
<td>0.91 [34]</td>
<td>23 [36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI discomfort, out-patient medical management, endoscopy: severe dyspepsia before seeking help</td>
<td>0.87 [34]</td>
<td>10 [25]</td>
<td>0.0295</td>
<td>0–0.058</td>
</tr>
<tr>
<td>out-patient endoscopy</td>
<td>0.5675 [35]</td>
<td>1 [35]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe dyspepsia after therapy</td>
<td>0.87 [34]</td>
<td>12 [36]</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>23 [36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI discomfort, out-patient medical management, no endoscopy: severe dyspepsia before seeking help</td>
<td>0.87 [34]</td>
<td>10 [25]</td>
<td>0.0271</td>
<td>0–0.054</td>
</tr>
<tr>
<td>severe dyspepsia after therapy</td>
<td>0.87 [34]</td>
<td>12 [36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate dyspepsia after therapy</td>
<td>0.91 [34]</td>
<td>23 [36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic ulcer, endoscopy: severe dyspepsia before seeking help</td>
<td>0.87 [34]</td>
<td>10 [25]</td>
<td>0.0318</td>
<td>0–0.064</td>
</tr>
<tr>
<td>out-patient endoscopy</td>
<td>0.5675 [35]</td>
<td>2 [35]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe dyspepsia after therapy</td>
<td>0.87 [34]</td>
<td>12 [36]</td>
<td></td>
<td></td>
</tr>
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<td>0.91 [34]</td>
<td>23 [36]</td>
<td></td>
<td></td>
</tr>
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<td>Symptomatic ulcer, no endoscopy: severe dyspepsia before seeking help</td>
<td>0.87 [34]</td>
<td>10 [25]</td>
<td>0.0271</td>
<td>0–0.054</td>
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<td>0.87 [34]</td>
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<td></td>
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<tr>
<td>moderate dyspepsia after therapy</td>
<td>0.91 [34]</td>
<td>23 [36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious GI complication, in-patient management, surgery, survive: severe dyspepsia before seeking help</td>
<td>0.87 [34]</td>
<td>10 [25]</td>
<td>0.0556</td>
<td>0–0.114</td>
</tr>
<tr>
<td>in-patient treatment for ulcer haemorrhage and surgery</td>
<td>0.46 [35]</td>
<td>10 [6]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe dyspepsia after therapy</td>
<td>0.87 [34]</td>
<td>12 [36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate dyspepsia after therapy</td>
<td>0.91 [34]</td>
<td>23 [36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious GI complication, in-patient management, surgery, die</td>
<td>0</td>
<td>NA</td>
<td>0.500</td>
<td>0</td>
</tr>
<tr>
<td>Serious GI complication, in-patient management, surgery, no surgery, survive: severe dyspepsia before seeking help</td>
<td>0.87 [34]</td>
<td>10 [25]</td>
<td>0.0551</td>
<td>0–0.11</td>
</tr>
<tr>
<td>in-patient treatment of complicated ulcer</td>
<td>0.49 [35]</td>
<td>10 [6]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe dyspepsia after therapy</td>
<td>0.87 [34]</td>
<td>12 [36]</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Serious GI complication, in-patient management, surgery, die</td>
<td>0</td>
<td>NA</td>
<td>0.500</td>
<td>0</td>
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<td>Serious GI complication, out-patient management: severe dyspepsia before seeking help</td>
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<td>23 [36]</td>
<td></td>
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</tbody>
</table>

Uncertainty around costs and outcomes

Probabilistic sensitivity analysis was used to generate measures of uncertainty (variance) because these were not available from data sources. Each variable had a mean value. The type of distribution was informed by the nature of each variable
GI discomfort: out-patient management

- 1 month first drug treatment
- 2 GP visits
- PPI for 28 days
- 1 outpatient visit
- 1 set of tests

Therapeutic endoscopy
- £1158.61
- £682.31
- £1532.73

GP visit
- £20
- £20
- £20

Surgical procedure
- £3181.80
- £1731.00
- £3804.13

Diagnostic endoscopy
- £435.38
- £282.68
- £650.67

Labs and tests
- £27
- £27
- £27

Helicobacter pylori

Blood products
- £111
- £111
- £111

Intravenous omeprazole
- £78.15
- £78.15
- £78.15

Celecoxib 100 mg o.d.
- £23.44
- £23.44
- £23.44

Ranitidine 150 mg b.d.
- £8.28
- £8.28
- £8.28

Omeprazole 20 mg o.n.
- £25.20
- £25.20
- £25.20

Misoprostol 200 μg b.d.
- £10.17
- £10.17
- £10.17

Omeprazole 20 mg o.n.
- £25.20
- £25.20
- £25.20

Ranitidine 150 mg b.d.
- £8.28
- £8.28
- £8.28

Meloxicam 7.5 mg b.d.
- £21.85
- £21.85
- £21.85

Celiac 100 mg o.d.
- £23.44
- £23.44
- £23.44

Intravenous omeprazole
- £78.15
- £78.15
- £78.15

Blood products
- £111
- £111
- £111

GP visit
- £20
- £20
- £20

Surgical procedure
- £3181.80
- £1731.00
- £3804.13

In-patient day
- £249
- £249
- £249

Serious GI complication: in-patient surgical

Symptomatic/endoscopic ulcer: endoscopy
- 3 months' first drug treatment
- 2 GP visits
- PPI for 28 days
- 2 outpatient visits
- 1 set of tests
- 1 diagnostic endoscopy
- 1 H. pylori test
- 2 in-patient days
- 5 months' switched drug treatment

Symptomatic/endoscopic ulcer: no endoscopy
- 3 months' first drug treatment
- 2 GP visits
- PPI for 28 days
- 2 outpatient visits
- 2 sets of tests
- 1 diagnostic endoscopy
- 1 therapeutic endoscopy
- 1 H. pylori test
- 3 months' paracetamol treatment

Serious GI complication: out-patient management
- 42 days' oral PPI
- 2 GP visits
- 2 outpatient visits
- 1 set of tests
- 1 diagnostic endoscopy
- 1 therapeutic endoscopy
- 1 H. pylori test
- 3 months' paracetamol treatment

Serious GI complication: in-patient surgical intervention: survive
- 1 course i.v. omeprazole
- 42 days' oral PPI
- 2 blood products
- 2 GP visits
- 2 outpatient visits
- 2 sets of tests
- 1 diagnostic endoscopy
- 1 therapeutic endoscopy
- 1 surgical procedure
- 10 in-patient days
- 1 ICU day
- 1 rebleed costs
- 33% patients
- 1 H. pylori test
- 3 months' paracetamol treatment

Serious GI complication: in-patient medical intervention: survive
- 1 course i.v. omeprazole
- 42 days' oral PPI
- 2 blood products
- 2 GP visits
- 2 outpatient visits
- 2 sets of tests
- 1 diagnostic endoscopy
- 1 therapeutic endoscopy
- 5 in-patient days
- 1 rebleed costs
- 33% patients
- 1 H. pylori test

Serious GI complication: in-patient medical intervention: die

Serious GI complication: in-patient surgical intervention: die

Serious GI complication: out-patient management
- 42 days' oral PPI
- 2 GP visits
- 2 outpatient visits
- 1 set of tests
- 1 diagnostic endoscopy
- 1 therapeutic endoscopy
- 1 H. pylori test

Serious GI complication: in-patient surgical intervention: die

Serious GI complication: in-patient medical intervention: die

Serious GI complication: in-patient surgical intervention:

Serious GI complication: in-patient medical intervention:

Serious GI complication: in-patient surgical intervention:

Serious GI complication: in-patient medical intervention:

Serious GI complication: in-patient surgical intervention:

Serious GI complication: in-patient medical intervention:

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The frontier is the uppermost combination of lines. The switch points show where the optimal strategy changes, and is equivalent to the ICER between these two options. If the decision-maker will pay up to £140 000 per extra QALY, the optimal strategy is COX-1/H2RA. If the decision-maker will pay over this the optimal strategy is tNSAID/PPI. tNSAID/misoprostol, COX-2 preferential inhibitors and COXIBs are never optimal.

### Discussion

This study examined the relative cost-effectiveness of newer against older gastroprotective strategies. Our model is unique in that it compares all strategies. This has limited our ability to stratify our patients by risk group. However, our economic analysis suggested that tNSAIDs + H2RAs are among the least effective of the GPAs, but may reduce gastrointestinal risk for the general population at a lower overall cost to the health-care provider than tNSAIDs alone. H2RAs are not as effective at reducing GI effects as the other GPA strategies, but they are effective. Other strategies are equally, or more, effective, but at an increased overall cost to the health-care provider than NSAIDs alone. Therefore, the decision-maker has to decide how much extra they are prepared, or are able, to pay to avoid undesirable outcomes.

The data for endoscopic ulcers were the most robust data obtained over all, although this analysis suggests that there is still an unacceptable level of uncertainty as far as decision-making is concerned. This was not the most clinically relevant measure because most endoscopic ulcers do not develop into clinically significant ulcers or bleeds [5]. If we had not included this parameter in the model, we would not have been able to identify the dominant effect of H2RAs.

In our systematic review, only 138 deaths and 248 serious GI events were reported for 74 666 participants in 112 trials [2]. It is likely that serious GI outcomes are underreported in trials as patients may be withdrawn before events occur. The use of validated health status data allowed us to generate estimates of changes in utility associated with all the GI outcomes in the model.

The model was constructed to provide a conservative estimate of cost-effectiveness and was biased in favour of COXIBs because we did not extend the effect of treatment beyond the length of the trials. Also, due to current widespread uncertainty associated with differences in cardiovascular outcomes caused by these medicines [21], we assumed equivalent cardiovascular safety.

Despite this, COXIBs were not the optimal strategy. Of the older strategies, misoprostol was dominated by H2RAs due to differences in acquisition costs and side-effect profile, and the extra effectiveness afforded by PPIs is only obtained at a large incremental cost per extra unit of outcome in a population with average risk of adverse GI events. A different outcome might have been obtained if only patients at high risk of GI adverse events had been considered.

Despite the large body of evidence in this area, there is very little information on the relative effectiveness of the five strategies...
due to the lack of head-to-head studies. This meant using indirect comparisons in the economic analysis, a method that can provide useful results [29] but which is not as robust as direct comparisons, and dependent on similarity of baseline risk in all groups. We were not able to assess the effect of baseline risk on cost-effectiveness, such as age, previous GI morbidity or aspirin taking due to the poor quality of subgroup reporting in the trials in the meta-analysis.

Direct healthcare costs were available only as reported estimates from clinicians [6]. There has been no head-to-head trial of gastroprotective strategies that has included an economic evaluation that collects prospective patient-based observational data. There is little or no patient-based information about the resource use consequences of NSAID-related GI events.

Recommendations for health care

The economic analysis suggests that there may be a case for prescribing H2RAs in all patients requiring NSAIDs. Other GPs are more effective, but are associated with a greater cost. Misoprostol is recommended by the National Prescribing Centre [30], but patient acceptability is so low that prescribers may be reluctant to follow this advice. Our recommendations are tentative due to the quality of the data available and the assumptions we have had to make in our model, and it is possible that other strategies may be preferred in patients with higher baseline GI risk.

Recommended H2RAs in all patients requiring NSAIDs will only be effective if prescribers prescribe, and patients adhere to, the medicines. However, low levels of prescribing [31] and non-adherence [32] to dual therapies have been reported, and patients’ exposure to increased costs from two medicines instead of one only be effective if prescribers prescribe, and patients adhere to, the medicines. However, low levels of prescribing [31] and non-adherence [32] to dual therapies have been reported, and patients’ exposure to increased costs from two medicines instead of one is likely to contribute to this. This low uptake of GPs increases cost-effectiveness ratios substantially [33]. Of related concern is the co-prescribing of GPs with COXIBs, reportedly as high as 20% [33], and this non-evidence-based practice should be discouraged.

Implications for further research

The prescribing of medicines involves the patient, the prescriber, the payer and society. The challenge for prescribers and policy-makers is to use drugs appropriately and cost-effectively. Information for all decision-makers needs to be greatly improved through use of head-to-head comparisons in pragmatic trials, rigorously reported major outcomes and patient-centred outcomes and acquisition of observational cost data and follow-up data about the treatment of patients suffering adverse events.

<table>
<thead>
<tr>
<th>Key messages</th>
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<tr>
<td>* tNSAID/H2RA is safer and less costly than tNSAIDs alone and equally safe and less costly than COX-2 preferential inhibitors and tNSAID/misoprostol.</td>
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<tr>
<td>* tNSAID/PPI and COXIBs are more effective but more costly.</td>
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LS, RAE, DS, TJB and CR conceived and designed the study; RAE, KP and LH analysed the data and interpreted the results, TJB collected and collated data, CR provided statistical support, RAE drafted the manuscript. RAE, LH, KP, DS, TJB and CR critically revised the manuscript. RAE will act as guarantor for the paper.

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References