

## Guidelines for the appropriate use of non-steroidal anti-inflammatory drugs, cyclo-oxygenase-2-specific inhibitors and proton pump inhibitors in patients requiring chronic anti-inflammatory therapy

R. W. DUBOIS\*, G. Y. MELMED†, J. M. HENNING‡ & L. LAINES§

\*Zynx Health Inc., Beverly Hills, CA, USA; †Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA; ‡TAP Pharmaceutical Products, Inc., Medical Affairs Department, Lake Forest, IL, USA; §School of Medicine, University of Southern California, CA, USA

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### SUMMARY

**Aim:** To rationalize decision making around the use of different non-steroidal anti-inflammatory drug (NSAID) treatment strategies in patients with varying degrees of gastrointestinal and cardiovascular risk.

**Methods:** The panel comprised nine physicians (three rheumatologists, two internists, two gastroenterologists and two cardiologists) from geographically diverse areas practising in community-based settings ( $n = 4$ ) and academic institutions ( $n = 5$ ). A literature review was performed by the authors on the risks, benefits and costs of NSAIDs, cyclo-oxygenase-2-specific inhibitors and proton pump inhibitor co-therapy. The RAND/UCLA Appropriateness Method was used to rate 304 clinical scenarios as 'appropriate', 'uncertain' or 'inappropriate'.

**Results:** In patients with no previous gastrointestinal event and not concurrently on aspirin (low risk), the panel rated the use of an NSAID alone as 'appropriate'

for those aged < 65 years, and the use of an NSAID + proton pump inhibitor or cyclo-oxygenase-2-specific inhibitor + proton pump inhibitor as 'inappropriate'. For patients aged > 65 years and at low risk, an NSAID or cyclo-oxygenase-2-specific inhibitor alone was rated as 'uncertain'. For patients with a previous gastrointestinal event or who concurrently received aspirin, an NSAID alone was rated as 'inappropriate', and either a cyclo-oxygenase-2-specific inhibitor or an NSAID + proton pump inhibitor was rated as 'appropriate'. Finally, for patients with a previous gastrointestinal event and on aspirin, an NSAID or cyclo-oxygenase-2-specific inhibitor in conjunction with a proton pump inhibitor was rated as 'appropriate'.

**Conclusions:** Clinicians and managed care entities need to balance the risks, benefits and costs of NSAIDs, cyclo-oxygenase-2-specific inhibitors and the prophylactic use of proton pump inhibitors. The guidelines given here can assist this process.

### INTRODUCTION

In the year 2000, US patients received 111 400 000 prescriptions for non-steroidal anti-inflammatory

drugs (NSAIDs), at a cost of nearly \$5 billion, with an additional \$2 billion spent on over-the-counter NSAIDs.<sup>1</sup> Thirty-four per cent of individuals aged 65 years or older have been reported to take NSAIDs on a daily basis, and 70% use them at least once a week.<sup>2</sup> NSAIDs reduce pain and inflammation. However, they are also associated with a significant risk of gastrointestinal events, with clinical<sup>3–5</sup> and economic<sup>6–8</sup> consequences. North American studies have indicated that, for each dollar spent on NSAIDs,

Correspondence to: Dr R. W. Dubois, Senior Vice President, Zynx Health Inc. (a subsidiary of the Cerner Corporation), Beverly Hills, CA 90212, USA.  
E-mail: rdubois@cerner.com

\$0.66 to \$1.25 is spent on gastrointestinal side-effects.<sup>6, 7</sup> In one assessment, 31% of the cost of managing arthritis resulted from dealing with the gastrointestinal adverse events caused by the treatment.<sup>9</sup> To address these gastrointestinal concerns, certain patients receive cyclo-oxygenase-2 (COX-2)-specific inhibitors, which have approximately half the associated gastrointestinal risks compared with non-selective NSAIDs.<sup>10, 11</sup> Alternatively, patients may receive an NSAID in conjunction with a proton pump inhibitor, which similarly reduces the gastrointestinal risk.<sup>12</sup> Unfortunately, these latter approaches have substantially higher costs than the use of a generic NSAID alone, which costs just pennies per day.<sup>13</sup> Further complicating the choice of therapy are recent concerns about the potential cardiovascular toxicity associated with COX-2-specific inhibitors.<sup>11, 14</sup>

In an ideal environment, physicians would possess compelling high-quality evidence to drive clinical decisions. Who should receive NSAIDs alone? What clinical factors would justify, clinically and economically, a COX-2-specific inhibitor, an NSAID in conjunction with a proton pump inhibitor or even a COX-2-specific inhibitor in conjunction with a proton pump inhibitor? Physicians confront these clinical questions on a daily basis, and payers routinely confront their economic consequences. These medications place significant financial burden on organizations and sometimes seemingly arbitrary hurdles are instituted to limit costs. In an effort to address these issues, we have utilized an evidence-based consensus process to develop guidelines for the use of these costly, common and, at times, controversial agents.

## METHODS

To develop appropriateness measures for the use of NSAIDs, we undertook a computer search of the literature to determine the risks and benefits associated with these agents, as well as measures to reduce the risks; developed a list of clinical scenarios for which these therapies might be considered; and convened a geographically diverse, multi-disciplinary consensus panel (representing the specialties of rheumatology, gastroenterology, cardiology and internal medicine) to review and rate each clinical scenario for the use of these therapies. We followed the validated RAND/UCLA Appropriateness Method for this process.<sup>15</sup>

## Literature summary

The consensus panel received a review of the literature describing the risks and benefits of non-selective NSAIDs and COX-2-selective inhibitors. This literature review also contained a synthesis of the clinical factors that increase (e.g. age, concomitant aspirin, steroid, anticoagulation) as well as decrease (i.e. co-administration of a proton pump inhibitor) the risk of gastrointestinal ulcer, bleeding, perforation or obstruction. Articles were identified by searching the PubMed database from 1991 to August 2002. Search terms and strategies were developed in co-operation with physicians with clinical and research expertise in this field. We identified further articles among the reference lists of papers located using PubMed and from the recommendations of clinicians with expertise in this area. The literature review synthesized information from meta-analyses and primary publications. The specific questions addressed (and the number of relevant studies synthesized) included the following.

- (a) What is the risk of gastrointestinal bleeding in the general population (i.e. non-users of NSAIDs) (one meta-analysis based on 20 individual studies)?
- (b) What is the risk of gastrointestinal bleeding in users of low-dose aspirin (three meta-analyses and one systematic review based on 47 individual studies)?
- (c) What is the risk of gastrointestinal bleeding in users of NSAIDs (two meta-analyses and two systematic reviews based on 41 individual studies)?
- (d) What risk factors increase the risk of gastrointestinal bleeding in NSAID users?: (i) low-dose aspirin (five studies); (ii) age (four meta-analyses); (iii) history of gastrointestinal event (two meta-analyses, one systematic review and one additional randomized controlled trial); (iv) gender (three meta-analyses and one additional study); (v) concomitant use of corticosteroids (one meta-analysis and three additional studies); (vi) anticoagulation (two studies); (vii) other risk factors and multiple risk factors (one study).
- (e) What is the risk of gastrointestinal bleeding in patients taking COX-2-specific inhibitors (two systematic reviews and four randomized controlled trials)?
- (f) How does concomitant (low-dose) aspirin use influence the gastrointestinal safety of COX-2-specific inhibitors (one study)?

- (g) What is the risk of gastrointestinal toxicity from COX-2-specific inhibitors in patients with risk factors for gastrointestinal bleeding (one systematic review and three additional studies)?
- (h) What is the ability of proton pump inhibitors to reduce the risk of gastrointestinal events in patients on long-term NSAIDs (one meta-analysis and three additional studies)?
- (i) What is the ability of proton pump inhibitors to reduce the risk of gastrointestinal events in patients on long-term COX-2-specific inhibitors (no studies identified)?
- (j) What is the ability of proton pump inhibitors to reduce the risk of gastrointestinal events in patients on long-term NSAIDs and aspirin (no studies identified)?
- (k) What is the risk of thrombotic events in patients taking NSAIDs (two studies)?
- (l) What is the risk of thrombotic events in patients taking naproxen (four studies)?
- (m) What is the risk of thrombotic events in patients taking COX-2-selective inhibitors (one meta-analysis, one pooled analysis and five randomized controlled trials)?

All data from the studies were extracted by one of three physicians trained in health services research and placed into evidence tables. These tables underwent subsequent review by two physicians with training in health services research (RWD) or gastroenterology (LL). The nine-member expert panel (see below) also reviewed the evidence synthesis for completeness and accuracy. In addition, the panel received data on the daily costs of NSAIDs, COX-2-specific inhibitors and proton pump inhibitors in various environments. As no single cost estimate applies uniformly for all patients, information was presented in three ways: adjusted average wholesale prices (AWP – 10%) as discussed by Motheral and Fairman,<sup>16</sup> cost in California's Medicare drug discount programme and cost at Kaiser Health Plan (personal communication with Douglas Corley, 2002).

#### *Clinical scenarios*

We attempted to create a comprehensive list of all possible clinical scenarios for the chronic use (> 1 month) of NSAID therapy (with or without proton pump inhibitor therapy). Preliminary scenarios were constructed by the authors, and then underwent a

two-round review process by the expert panel. The final scenarios categorized patients on the basis of permutations of various clinical factors. These factors included: (i) no previous gastrointestinal event vs. previous uncomplicated gastrointestinal event (ulcer discovered by a clinically indicated work-up) vs. previous complicated gastrointestinal event (bleeding, obstruction or perforation); (ii) concomitant therapy (none vs. aspirin vs. steroids vs. warfarin vs. aspirin + steroids vs. aspirin + warfarin); (iii) cardiovascular risk ( $\leq 15\%$  10-year risk vs.  $> 15\%$  10-year risk); (iv) age ( $< 65$  years vs.  $\geq 65$  years).

The permutation of these four factors created 72 ( $3 \times 6 \times 2 \times 2 = 72$ ) different clinical scenarios. These scenarios were then evaluated for each of four therapeutic options (NSAID alone, NSAID in conjunction with a proton pump inhibitor, COX-2-specific inhibitor alone and COX-2-specific inhibitor in conjunction with a proton pump inhibitor) creating 288 ( $4 \times 72 = 288$ ) base scenarios. An additional 16 scenarios reflected diagnostic subdivisions (rheumatoid arthritis 'present' or 'absent') for patients with no previous gastrointestinal events and on none of the above concomitant therapies.

Although misoprostol has also been shown to be effective in decreasing the development of endoscopic ulcers and upper gastrointestinal complications,<sup>17, 18</sup> its use is quite uncommon when compared with the use of proton pump inhibitors, perhaps related to the issues of multiple daily dosing and gastrointestinal side-effects with misoprostol.<sup>17</sup> We sought to simulate routine clinical practice in our scenarios and also to simplify our process. Therefore, we chose to evaluate only the commonly used medical co-therapy, proton pump inhibitors, rather than assessing each clinical scenario separately for proton pump inhibitors and for misoprostol.

#### *Consensus panel*

We convened a panel of nine physicians representing a diversity of specialities (two gastroenterologists, three rheumatologists, two cardiologists and two internists), practice settings (five university and four community) and geographical sites. A pool of potential panellists was identified from a combination of speciality society recommendations (American College of Rheumatology, American Gastroenterological Association), authors of key clinical trials and recognized community-based practitioners. The final selection balanced the speciality, setting and geographical factors. All members of the

panel resided in the USA. A list of consensus panel members and their specialities is given in the Appendix. The process of selecting panel members on the basis of specific characteristics minimizes the potential for speciality, practice environment or geographical bias.

The panellists received the literature review and an initial set of scenarios by mail, which they rated. During the meeting, the panellists reviewed the summarized first-round ratings, revised the structure of the clinical scenarios (e.g. added the distinction between rheumatoid arthritis and osteo-arthritis for selected situations), modified the definitions of key terms (e.g. specifying that 'chronic' therapy means > 1 month, or that an 'ulcer' reflects that identified by clinically indicated work-up rather than discovered by routine endoscopy), discussed reasons for the degree of agreement or disagreement in the ratings from the first round, and confidentially re-rated all indications. Each indication was rated on a nine-point scale of appropriateness (9 indicated extremely 'appropriate', 5 'uncertain' and 1 extremely 'inappropriate'). Appropriateness was defined when the expected health benefits of the therapy exceeded its expected negative health consequences by a sufficiently wide margin to justify prescribing the therapy, given the financial constraints of the current health care environment.

The final rating was the median score of the nine panellists. We considered that indications were 'appropriate' for median ratings between 7 and 9 (without disagreement), 'inappropriate' for median ratings between 1 and 3 (without disagreement) and 'uncertain' for median ratings between 4 and 6 or if the panellists disagreed. The consensus method did not force agreement. We defined disagreement as occurring when at least two panellists rated the indication as 'appropriate' and at least two rated the indication as 'inappropriate', regardless of the median rating.

#### *Statistical analysis*

Comparison of similar scenarios was performed to determine the impact of individual clinical factors. As an example, the median rating for the scenario of 'patients aged < 65 years, not on concomitant therapy and with no previous gastrointestinal event' could be compared with the same scenario except for the single change to 'previous complicated gastrointestinal event'. In addition, the data from the panel results were subjected to a four-way analysis of variance (ANOVA)

model with all terms included (two-, three- and four-way interactions). This approach allows for the inclusion of variability due to the primary design variables in the study, i.e. main effects of age of the patient, cardiovascular risk, previous gastrointestinal problems and concurrent aspirin usage, as well as the various interactions between these variables. This analysis assesses the statistical significance of each factor. Also, when a variable was found to be significant, further analyses were performed using the Tukey-Kramer method to assess what specific categories of the effects were significant.<sup>19</sup> Furthermore, the results were further manipulated to estimate variance components, providing a numerical estimate of the percentage of the total variation that could be attributed to the given factor, together with an amount due to random variation, i.e. attributable to variables not observed or simply 'natural variation'. After the initial model had been evaluated, an additional model included a fifth factor that corresponded to the speciality of each physician to determine whether speciality (e.g. gastroenterology vs. cardiology vs. rheumatology vs. internal medicine) influenced the ratings.

## RESULTS

### *Literature review results*

The panel received a literature review and evidence tables that exceeded the scope of this paper. A brief summary of the major conclusions with regard to the clinical gastrointestinal and cardiovascular effects of NSAIDs and COX-2-specific inhibitors, as well as the gastrointestinal protective effects of proton pump inhibitors in NSAID users, is provided below.

The use of traditional non-selective NSAIDs increases the risk of serious gastrointestinal complications by approximately 2.5–5-fold compared with patients not receiving these medications.<sup>20–22</sup> Patients taking low-dose aspirin alone have an increase in risk of approximately 1.5–3-fold.<sup>23–25</sup> When low-dose aspirin users add a non-selective NSAID, the risk may increase by two- to four-fold when compared with the use of low-dose aspirin alone.<sup>25–27</sup> Data on the risk of adding low-dose aspirin to an NSAID are not as clear-cut. Epidemiological studies do not document a significant increase in the risk of complications,<sup>26–28</sup> although subset analysis of aspirin and non-aspirin cohorts in study arms of prospective investigations suggest up to a two- to three-fold increase.<sup>10, 29</sup>

Important risk factors for the development of gastrointestinal complications in patients taking NSAIDs include: increasing age, previous gastrointestinal events, concomitant use of anticoagulation therapy, such as warfarin, and concomitant use of corticosteroids. The risk of gastrointestinal complications in NSAID users over the age of 65 years is increased approximately 2–3.5-fold when compared with younger patients.<sup>18, 21, 30</sup> In patients with a previous gastrointestinal event, the risk of a subsequent gastrointestinal event is increased by approximately 2.5–4 times when compared with those without previous events;<sup>18, 21, 22, 30</sup> the risk may be greater with a previous complicated event than with any previous gastrointestinal clinical event.<sup>30</sup> NSAID users taking warfarin have approximately a three-fold increase in gastrointestinal bleeding,<sup>31, 32</sup> whereas those taking corticosteroids have approximately a two-fold increase in gastrointestinal events,<sup>21, 30, 32</sup> when compared with those not taking these medications.

The use of COX-2-specific inhibitors decreases the risk of developing gastrointestinal clinical events and complications by approximately 50%.<sup>10, 11, 29, 33, 34</sup> No conclusions could be drawn with regard to COX-2-specific inhibitors plus low-dose aspirin because no study designed to evaluate the gastrointestinal effect of this combination was identified. Subgroup analysis of pooled randomized endoscopic studies suggested a trend to more endoscopic ulcers with valdecoxib plus aspirin vs. placebo plus aspirin. Furthermore, a greater proportion of aspirin users developed endoscopic ulcers in those taking ibuprofen and diclofenac (but not naproxen) than in those taking valdecoxib.<sup>35</sup> In contrast, subgroup analysis of the Celecoxib Long-Term Arthritis Safety Study (CLASS) showed no indication of a difference in gastrointestinal clinical events for NSAIDs + low-dose aspirin vs. celecoxib + low-dose aspirin,<sup>10</sup> but this study was not powered or designed to assess this issue.

Proton pump inhibitors decrease the risk of bleeding ulcers in high-risk NSAID or aspirin users with very recent ulcer bleeding by approximately 75–85%.<sup>36, 37</sup> A recent head-to-head randomized comparison of two preventive strategies (proton pump inhibitor plus non-selective NSAID vs. COX-2-specific inhibitor) in patients with bleeding ulcers revealed recurrent bleeding ulcers in 4.9% of the COX-2-specific inhibitor group and 6.4% of the proton pump inhibitor + NSAID group at 6 months (95% confidence interval of difference, – 6.8%

to 3.8%).<sup>36</sup> No studies were available to assess the potential protective effect of proton pump inhibitors in patients taking low-dose aspirin plus non-selective NSAIDs or in those taking COX-2-specific inhibitors, and therefore no conclusions could be drawn regarding these scenarios.

The use of non-selective NSAIDs as a whole probably does not increase or decrease the risk of cardiovascular events.<sup>38, 39</sup> Whether naproxen decreases the risk of cardiovascular events is uncertain. Four epidemiological studies published in 2002 addressed this issue: a cohort study indicated that naproxen was not cardioprotective,<sup>39</sup> whereas three subsequent case-control studies reported a decrease in cardiovascular events with naproxen.<sup>38, 40, 41</sup>

The data on COX-2-specific inhibitors and cardiovascular events were conflicting and no definitive conclusion could be drawn. Results of the VIGOR outcomes study raised the concern that COX-2-specific inhibitors might be prothrombotic, as the rate of myocardial infarctions with rofecoxib was noted to be significantly higher than that with naproxen (0.4% vs. 0.1%).<sup>11</sup> A subsequent pooled analysis found that the rate of cardiovascular events with rofecoxib was similar to that with placebo and non-naproxen NSAIDs, raising the possibility that the results in VIGOR may have been related to the antiplatelet effects of naproxen.<sup>42</sup> CLASS showed no significant difference in cardiovascular events between celecoxib and non-selective NSAIDs.<sup>10</sup>

### Study results

Of the 304 scenarios, the panel rated 45% 'appropriate', 28% 'inappropriate' and 27% 'uncertain.' According to our definition, the panel disagreed about 12% of the indications in the final ratings, falling from 44% in the first-round ratings.

Despite the complexity of the rating structure and its permutation of multiple clinical factors, the final ratings were readily grouped for simpler presentation. We collapsed the separate indications in which the categorization of appropriateness did not differ on the basis of clinical factors (e.g. all were 'appropriate', 'uncertain' or 'inappropriate'). This process resulted in 57 different scenarios (Tables 1–6). In patients aged < 65 years with no previous gastrointestinal events, and not on aspirin, steroids or warfarin, the panel rated most uses of NSAIDs 'appropriate', the use of a COX-2-specific inhibitor 'uncertain' and the use of either an

|                                | COX2        | COX2 + PPI    | NSAID          | NSAID + PPI    |
|--------------------------------|-------------|---------------|----------------|----------------|
| No ASA, steroids or warfarin   | Uncertain   | Inappropriate | Appropriate    | Inappropriate* |
| On ASA or steroids or warfarin | Appropriate | Inappropriate | Inappropriate† | Appropriate    |
| On ASA and steroids            | Uncertain   | Uncertain     | Inappropriate† | Appropriate    |
| On ASA and warfarin            | Uncertain   | Appropriate   | Inappropriate† | Appropriate    |

ASA, aspirin; COX2, cyclo-oxygenase-2-specific inhibitor; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

\* Uncertain for patients with elevated cardiovascular risk.

† Uncertain for patients with elevated cardiovascular risk and on ASA alone.

|                                   | COX2        | COX2 + PPI     | NSAID         | NSAID + PPI |
|-----------------------------------|-------------|----------------|---------------|-------------|
| No ASA, steroids or warfarin      | Appropriate | Inappropriate* | Inappropriate | Appropriate |
| On ASA                            | Uncertain   | Appropriate*   | Inappropriate | Appropriate |
| On steroids                       | Appropriate | Uncertain      | Inappropriate | Appropriate |
| On warfarin                       | Appropriate | Uncertain      | Inappropriate | Appropriate |
| On ASA and (steroids or warfarin) | Uncertain   | Appropriate    | Inappropriate | Appropriate |

ASA, aspirin; COX2, cyclo-oxygenase-2-specific inhibitor; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

\* Uncertain for patients with elevated cardiovascular risk.

|                                   | COX2        | COX2 + PPI   | NSAID         | NSAID + PPI |
|-----------------------------------|-------------|--------------|---------------|-------------|
| No ASA, steroids or warfarin      | Appropriate | Appropriate* | Inappropriate | Appropriate |
| On ASA                            | Uncertain   | Appropriate* | Inappropriate | Appropriate |
| On steroids                       | Appropriate | Uncertain    | Inappropriate | Appropriate |
| On warfarin                       | Appropriate | Appropriate  | Inappropriate | Appropriate |
| On ASA and (steroids or warfarin) | Uncertain   | Appropriate  | Inappropriate | Uncertain†  |

ASA, aspirin; COX2, cyclo-oxygenase-2-specific inhibitor; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

\* Uncertain for patients with elevated cardiovascular risk and not on ASA, steroids or warfarin.

† Appropriate for patients on ASA and steroids with elevated cardiovascular risk.

|                                     | COX2        | COX2 + PPI     | NSAID         | NSAID + PPI |
|-------------------------------------|-------------|----------------|---------------|-------------|
| OA and no ASA, steroids or warfarin | Uncertain   | Inappropriate* | Uncertain     | Uncertain   |
| RA and no ASA, steroids or warfarin | Appropriate | Inappropriate* | Uncertain     | Appropriate |
| On ASA, steroids or warfarin        | Appropriate | Uncertain      | Inappropriate | Appropriate |
| On ASA and (steroids or warfarin)   | Uncertain   | Appropriate*   | Inappropriate | Appropriate |

ASA, aspirin; COX2, cyclo-oxygenase-2-specific inhibitor; NSAID, non-steroidal anti-inflammatory drug; OA, osteo-arthritis; PPI, proton pump inhibitor; RA, rheumatoid arthritis.

None of the treatment options was rated as 'appropriate' for OA patients on no other medications.

\* Uncertain for patients with elevated cardiovascular risk.

Table 1. Treatment strategy for patients aged < 65 years with no previous gastrointestinal events

Table 2. Treatment strategy for patients aged < 65 years and with previous uncomplicated gastrointestinal event

Table 3. Treatment strategy for patients aged < 65 years and with previous complicated gastrointestinal event

Table 4. Treatment strategy for patients aged ≥ 65 years and with no previous gastrointestinal event

Table 5. Treatment strategy for patients aged ≥ 65 years and with previous uncomplicated gastrointestinal event

|                                   | COX2        | COX2 + PPI   | NSAID         | NSAID + PPI |
|-----------------------------------|-------------|--------------|---------------|-------------|
| No ASA, steroids or warfarin      | Appropriate | Uncertain    | Inappropriate | Appropriate |
| On ASA                            | Uncertain   | Appropriate* | Inappropriate | Appropriate |
| On steroids or warfarin           | Appropriate | Uncertain    | Inappropriate | Appropriate |
| On ASA and (steroids or warfarin) | Uncertain   | Appropriate  | Inappropriate | Appropriate |

ASA, aspirin; COX2, cyclo-oxygenase-2-specific inhibitor; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

\* Uncertain for patients with elevated cardiovascular risk.

Table 6. Treatment strategy for patients aged ≥ 65 years and with previous complicated gastrointestinal event

|  | COX2         | COX2 + PPI   | NSAID         | NSAID + PPI |
|--|--------------|--------------|---------------|-------------|
| No ASA, steroids or warfarin           | Appropriate* | Uncertain    | Inappropriate | Appropriate |
| On steroids or warfarin                | Appropriate* | Appropriate* | Inappropriate | Appropriate |
| On ASA alone or with steroids/warfarin | Uncertain    | Appropriate  | Inappropriate | Appropriate |

ASA, aspirin; COX2, cyclo-oxygenase-2-specific inhibitor; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

\* Uncertain for patients with elevated cardiovascular risk.

NSAID + proton pump inhibitor or a COX-2-specific inhibitor + proton pump inhibitor as ‘inappropriate.’ In contrast, if the same patient was receiving aspirin or steroids or warfarin, an NSAID + proton pump inhibitor or a COX-2-specific inhibitor was rated as ‘appropriate.’ An NSAID alone or a COX-2-specific inhibitor + proton pump inhibitor in these patients was rated as ‘inappropriate.’ In patients receiving aspirin and warfarin, both an NSAID + proton pump inhibitor and a COX-2-specific inhibitor + proton pump inhibitor were rated as ‘appropriate.’ Tables 2 and 3 address the patient aged < 65 years with previous uncomplicated

or complicated gastrointestinal events, respectively. Tables 4–6 mirror the previous tables except for a change to patients aged ≥ 65 years.

Table 7 summarizes those clinical scenarios rated as ‘appropriate’ or ‘inappropriate’ by therapeutic option. Those scenarios rated as ‘uncertain’ are not listed in this table. As an example, the panel rated the use of an NSAID alone as ‘appropriate’ only for patients aged < 65 years with no previous gastrointestinal event and not currently on aspirin, and ‘inappropriate’ if the patient had a previous gastrointestinal event (either uncomplicated or complicated) or was receiving aspirin,

Table 7. Summary of recommendations for patients requiring chronic non-steroidal anti-inflammatory drug (NSAID) therapy

|               | NSAID alone                                       | NSAID + PPI                               | COX2  | COX2 + PPI   |
|---------------|---|---|---|--|
| Appropriate   | < 65, no ASA and no previous GI event             | On ASA<br>Previous GI event               | On ASA and no previous GI event<br>Not on ASA and previous GI event | Previous GI event and on ASA<br>On ASA and steroids/warfarin   |
| Inappropriate | Previous GI event<br>On ASA, steroids or warfarin | < 65, not on ASA and no previous GI event |   | Not on ASA and no previous GI event<br>< 65, on ASA but no previous GI event<br>< 65, previous uncomplicated GI event and not on ASA/steroids/warfarin |

ASA, aspirin; COX2, cyclo-oxygenase-2-specific inhibitor; GI, gastrointestinal; PPI, proton pump inhibitor.

Table 8. Appropriate choice of medications based on key clinical factors

|            | No previous GI event | Previous GI event         |
|------------|----------------------|---------------------------|
| Not on ASA | NSAID alone (< 65)   | COX2<br>NSAID + PPI       |
| On ASA     | COX2<br>NSAID + PPI  | NSAID + PPI<br>COX2 + PPI |

ASA, aspirin; COX2, cyclo-oxygenase-2-specific inhibitor; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

steroids or warfarin. An NSAID + proton pump inhibitor was rated as 'appropriate' for patients receiving concomitant aspirin or in those with a previous gastrointestinal event. A COX-2-specific inhibitor was rated as 'appropriate' for patients with no previous gastrointestinal event and on aspirin, or a previous gastrointestinal event and not on aspirin. No COX-2-specific inhibitor scenario was rated as 'inappropriate' (although many were rated as 'uncertain'). The use of a COX-2-specific inhibitor + proton pump inhibitor was rated as 'appropriate' if the patient had a previous gastrointestinal event and was receiving aspirin or a combination of aspirin plus steroids (or warfarin).

The 25 scenarios rated as 'appropriate' could be collapsed into a 2 × 2 table (Table 8) on the basis of two clinical factors: concomitant aspirin use and previous gastrointestinal event status. In patients not receiving aspirin, an NSAID alone (for patients aged < 65 years) was rated as 'appropriate' for those without a previous gastrointestinal event, and a COX-2-specific inhibitor or NSAID + proton pump inhibitor as 'appropriate' for those with a previous gastrointestinal event. In contrast, for patients receiving aspirin, a COX-2-specific inhibitor or an NSAID + proton pump inhibitor

was rated as 'appropriate' for those without a previous gastrointestinal event, and an NSAID + proton pump inhibitor or a COX-2-specific inhibitor + proton pump inhibitor as 'appropriate' for those with a previous gastrointestinal event.

Table 9 shows the impact of the individual clinical factors of age, aspirin and previous complicated gastrointestinal event, and their combination, on the median ratings. Compared with the base scenario (< 65 years, no previous gastrointestinal event, not on aspirin), a similar patient aged ≥ 65 years had a four-point lower score (less appropriate), a patient receiving aspirin had a six-point lower score and a patient with a previous complicated gastrointestinal event had an eight-point lower score. Conversely, the ratings rose by four, five and five points, respectively (more appropriate), for the use of an NSAID + proton pump inhibitor, and one, one and six points, respectively, for the use of a COX-2-specific inhibitor + proton pump inhibitor. This table also includes the relative increased risk of gastrointestinal events based on the literature review.

Results from the ANOVA for the use of NSAIDs alone showed that three factors accounted for 62% of the total variation. The most important explanatory variable was whether the patient had suffered a previous gastrointestinal event, with aspirin use and age having significant, but lesser, impact. The addition of speciality to the model did not appreciably increase this amount. For the therapeutic option NSAID + proton pump inhibitor, the four-way model explained 27% of the variation. A previous gastrointestinal event and age had a significant impact. The addition of panellist speciality did not explain any additional variation. For the use of a COX-2-specific inhibitor + proton pump inhibitor, the analysis explained about 65% of the variation, with

Table 9. Impact of clinical factors on median ratings\*

|                               | Literature RR<br>in NSAID users | NSAID  |        | NSAID + PPI |        | COX2   |        | COX2 + PPI |        |
|-------------------------------|---------------------------------|--------|--------|-------------|--------|--------|--------|------------|--------|
|                               |                                 | Median | Change | Median      | Change | Median | Change | Median     | Change |
| Base scenario†                |                                 | 9      |        | 2           |        | 4      |        | 1          |        |
| Age                           | 2–3                             | 5      | – 4    | 6           | + 4    | 6      | + 2    | 2          | + 1    |
| ASA                           | 1–3                             | 3      | – 6    | 7           | + 5    | 7      | + 3    | 2          | + 1    |
| Previous complicated GI event | 5–13                            | 1      | – 8    | 7           | + 5    | 8      | + 4    | 7          | + 6    |
| ASA + age + complicated       | Unknown                         | 1      | – 8    | 7           | + 5    | 4      | 0      | 8          | + 7    |

ASA, aspirin; COX2, cyclo-oxygenase-2-specific inhibitor; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; RR, relative risk.

\* Compared with the same scenario without the listed clinical factor.

† Age < 65 years, no previous GI event and not on ASA.

differences in previous gastrointestinal risk and aspirin usage being the primary explanatory factors, with age having a lesser, but significant, role.

Modelling for the use of a COX-2-specific inhibitor alone was not performed due to the non-linearity of the decision (e.g. initially, with increasing gastrointestinal risk, the use of a COX-2-specific inhibitor was more appropriate; however, at the highest risk, the use of a COX-2-specific inhibitor alone became less appropriate in favour of a COX-2-specific inhibitor in conjunction with a proton pump inhibitor).

## DISCUSSION

We used an evidence-based and validated expert panel consensus process (the RAND Appropriateness Method<sup>15</sup>) to develop guidelines for the appropriate use of NSAIDs, COX-2-specific inhibitors and/or prophylactic proton pump inhibitor co-therapy. These guidelines are timely given the frequency, cost and controversy surrounding the use of these agents.

The panel rated 304 separate clinical scenarios. Despite the large number of ratings, common themes arose and allowed a significant simplification of the results (Table 7). Examining the ratings from the vantage point of specific therapeutic option, the panel rated the use of an NSAID by itself as 'appropriate' when the patient was < 65 years of age and had no previous gastrointestinal events related to the use of an NSAID. They rated it 'inappropriate' to use an NSAID alone when the patient had a previous gastrointestinal event (i.e. bleeding, perforation, obstruction or an ulcer discovered by a clinically indicated work-up) or concomitantly received aspirin. However, these latter circumstances were rated 'appropriate' for the use of an NSAID in conjunction with a proton pump inhibitor.

For a COX-2-specific inhibitor, the panel rated its use as 'appropriate' when the patient was receiving concomitant aspirin but had no previous gastrointestinal event or, conversely, had a previous gastrointestinal event but was not receiving aspirin. In patients with both risk factors (aspirin and a previous gastrointestinal event, or the combination of aspirin and steroids/warfarin), the panel rated the use of a COX-2-specific inhibitor in conjunction with a proton pump inhibitor 'appropriate'. No clinical trials have examined the efficacy of a COX-2-specific inhibitor + proton pump inhibitor. However, a recent trial showing that gastrointestinal bleeding frequently recurred in patients even

though they received either an NSAID + proton pump inhibitor or a COX-2-specific inhibitor may have contributed to the panel's extrapolation beyond the current evidence for this very high-risk patient subcategory.<sup>36</sup> In the patient with no elevated gastrointestinal risk, the panel rated the use of a COX-2-specific inhibitor 'uncertain', finding a balance between the potential for reduced gastrointestinal events with the reality of increased cost.

Three clinical factors, the presence of a previous gastrointestinal event, current aspirin use and age, had the greatest impact on the ratings. Based on the nine-point appropriateness scale, the history of a previous complicated gastrointestinal event (i.e. perforation, obstruction or bleeding) caused the score for NSAIDs to fall by eight points, or become significantly less appropriate (and the corresponding ratings for the use of an NSAID + proton pump inhibitor to increase by five points, or become more appropriate). Similarly, aspirin use decreased the NSAID rating of appropriateness by six points and increased the NSAID + proton pump inhibitor rating by five points. Finally, patients aged ≥ 65 years had ratings that were four points lower for the use of an NSAID alone (vs. those aged < 65 years), and four points higher for the use of an NSAID in conjunction with a proton pump inhibitor. The more sophisticated ANOVA model confirmed the statistical importance of these clinical factors. Neither the simpler comparison of ratings method nor the ANOVA model showed an impact of cardiovascular risk on the ratings.

On the basis of these results, an alternative configuration of the guidelines begins with the patient's clinical presentation to depict the choice of 'appropriate' therapy (Table 8). In patients with no previous gastrointestinal event and not on aspirin, the panel rated the use of an NSAID alone as 'appropriate' for those aged < 65 years. If the patient was receiving aspirin, either a COX-2-specific inhibitor or an NSAID + proton pump inhibitor was rated as 'appropriate.' In patients with a previous gastrointestinal event but not on aspirin, either a COX-2-specific inhibitor or an NSAID + proton pump inhibitor was rated as 'appropriate.' Finally, for patients with both risk factors, an NSAID or a COX-2-specific inhibitor in conjunction with a proton pump inhibitor was rated as 'appropriate'.

The panel considered cardiovascular risk as a factor in each of the scenarios. In general, this clinical issue did not influence the appropriateness ratings and, where it had an impact, it was minimal. The lack of substantial

cardiovascular impact reflects the panel's review of the evidence and the belief that the cardiovascular toxicity of COX-2-specific inhibitors, especially at the doses typically used in clinical practice (e.g. 25 mg rofecoxib or less in 89% of patients),<sup>43, 44</sup> is minimal or non-existent.

The panel did not specifically review the literature on the lower gastrointestinal side-effects of NSAIDs or discuss the implications of these side-effects in their deliberations. Epidemiological studies suggest an increased risk of lower gastrointestinal clinical events with NSAID use, although the incidence of lower gastrointestinal events is lower than that of upper gastrointestinal events.<sup>45, 46</sup> However, risk factors for the development of lower gastrointestinal events with NSAID use have not been determined. Furthermore, no prospective randomized controlled trials regarding the development of NSAID-associated lower gastrointestinal events or the effect of any protective strategies were available. Since the panel met, a single *post hoc* analysis of a prospective outcomes study has reported that a COX-2-specific inhibitor appears to decrease the rate of lower gastrointestinal clinical events by approximately 50%.<sup>47</sup> As more information becomes available on the incidence, risk factors and prevention of NSAID-induced lower gastrointestinal events, it will be important to consider these data formally in future decision making on the use of NSAIDs in clinical practice.

These guidelines were developed using the RAND Appropriateness Method, which utilizes evidence synthesis in conjunction with a quantitative and specified multi-speciality physician consensus process.<sup>15</sup> Guidelines created by this method are enlightened by the evidence, but use quantitative judgement to evaluate the individual clinical scenarios. This approach has undergone various assessments of reliability and validity.<sup>48–50</sup> We have added to this body of literature by comparing the impact of selected clinical factors on the panel ratings with the relative risks of these factors in the literature. As shown in Table 9, age, aspirin use and, more importantly, previous complicated gastrointestinal events had a significant impact on the panel ratings, which correlates with the relative risk increases observed in prospective and retrospective clinical studies. Thus, the panel ratings incorporated the evidence where it existed. In the absence of evidence (e.g. the combined risk of elevated age, aspirin and previous complicated gastrointestinal event, which has not been studied), the panel made logical extensions — that the combination of clinical factors was at least as important as each factor alone.

In conclusion, clinicians and managed care entities need to balance the risks, benefits and costs of NSAIDs, COX-2-specific inhibitors and the prophylactic use of proton pump inhibitors. These clinically detailed evidence-based and economically sensitive guidelines can assist this process and potentially replace the administrative hurdles that now exist.

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#### APPENDIX: PANEL OF EXPERTS

Dr Steven J. Bernstein (Associate Professor of Medicine, University of Michigan, Ann Arbor, MI, USA); Dr Douglas Corley (Adjunct Investigator, Kaiser Division of Research, Assistant Clinical Professor, University of California, San Francisco, Oakland, CA, USA); Dr Michael Hattwick (Medical Director, Northern Virginia Healthcare, Fairfax, VA 22031, USA); Dr Loren Laine (Professor of Medicine, Director, GI Liver Division, University of Southern California, Los Angeles, CA, USA); Dr Brendan McAdam (Assistant Professor of Medicine, Vanderbilt University, Nashville, TN, USA); Dr John Tesser (Director, Arizona Rheumatology Center, Phoenix, AZ, USA); Dr Arthur Weaver (Clinical Professor of Medicine, University of Nebraska Medical Center, Past President of the American College of Rheumatology, Lincoln, NE, USA); Dr Michael Weinblatt (Professor of Medicine, Harvard School of Medicine, Past President of the American College of Rheumatology, Boston, MA, USA); Dr William White (Professor of Medicine, Chief of Hypertension and Clinical Pharmacology, University of Connecticut, Farmington, CT, USA).