Are selective COX 2 inhibitors superior to traditional MAIM? [Reply]
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Are selective COX 2 inhibitors superior to traditional NSAIDs?

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Are selective COX 2 inhibitors superior to traditional NSAIDs?

Rofecoxib did not provide unequivocal benefit over traditional NSAIDs

Editor—In their editorial Jüni et al say that celecoxib is no safer than diclofenac or ibuprofen and that the CLASS authors “spun” their analysis to suggest otherwise. They also state: “In contrast with the CLASS trial, the VIGOR trial, which was similar in design and outcomes, found an unequivocal benefit of another selective COX 2 inhibitor, rofecoxib, over traditional non-steroidal anti-inflammatory agents [NSAIDs].”

I disagree. Although serious gastrointestinal adverse effects were less frequent in rofecoxib users than in patients with rheumatoid arthritis treated with naproxen (number needed to treat to prevent one serious upper gastrointestinal event 191; 95% confidence interval 114 to 586), rofecoxib was in fact less safe than naproxen. The published version of the VIGOR trial focused on the narrow outcome of serious gastrointestinal complications.

The US Food and Drug Administration took the unprecedented step of presenting its review of both the CLASS trial and the VIGOR trial on its website. Review of the complete data presented there shows that when all serious adverse events are included—not just gastrointestinal events—patients treated with naproxen had fewer serious events. Among patients treated with rofecoxib, 9.3% experienced a serious adverse event compared with 7.8% of those treated with naproxen (relative risk 0.81; 0.62 to 0.97). When all serious adverse events are counted, the number needed to harm when rofecoxib is used compared with naproxen is 66 (36 to 532).

The increased risk of serious adverse events was due to an increase of serious adverse cardiovascular events, including a 300% greater risk of myocardial infarction in those treated with rofecoxib.

The VIGOR results, examined fully, show that at least one traditional non-steroidal anti-inflammatory drug—naproxen—is unequivocally safer than rofecoxib, albeit with an increased risk of adverse events limited to the gastrointestinal tract.

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4 Three other responses on bmj.com (bmj.com/cgi/eletters/324/7349/1287) made similar points.

Pharmacia’s response to editorial

Editor—Contrary to the assertions of Jüni et al in their editorial,1 the CLASS design, analyses, and outcome definitions were predefined. The CLASS authors reviewed all the data and decided that the six month analyses were most appropriate for initial publication while the Food and Drug Administration chose nine month data as most appropriate for a recent label change.2 Despite differing medical judgment for the time interval that best reflected the data, and contrary to the allegations in the editorial, the conclusions were similar.

CLASS was a single study using two protocols to ensure treatment blinding, but analysis of the combined results was prespecified. The protocols were similar; however, one included celecoxib 400 mg twice daily and ibuprofen 800 mg thrice daily while the other used celecoxib 400 mg twice daily and diclofenac 75 mg twice daily.

Low dose aspirin was allowed, and the minimum expected duration of participation in the study was six months. The primary end point was ulcer complications (bleeding, perforation, and outlet obstruction) verified by endoscopy or contrast radiography, but analysis of symptomatic ulcers was also prespecified. Early withdrawal for an uncomplicated ulcer—that is, symptomatic ulcer—was mandated in the protocol.

The primary analysis was a comparison of ulcer complication rates between celecoxib and the combined non-steroidal anti-inflammatory group (ibuprofen and diclofenac). To control the overall alpha-level, comparisons of celecoxib with each non-steroidal agent were allowed only if the primary analysis was statistically significant.

Analyses of ulcer complication risk factors—for example, use of low dose aspirin—were also preplanned. Study assumptions included (a) constant complication rates for non-steroidal anti-inflammatory drugs3 and (b) a rate of use of low dose aspirin of around 11%.

Ulcer complication rates were not significantly different for the two groups. However, the rate of the combined end point of symptomatic/complicated ulcers was significantly lower with celecoxib. Since the primary analysis was not significant, comparisons with the individual non-steroidal anti-inflammatory drugs were not valid.

Important design assumptions did not prove to be true. Ulcer complication rates with non-steroidal anti-inflammatory drugs decreased over time instead of remaining constant (figure). Those given non-steroidal anti-inflammatory drugs had a significantly greater withdrawal rate for symptomatic ulcers than those given celecoxib, which was most evident after the first six months (figure). Since symptomatic ulcers are precursors of ulcer complications, patients at high risk who were given non-steroidal anti-inflammatory drugs were being withdrawn more quickly than high risk patients given celecoxib. This differential withdrawal rate introduced study bias, which reduced statistical and medical validity of the analyses over time. Therefore, the CLASS oversight committees judged the six month data to be most valid and reported: “The data after six months were so confounded as to be difficult to interpret for assessing...
Letters

Differ substantially from the six month analyses. Jüni et al misrepresented CLASS.1 We continue to stand behind the study design, analyses, and conclusions.2 Furthermore, we invite you any discussions that will ensure an understanding of the facts and help in clarifying the safety profile of celecoxib.

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7 Goldstein JL, for the CLASS investigators. Gastrointestinal (GI) event rates in the CLASS study: six months vs longer-term follow-up analyses. Gastroenterology 2002;122 (suppl 1):A-49.

Little is known about COX 2 inhibitors

Editor—The editorial by Jüni et al focuses attention not only on the reporting of clinical trials in peer-reviewed journals but also on the interpretation of available evidence.1 We agree more needs to be done to determine whether COX 2 inhibitors are superior to traditional non-steroidal anti-inflammatory drugs (NSAIDs) and have some suggestions of how that might be done.

Firstly, understanding of the cellular effects of the COX 2 inhibitors is evolving, and conclusions about the comparative safety of these agents based on in vitro data cited by Jüni et al may be premature. Although whole blood assays show that rofecoxib is more selective than celecoxib for COX 2,2 such assays have been criticised for having limited clinical relevance.3

Furthermore, studies of cancer cell lines indicate that celecoxib has far greater antiproliferative effects than rofecoxib, implying that celecoxib has greater COX 2 selectivity.4,5 Recent evidence also suggests, however, that celecoxib may possess unique and largely unknown COX independent characteristics over rofecoxib.6 The clinical implications of such differences on the gastrointestinal and cardiovascular safety of these two agents are not known. In short, this is a new class of drugs about which comparatively little is known.

Secondly, meta-analysis of existing trial data cannot overcome the important design issues associated with the existing randomised trials of selective COX 2 inhibitors, including the choice of comparison drugs and outcomes. What is needed, and perhaps what should have been ordered by licensing bodies at the outset, is a study or set of studies designed to allow direct comparisons of COX 2 agents with appropriate existing alternative treatments.

Thirdly, regardless of the debate about phase III trials, there is an important role for phase IV pharmacovigilance studies. While the clinical findings of well designed randomised trials are awaited, phase IV studies will shed light on the impact of COX 2 inhibitors in comparison with other agents in “real world” settings; provide much needed information on rare adverse events such as gastrointestinal haemorrhage, and acute myocardial infarction that may be associated with COX 2 inhibitors; and clarify the extent to which these agents are being used in patients who are most likely to benefit.

As noted by Jüni et al billions of dollars are being spent on COX 2 inhibitors. It seems prudent to determine whether that investment is justified.

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Both the CLASS and VIGOR trials support the COX 2 hypothesis

Editor—With respect to the recent editorial by Jüni et al on the CLASS trial,1 the statistical flaws in the trial’s design have been well documented, and the manner in which the data were reported have been widely criticised.

Yet, the question raised in the title of this editorial seems far fetched. Clearly, the CLASS protocol was doomed at the outset by permitting aspirin use. Aspirin, after all, is the grandfather of all non-steroidal anti-inflammatory drugs (NSAIDs) with profound COX 1 inhibition. Thus, the Kaplan-Meier curves in figure 2 of the editorial do not reflect any true test of the COX 2 specific hypothesis with celecoxib.

Notwithstanding Jüni et al’s protestations of the analytical presentations of the CLASS trials, the incidence of ulcers with COX 2 selective treatment with celecoxib in the CLASS trial was considerably below the 2-4% per year.

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[Graph]
The US Food and Drug Administration’s labelling of celecoxib shows a Kaplan-Meier rate of complicated ulcers at nine months of 0.32% with celecoxib alone vs 1.12% among patients taking aspirin with celecoxib. For rofecoxib the rate (at 10.5 months) was 0.52% vs 1.22% for naproxen.

Similarly, the rate of symptomatic ulcers for patients taking celecoxib was 0.78% vs 2.19% for those taking aspirin and celecoxib. For rofecoxib the labelling shows a rate of 1.80% vs 3.87% for naproxen.

Presumably, the FDA has made the appropriate adjustments to the analysis.

It should be noted that CLASS enrolled a more elderly, at risk, population. In the CLASS trial 34.8% of patients taking celecoxib alone were aged 65 or over vs 24.6% of patients taking rofecoxib in the VIGOR trial.

It would have been instructive to see what the rates were with ibuprofen and diclofenac. I agree with Jüni et al’s recommendation for a meta-analysis. I think that within the CLASS trial the P value would be < 0.05 if patients treated with celecoxib alone were compared with all patients who received a COX 1 inhibitor (aspirin, ibuprofen, diclofenac) using the Food and Drug Administration’s methods.

Today, celecoxib, rofecoxib, and valdecoxib carry the traditional warning for non-steroidal anti-inflammatory drugs, implying that they are associated with ulcer rates of 2%–6% per year. I think that this represents mislabelling of the cruellest sort to patients and which is not supported by any scientific or clinical data. In the United States it enables managed care to deprive patients of the safer alternatives.

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Authors’ reply

Editor—We agree with Budenholzer, who criticises our statement on the “unequivocal benefit” of rofecoxib found in the VIGOR study.1 We were referring to ulcer complications, and should have reported VIGOR to have found an “unequivocal gastrointestinal benefit” only. Rofecoxib’s fivefold increase in myocardial infarctions observed in VIGOR is particularly worrying.2 Incidentally, whereas patients in the CLASS study randomised to celecoxib had similar rates of myocardial infarction to those randomised to ibuprofen, they tended to experience more myocardial infarctions than patients randomised to diclofenac (relative risk 2.21, 95% confidence interval 0.74 to 6.94, P=0.14).3

According to Geis, CLASS was a single study, and the JAMA article reported patients to be “randomly assigned on a 2:1:1 basis.” This is misleading. There were two trials with separate patient recruitment and randomisation procedures requiring separate analyses to preserve randomisation. None the less, the two trials were combined by simply summing them.1 This would be appropriate only if allocation of patients to trials was ruled by chance. However, there were highly significant differences at baseline between trials in patients’ age, disease severity, ethnic group, and histories of intolerance to non-steroidal anti-inflammatory drugs and use of alcohol. The probability that these differences occurred by chance is P<10^{-15}.1 Considering this and different follow up durations and COX 2 selectivities of comparator drugs,2 simply summing results is inappropriate.

The figure (top) shows relative risks and 95% confidence intervals calculated from proportions for primary and secondary outcomes in CLASS study according to separate and combined analyses of the two trials for different follow up durations and different groups of patients. Black squares indicate main outcome measures as prespecified in CLASS protocols, grey squares indicate main outcome measures as reported.1 Identical event rates were assumed in celecoxib groups of both trials for secondary outcome because separate trial data were unavailable. Arrowheads indicate truncation of confidence intervals. Bottom: Analysis of percentage inhibition of COX 1 when COX 2 is inhibited by 80%. Horizontal line indicates equiactivity—80% inhibition of COX 1. Adapted from Warner et al.4

Figures:

1 Alternative definition of ulcer related complications
2 Traditional definition of ulcer related complications
3 Traditional definition of ulcer related complications plus symptomatic ulcers
4 Alternative definition of ulcer related complications prespecified by US Food and Drug Administration

Top: Relative risks and 95% confidence intervals calculated from proportions for primary and secondary outcomes in CLASS study according to separate and combined analyses of the two trials for different follow up durations and different groups of patients. Black squares indicate main outcome measures as prespecified in CLASS protocols, grey squares indicate main outcome measures as reported.1 Identical event rates were assumed in celecoxib groups of both trials for secondary outcome because separate trial data were unavailable. Arrowheads indicate truncation of confidence intervals. Bottom: Analysis of percentage inhibition of COX 1 when COX 2 is inhibited by 80%. Horizontal line indicates equiactivity—80% inhibition of COX 1. Adapted from Warner et al.4

References:

3 Geis RL. CLASS: A single study or a single result? JAMA 2002;287:1442-3.
Geis misuses CLASS's analytical two step procedure, which should have been a safeguard against a type I error, as a justification for obscuring individual trial results and as a rationale to commit a type I error by inappropriately pooling secondary outcomes. Disturbingly, Pharmacia has also presented pooled results from different protocols with different comparator drugs for SUCCESS-I, the successor study to CLASS.3

The main argument for reporting only six month data from CLASS was that patients dropping out because of gastrointestinal adverse events/symptomatic ulcers were at increased risk of ulcer complications.7 However, only 11 out of 44 patients with ulcer complications in CLASS developed gastrointestinal symptoms before an ulcer complication occurred (25%) and none had a symptomatic ulcer as a precursor.7 Patients who experience gastrointestinal adverse events may be monitored and treated more carefully than patients without any gastrointestinal symptoms, with ulcer complications avoided particularly in patients with symptoms. It is therefore not surprising that gastrointestinal adverse events were associated with a significantly decreased risk of subsequent ulcer complications in CLASS (relative risk 0.28, 0.12 to 0.66, P = 0.0018).3

The wide confidence intervals of comparisons in the figure (top) indicate that CLASS trials were underpowered. We therefore fully agree with Mandandi et al's suggestions about future research. A meta-analysis of individual patient data will allow adequately powered explorative comparisons between COX 2 inhibitors and traditional non-steroidal anti-inflammatory drugs. Subsequently, an industry independent long term trial is needed, allocating patients to one of four agents: celecoxib, rofecoxib, diflufenox, or naproxen.

Stover suggests unfair testing of the COX 2 hypothesis in CLASS because of aspirin use in some patients. The figure (top) shows no consistent pattern distinguishing aspirin users from non-users, suggesting that CLASS comparisons were not confounded by aspirin use. According to the results of an in vitro analysis by Warner et al summarised in the figure (bottom), celecoxib and diclofenac actually have similar COX 2 selectivity. Therefore CLASS's failure to demonstrate celecoxib's superiority may have more to do with celecoxib's shortcomings as a COX 2 inhibitor. Not surprisingly, the US Food and Drug Administration refused to change celecoxib's labelling, which still states as of 7 June 2002 that "serious gastrointestinal toxicity such as bleeding, ulceration, and perforation can occur at any time."

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We thank Yvain Ben-Shlomo for helpful comments, and Ben Calman for data management and entering.

3 Juni P, Rutjes AW, Dieppe PA. Pharmacia addresses June 1 editorial regarding CLASS study: authors' response. bmj.com 2002; bmj.com/cgi/content/full/324/7349/1257/27566 (accessed 12 July 2002).

NHS Direct audited

NHS Direct is value for money and improving

Editor—George selectively highlights negative points from the positive report by the National Audit Office on NHS Direct, drawing conclusions which merit further scrutiny.4

He notes no visible effect on demand for NHS services since NHS Direct started. Reducing demand was not its primary objective. It aimed to provide the public with a confidential, reliable, and consistent service of professional advice 24 hours a day with easy access to comprehensive health information.5

He later comments that the “inevitable consequences” of nurse telephone advice is “to fill a health system with people who do not need to be there,” directly contradicting the overall unchanged demand he cited earlier. The key is appropriate use of health-care services. NHS Direct undoubtedly advises some callers to access NHS services who would not have done so in the absence of the telephone advice service. Equally, there is frequent redirection of callers from a previous intention to call their general practitioner or attend accident and emergency department to self care. The net numerical effect may be neutral, but the movement of callers above and below the waterline of the “iceberg of illness”6 should increase appropriate use of services. Early evaluation did not address this, but such investigation is now under way.

Service use and awareness is not universal, but in a service that has only been nationally available for 18 months, this is not surprising. Specific campaigns targeted at hard to reach groups are now being developed.

Access to the content of NHS Direct Online is less limited than George suggests. It is available in touch screen format in 200 (expanding to 500 by 2004) health information points in the United Kingdom to be found in libraries, post offices, and health centres, so allowing use without internet access or computer skills. The content has also been used in recent pilot studies with digital television, which will potentially broaden internet access significantly. A popular part of the website is the self help guide, also available in hard copy.7

The sum of £45m represents around 0.1% of the total NHS budget. For this net outlay the NHS has delivered a service with over 7m consultations, with a safety record at least comparable to any other part of the NHS, a rate of satisfaction among users that has been consistently greater than 95%, and information management and availability far in advance of the rest of the NHS. It is now acting as a focus point for the integration of out of hours and emergency care around a single prioritisation and assessment process. Value for money? I think so.

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Audit neglected children

Editor—In its audit of NHS Direct the National Audit Office failed to examine how it serves children; at least 20% of calls to NHS Direct are about the under 5s.8

Perhaps if the children had made the calls themselves they would have been identified as sufficiently distinct a group to warrant at least some interest from the auditors. This audit is so superficial that the auditors failed to wonder whether adults might be calling about children and, if so, what specific systems were in place to respond, how appropriate the responses might be, and whether any concerns might emerge. What could their reasoning have been?

The reasoning was probably all too typical—that children, being small people, must have correspondingly small needs. The National Audit Office would do well to commission an audit specifcated about children and NHS Direct. That might restore their credibility. It would certainly prove a service to children and their parents.


Telephone consultations in general practice should be tested


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| 1 Dyer O BMA says nurses could become NHS gatekeepers. BMJ 2002;324:563-5. (9 March.) |


| Using nurses might influence developing countries |


Can nurse practitioners provide equivalent care to GPs?

Nurses and doctors working together can complement each other

Editor—Horrocks et al state in their systematic review that its focus is the role of nurse practitioners in primary care.1 They concede that ambiguity exists over the definition of a nurse practitioner yet go on to include studies involving nurses working in hospital departments.2

Before large sums of money are thrown at such projects, it would be wise to compare like with like. In addition, policy implementers ought to consider several other points not covered by Horrocks et al’s review.

Firstly, general practitioner registrars in their first three months of training have a minimum of four years of postgraduate work experience, yet are deemed unfit to practise without first passing various elements of summative assessment. Nurse practitioners are not required to have their video consultation technique checked.

Secondly, if nurse practitioners wish to be considered as independent practitioners then they need to have their own comprehensive indemnity, so that litigation stops with them, rather than their employing practice.

Thirdly, during employment of a nurse practitioner on a three month trial basis, doctors at my practice asked our trainer to review each of the nurse practitioner’s surgeries, as he would with a general practitioner registrar. The trainer thought that little insight was shown into why specific questions, investigations, or drugs were used. The basic understanding of the pathology and pharmacology lagged far behind the automated efficiency of following guidelines.

There certainly seems to be an evolving role for nurse practitioners, but future studies must clearly document the context in which patients are seen. There must also be some form of assessment of nurse practitioners’ consultation technique, similar to that in general practice.

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More studies of these nurses’ technique are needed

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More methodologically sound investigations are needed

Editor—Horrocks et al report higher levels of patient satisfaction among patients of nurse practitioners.1 Though this is important, it is unclear whether patient satisfaction is a valid measure of the quality of practice. Moreover, of the live trials presented that looked at patient satisfaction, three asked prospective patients whether they found it
acceptable to see a nurse practitioner rather than a doctor.1 2 Thus only those patients predisposed to accept nurse practitioners were included in the studies.

The authors also report that nurse practitioners undertook more investigations and had longer consultations than did doctors. The absolute difference of less than four minutes in consultation time is of questionable clinical importance and may reflect the practice setting used by the nurse practitioners. Whether the finding that nurse practitioners ordered more tests per patient is a marker of better or worse practice is unclear; it may inflate costs.

We believe that the authors’ assertions about the quality of care are not supported by the data presented. The authors state that nurse practitioners identified physical abnormalities more often than doctors did, without qualifying that the cited data are from 1975 and refer only to well-baby examinations.3 The observations that nurse practitioners made more complete records, communicated better, and were as proficient practitioners made more complete records, methodologically sound investigations. They propose that their review supports the increased involvement of nurse practitioners in primary care. We think that this conclusion is based on incomplete evidence that nurse practitioners ordered more tests per patient is a marker of better or worse practice—there is no evidence that these are complementary goals, not conflicting ones.4

The reaction of the Australian Medical Association is the same as that of organised medicine to funding in Britain and to budget holding in New Zealand almost a decade ago. In New Zealand, newly formed independent practitioner associations, similar in many respects to Australian divisions of general practice and the English primary care trusts, embarked on budget holding for pharmaceutical and pathology services.5 Outrage followed from the New Zealand Medical Association, Royal New Zealand College of General Practitioners, pathologists, and specialists. But visionary general practice leaders, with a strong focus on quality, saw the opportunities being offered and pressed on; now nearly 90% of all general practitioners are in some form of pharmaceutical budget management. The process is strongly driven by quality.

The main threat to the Australian divisions, though, is not the medical profession. As we have found in New Zealand, it is the bureaucrats who see the process as primarily a cost cutting strategy, not a quality strategy. Australian bureaucrats seem to support general practice, but the New Zealand experience will be relevant to Australia.6 Success in such a controversial strategy depends on clearly articulated, common goals, full collaboration between all parties; appreciable financial support; and reasonable expectations about what can be achieved.

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1 Zinn C. News roundup: Australia’s plan to reduce drug spending attacked by doctors. BMJ 2002;324:819-25. (20 April)

Oncologist who stood up to US insurance companies lost work

Entrow—From early reports of the success of high dose chemotherapy and autologous bone marrow infusion some oncologists, including me, recognised that the procedure was far from proved, dangerous, and expensive.1 I was a reviewer for several insurance companies at the time and rejected all requests for payment for both primary and metastatic disease. The companies welcomed the first few opinions, but when lawsuits started to be filed consultation requests decreased and then stopped. Yet other physicians were still being sent consultations.

I got the message. It was cheaper to grant payment than to fight in court and lose. But I could not change my opinion, because the evidence for effectiveness did not exist. I saw the lack of randomisation, the selected patients, the data from studies for other purposes—it was all there, and obvious.

I was near retirement and wanted to start a new career reviewing insurance cases for appropriateness of care, but as companies dropped me from their lists I could not obtain consultations. Fortunately, I was asked to head the oncology division at a teaching hospital. For the next six years until retirement I never referred a patient with breast cancer for high dose chemotherapy and autologous bone marrow infusion; the patients and I were all the better for it.

I recall the article on variations and attitudes of insurance companies in the New England Journal of Medicine, and was surprised that it was published.2 Things were getting out of hand, and as a labouring doctor I had little voice. I suppose I was one of the few people not surprised at the final outcome in 1999.

I now investigate anomalous claims of the complementary medicine system. Here again, pressure groups, deluded elected officials, and officials lacking wisdom and principle are mandating payment for even more implausible methods.

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