Evidence in practice — number 3: Cox 2 inhibitors

Clinical question — Are second generation Cox-2 inhibitors, such as lumiracoxib, a sensible and safe alternative to naproxen or ibuprofen in patients with osteoarthritis?

The evidence. Schnitzer TJ, Burmester GR, Mysler E, *et al*. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastro-intestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet* 2004; **364(9435):** 665-674.[1]

Farkouh ME, Kirshner H, Harrington RA, *et al*. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *Lancet* 2004; **364(9435):** 675-684.[2]

Background. In 2001 the National Institute of Clinical Excellence produced guidance on the use of the first generation Cox-2 inhibitors (celecoxib, rofecoxib, meloxicam, and etodolac) and suggested that these drugs could have a role in patients requiring a non-steroidal anti-inflammatory drug (NSAID) who may be at 'high risk' of developing gastrointestinal adverse effects. However, some concerns were expressed about the prescription of Cox-2s in patients with cardiovascular disease, particularly those on low dose aspirin. In the VIGOR trial refecoxib was associated with an increase in myocardial infarctions compared with naproxen.[3]

Study design and intervention. TARGET was a double-blind, double-dummy parallel group randomised, controlled trial. In such a design, each group of participants receives one of the active interventions and a placebo (in this case called a dummy) that looks and tastes the same as the alternative intervention. The study involved 18 325 patients across 29 countries and was 90% powered to detect a 50% reduction in definite or probable upper gastrointestinal ulcer complications in patients not taking low-dose aspirin. The study was divided into two similar sized sub-studies groups, which were stratified, before randomisation, by age and aspirin use. One sub-study compared lumiracoxib 400mg daily with ibuprofen 800mg three times daily; the second compared lumiracoxib 400mg daily with naproxen 500mg twice daily. To be included, patients had to be aged 50 years or older and have a clinical diagnosis of osteoarthritis of the hip, knee, or hand, or radiographic evidence of cervical or lumbar spine osteoarthritis. They also had to be in moderate pain and likely to require treatment for at least a year. Patients were excluded if they were taking gastroprotective drugs and/or had a history of gastointestinal ulceration (in the last 30 days), upper gastrointestinal bleeding (in the last year), or gastroduodenal perforation or obstruction. Patients were also excluded if they had a history of significant cardio-vascular disease encompassing myocardial infarction, stroke, coronary surgical inter-ventions, or new-onset angina (within the previous 6 months). However, 46% of the study population had hypertension, 20% dyslipidaemia, 8% diabetes, and 10% were current smokers. Of patients, 13% were classified as being at elevated cardiovascular risk (2% from Framingham risk scoring and 13% by virtue of a history of vascular disease). In terms of cotreatments, 24% were on aspirin, 12% on β-blockers and 26% on drugs affecting the renin-angiotensin system.

Outcomes and analysis. The primary endpoint was the cumulative 1-year incidence of definite or probable upper gastrointestinal ulcer complications (defined as clinically significant bleeding, perforation, or obstruction from erosive or ulcer disease).

In relation to cardiovascular outcomes, the investigators sought to identify all patients with confirmed or probable cardiovascular death, myocardial infarction, or stroke. Together these outcomes constituted the 'composite cardiovascular endpoint'.

Results. Significantly fewer patients on lumiracoxib (29 [0.32%]) developed upper gastrointestinal complications compared with 83 (0.91%) on ibuprofen/naproxen. The difference was also significantly in favour of lumiracoxib for the individual comparisons between drugs (that is, naproxen versus lumiracoxib $P = 0.0002$ and ibuprofen versus lumiracoxib $P = 0.0006$). These significant differences were maintained in the sub-group of patients not taking aspirin, but not for patients also taking aspirin.
No significant differences were recorded in the overall composite cardiovascular endpoint for lumiracoxib versus ibuprofen/naproxen. Focusing down on myocardial infarction it seems that, compared with lumiracoxib, fewer patients on naproxen sustained an infarction and more patients on ibuprofen infarcted. However, neither of these differences achieved statistical significance.

Commentary. Considering the TARGET trial in context, it is important to be aware that all NSAIDs (including Cox-2s) have side-effects and the decision on which variety to select should be reserved until after a decision to prescribe an NSAID-

References
1.Schnitzer TJ, Burmester GR, Mysler E, *et al*. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet* 2004; **364(9435):** 665-674.
2. Farkouh ME, Kirshner H, Harrington RA, *et al*. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *Lancet* 2004; **364(9435):** 675-684.
3. Bombardier C, Laine L, Reicin A, *et al*. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *New Engl J Med* 2000; **343(21):** 1520-1528.

type treatment has been made. Clearly, alternative management approaches will also require consideration, such as analgesics, physical treatments, and referral. From a population-based perspective, it is self-evident that over-enthusiastic prescription of an NSAID (including a Cox-2) with a lower level of gastrointestinal side effects could easily result in an increase in the overall numbers of adverse gastrointestinal events (and with more costly prescribing) in comparison with the more restricted prescribing of an NSAID with a higher level of gastrointestinal adverse effects.

Over the course of a year, patients may discontinue prescribed NSAIDs for a variety of reasons — this must be borne in mind when reviewing any trial of NSAID-type treatment. In TARGET, over a third of patients failed to complete the trial with significantly more of these 'lost' patients (248) being those treated with ibuprofen/ naproxen than with lumiracoxib. As the analysis focused on all patients randomised who received at least one dose of study drug, this places lumiracoxib at a slight statistical disadvantage compared with ibuprofen/ naproxen ... adding some further weight to the study findings.

The bottom line. In patients over the age of 50 years with osteoarthritis, lumiracoxib showed a three- to fourfold reduction in ulcer complications compared with naproxen/ ibuprofen without a significant increase in the rate of serious cardiovascular events.

Nick Summerton

Conversations remembered and imagined ...

One day I was on my rounds and taking with me an academic psychologist whom I wanted to impress. The patient had left a message for me to let myself in. It was a semi-detached house and I was probably talking to my colleague when we went in.

We were greeted by a lady, and sat down for a chat with her. I was thinking how informal and friendly this must seem to my visiting colleague. After a time in pleasant conversation, I introduced the topic of the problem about which I had called.

The patient continued to talk, equally relaxed. We must want to speak with Mrs S, next door, she said, and offered to show us the way.

Leone Ridsdale

flora medica theophrastus bombastus

From the journals, September and October 2004

***New Eng J Med* Vol 351 — 16 Sep–7 Oct**
1175 Talking about death to your dying child must be one of the hardest tasks a parent can face, but those who managed to do it never regretted it, as detailed in this study of Swedish parents bereaved of a child by cancer.
1285 Kidney function and heart function are closely inter-related, and patients with renal impairment tend to fare badly following myocardial infarction, according to data from the VALIANT study.
1306 The croup season is about to begin, and the strange bark of parainfluenza will be heard throughout the land. Spare a thought for the exhausted child, parents, and out-of-hours doctor, and prescribe a single dose of dexamethasone early in all but the mildest cases.
1493 Carotid endarterectomy has become quite a common procedure, made safer by the arrival of emboli-preventing filters. This trial added a stent in high-risk cases; the stented group did better.

***Lancet* Vol 364 — 18 Sep–9 Oct**
1039 Painstaking, old-fashioned bacteriology may have finally discovered the causal agent of Crohn's disease. A subspecies of Mycobacterium avium was grown from the blood of 50% of patients with active Crohn's, but none of the controls.
1045 When the first studies appeared showing the clear superiority of immediate revascularisation over thrombolysis for myocardial infarction, I wondered how the United Kingdom's system would ever cope. Fortunately, a Spanish study (GRACIA-1) has shown that immediate thrombolysis followed by revascularisation a day or two later works just as well. There is a GRACIA-2 trial to follow. *Muchas gracias*.
1141 We tend to think of intravenous antibiotics as more effective than oral, but this need not be true. This study shows equivalent outcomes even in severe childhood pneumonia.
1149 We are still seeking the magic cure for multiple sclerosis, and may be quite near. But it is not intravenous immunoglobulin, which did the same as placebo in this blinded RCT.
1219 Antioxidant vitamins seemed to increase overall mortality in this study of supplementation to prevent bowel cancer. Is nothing sacred?
1334 If you got drunk enough to end up in A&E, you might be forced to realise you had an alcohol problem. This useful London study proves just that — people in this situation are amenable to advice and change.

JAMA Vol 292 — 15 Sep–6 Oct
1326 A study that suggests that beta blockers reduce the risk of fractures.
1433 The 'Mediterranean diet' is a somewhat flexible concept in this study, which gives Brownie points for fruit, nuts, and vegetables, and finds that they do indeed improve life expectancy and reduce cardiovascular events.
1447 It is also a good idea to walk a lot, to prevent dementia as well as cardiovascular disease, in both men (this study) and women (see page 1454).
1573 A big placebo-controlled randomised trial (part of the Women's Health Initiative Study) proves that women taking conjugated equine oestrogen plus medroxyprogesterone have twice the risk of venous thrombosis.
1581 But exactly which ingredient was to blame? This case-control study finds some added risk from conjugated oestrogen taken alone, but none from esterified oestrogen taken alone. Combine either with progestagen, and the risk increases. So the HRT debate gets ever more complicated ... because you also need to factor in the risks for breast cancer and cardiovascular events.

Other Journals
Arch Intern Med **(164:** 1788) discusses the inadequacy of serum creatinine alone as an index of renal function, and shows that general practitioners can be taught to understand laboratory reports giving an estimated glomerular filtration rate (as used in the *New Engl J Med* study cited above). More from the Whitehall II Study on page 1873: the more poorly paid and frustrated a civil servant, the more likely s/he is to develop type 2 diabetes. For long-term success in treating insomnia, cognitive behavioural therapy (page 1888) may be best.
The Norfolk–EPIC study yields more intriguing associations in *Ann Intern Med* **(141:** 413), with glycosylated haemoglobin (HbA1c) levels predicting cardiovascular disease even in the 'normal' range.

Epidemiology **(15:** 573) analyses data from a large Swedish population study to find out what sort of everyday activity prevents myocardial infarction. Walking or standing at work, or strenuous housework are beneficial, so if you spend the day sitting in a consulting room, get the hoover out as soon as you reach home.

Plant of the Month: ***Mahonia gracilipes***
An elegant little shrub, if you can find it, with sprays of scented white flowers, dark red on the outside.