Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

ScriptSwitch™ Rapid Update 3 – December 2016

Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis

A randomised, double-blind, non-inferiority trial (PRECISION) in over 24,000 people with arthritis found that the cardiovascular (CV) risk of moderate celecoxib doses was no greater than that with moderate to high doses of naproxen or ibuprofen. Limitations of the study included a low rate of adherence (almost 70% stopped taking the drugs during the trial), those enrolled had a lower CV risk than anticipated and there was inconsistency in the doses studied. Overall, the findings do not change current practice and prescribers should continue to follow MHRA and NICE guidance where, if needed at all, NSAIDs (naproxen or low dose ibuprofen as first choice) should be used at the lowest effective dose for the shortest time possible, with gastroprotection cover and regular review and monitoring.

Reference: Nissen SE, Yeomans ND, Solomon DH, Luscher TF, Libby P et al for the PRECISION Trial Investigators. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med 2016; DOI: 10.1056/NEJMoa1611593

What do we know already?

- It is well-recognised that non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors, are associated with an increased risk of gastrointestinal (GI), CV and renal adverse events.
- Several European-wide reviews of the CV safety of NSAIDs have been undertaken in the last decade. The key findings are summarised in guidance from the MHRA in 2015, which are that diclofenac and COX-2 selective NSAIDs (e.g. celecoxib) have higher CV risks (for arterial thrombotic disease) than other non-selective NSAIDs. Naproxen and low-dose ibuprofen (up to 1,200mg per day) have the most favourable CV safety profiles of all the non-selective NSAIDs. A review of higher doses of ibuprofen (2,400mg/day or higher) found that they are associated with an increased CV risk, similar to that observed with COX-2 inhibitors and diclofenac. Both dose and duration of NSAID therapy may influence risk.
- There is less evidence available for the CV safety of other non-selective NSAIDs but it is possible that all may be associated with a small increased risk of thrombotic events.
- The NICE Clinical Knowledge Summary on NSAIDs advises that the decision to prescribe an NSAID should be based on an assessment of a person's individual risk factors, including any history of CV and GI illness. The lowest effective dose should be used for the shortest duration necessary to control symptoms. A person's need for symptomatic relief and response to treatment should be re-evaluated periodically.

What does this evidence add?

- This RCT found that the risk of CV events with celecoxib was no greater than that with naproxen or ibuprofen. The risk of GI adverse events was lower with celecoxib. However there were several limitations to the study:
  - The low rate of adherence (non-retention) across the three treatment groups, although results were consistent across the intention-to-treat and 'on-treatment' analyses.
  - The doses of NSAIDs used may not be comparable in terms of possible CV risk. The mean daily doses taken (±SD) were 209±37mg celecoxib, 852±103mg naproxen, 2045±246mg ibuprofen. The daily dose of celecoxib was restricted to 100mg bd in the 90% of patients who had OA. It cannot be assumed that the results of this study are transferrable to higher celecoxib doses.
  - Most participants (90%) had OA and relatively low CV risk (around 10% over 10 years) based on the incidence of CV events in the trial.
  - Aspirin use was stratified in randomisation but the trial did not address the effects/interaction between cardioprotective aspirin and NSAID therapy, or whether any possible interaction may have influenced the results.
- An editorial published in a separate journal discusses the limitations of this study concluding that there are so many problems with interpretation of the trial that it fails to inform clinical practice.

Study details

- PRECISION was a randomised, multicentre (926 centres in 13 countries), double-blind, non-inferiority trial. The focus of the study (the CV safety of celecoxib) was mandated by the USA Food and Drugs Administration after the withdrawal of rofecoxib for CV adverse effects in 2004.
- A total of 24,222 patients were randomized; 141 were excluded from the analysis (106 fraudulently enrolled, and 35 enrolled more than once), leaving 24,081 included in the analysis.
- 68.8% discontinued the study drug during the trial (adverse events 36.3%, patient decision 25.3%, 'other' 20%, insufficient clinical response 12.7%, lost to follow-up 4.2%, death 1.4%). A further 27.4% discontinued follow-up.

Participants:

- Adults aged 18 year or over (mean age ~63 years) requiring daily NSAID treatment for arthritis pain (RA [10%] or OA [90%]), and who had established CV disease (23%) or an increased risk of developing CV disease (77%).
- Approximately 64% were female. Mean BMI was ~32kg/m^2, ~35% had a history of diabetes, 78% hypertension, and 62% dyslipidaemia. Approximately 20% were current smokers.
- Patients taking 325mg aspirin or less were allowed to continue this treatment; ~46% were previous aspirin users.
- Exclusion criteria included: unstable angina, myocardial infarction (MI), CVA, CABG; planned revascularisation, uncontrolled hypertension or arrhythmia, NYHA III-IV heart failure or ejection fraction ≤35%, GI ulceration, treatment with aspirin >325mg/day, prednisolone >20mg/day, warfarin, or lithium; inflammatory bowel disease.

Intervention and comparison:

- Celecoxib 100mg twice daily (n=8,072), naproxen 375mg twice daily (n=7,969), or ibuprofen 600mg three times daily (n=8,040), with matching placebo. Doses could be increased for the treatment of RA to celecoxib 200mg bd, naproxen 500mg bd, or ibuprofen 800mg tds. For patients with OA increases in doses of naproxen and ibuprofen were permitted but not for celecoxib for regulatory dosing restrictions reasons. Mean daily doses taken (±SD) were 209±37mg celecoxib, 852±103mg naproxen, 2045±246mg ibuprofen.
- Naproxen was designated the primary comparator for the assessment of the non-inferiority of celecoxib.
- All patients received esomeprazole 20mg to 40mg daily for gastric protection (adherence to this not reported).
- Participants also received CV preventive management in accordance with local standards and guidelines.

Outcomes and results:

- Mean **duration of treatment and follow-up** were 20.3±16.0 and 34.1±13.4 months overall; celecoxib 20.8±16.0 and 34.2±13.4; naproxen 20.5±15.9 and 34.2±13.3, and ibuprofen 19.6±16.0 and 33.8±13.6.
- The **primary composite outcome** was time to first occurrence of an adverse event (death from CV causes, including haemorrhagic death; nonfatal MI, or nonfatal stroke). Event rates were: celecoxib 2.3%, naproxen 2.5%, ibuprofen 2.7% (hazard ratio [HR] celecoxib vs. naproxen 0.93, 95% confidence interval [CI] 0.76 to 1.13, p<0.001 for non-inferiority; HR celecoxib vs ibuprofen 0.85, 95% CI 0.70 to 1.04, p<0.001 for non-inferiority; HR ibuprofen vs naproxen 1.08, 95% CI 0.90 to 1.31, p=0.02 for non-inferiority. Analysis for the 'on-treatment' population (whilst taking the study drug and for 30 days afterwards) showed a similar pattern of results to the intention-to-treat analysis above i.e. non-inferiority of celecoxib compared with naproxen or ibuprofen.
- The **secondary composite outcome** (major adverse CV events) included the components of the primary outcome plus coronary revascularisation or hospitalisation for unstable angina or transient ischaemic attack. No significant differences were found between celecoxib and the other NSAIDs (HR celecoxib vs. naproxen 0.97, 95% CI, 0.83 to 1.12, p=0.64; HR celecoxib vs. ibuprofen 0.8, 95% CI 0.75 to 1.01, p=0.06).
- The event rate of **clinically significant GI events** was lower in patients treated with celecoxib than naproxen or ibuprofen (defined as symptomatic gastric or duodenal ulcer; gastroduodenal, small bowel or large bowel perforation or haemorrhage; gastric outlet obstruction, or acute GI haemorrhage of unknown origin). HR celecoxib vs. naproxen 0.71, 95% CI, 0.54 to 0.93, p=0.01; HR celecoxib vs ibuprofen 0.65, 95% CI 0.50 to 0.85, p=0.002; HR ibuprofen vs naproxen 1.08, 95% CI 0.85 to 1.39, p=0.53.
- **Clinically significant renal events** occurred in significantly fewer celecoxib-treated patients compared with ibuprofen (but not naproxen): HR celecoxib vs naproxen 0.79, 95% CI 0.56 to 1.12, p=0.19; HR celecoxib vs ibuprofen 0.61, 95% CI 0.44 to 0.85, p=0.0004.
- Changes in baseline **arthritis pain scores** did not reach the pre-defined clinically meaningful difference of >13.7mm on a 0-100mm visual analogue scale in any group. Improvements in scores ranged from 9.3 to 10.2.
- Other outcomes assessed included iron deficiency anaemia of GI origin, hospitalisation for heart failure or hypertension, and death from any cause. Results for these outcomes were selectively reported.

Level of evidence:
Level 1 (good quality patient-oriented evidence) according to the SORT criteria.

Study funding:
The study was funded by Pfizer.