

Trelle S, Reichenbach S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086.

Design: Meta-analysis of randomized clinical trials

PICOS:

- **Patients:** patients treated with NSAIDs for any indication other than cancer
- **Interventions:** Any NSAID
- **Comparison:** Any other NSAID, acetaminophen, or placebo
- **Outcomes:** primary outcome was fatal or nonfatal MI; secondary outcomes were fatal or non-fatal stroke, cardiovascular death (any death due to MI, low output heart failure, fatal arrhythmia, pulmonary embolism, or stroke); death from any cause, death of unknown cause, and the Anti-platelet Trialists' Collaboration (APTC) composite outcome of non-fatal MI, non-fatal stroke, or cardiovascular death
- **Studies:** Randomized clinical trials with at least 2 treatment arms and at least 100 patient years of follow-up; for an NSAID to be included in the analysis, at least 10 patients allocated to that NSAID had to have had an MI in all trials combined; trials with zero events in both treatment groups were excluded

Search strategy and study selection:

- Databases included MEDLINE, EMBASE, and CENTRAL through December 2008, and updated in July 2009
- In addition, searches were done of proceedings of major rheumatological conferences, study registries, and the FDA website; manual searches of reference lists and the Science Citation Index were also used
- Google was used to identify additional reports and information sources

Results:

- 31 trials evaluating 7 NSAIDs were included in the analyses
- Trial results were pooled using network meta-analysis, which can combine direct (head-to-head) and indirect (drug A to placebo and drug B to placebo to derive a comparison of drug A to drug B) comparisons
- A Bayesian model was used, which derives a distribution of NSAID-associated risk ratios from incorporating prior knowledge and new study data by means of linking the prior and new data using a mathematical likelihood function; instead of deriving 95% confidence intervals, the function derives 95% credibility intervals
- A rate ratio of 1.30 (30% increased risk) was considered the cutoff point for a clinically important risk increase
- Celecoxib was the most investigated (15 trials) and ibuprofen the least investigated (2 trials)
- Three NSAIDs in the analysis (rofecoxib, etoricoxib, and lumiracoxib) are not licensed for use in the USA by the FDA
- For fatal and non-fatal MI, rate ratios greater than 1.30 were found for ibuprofen (1.61, 95% credibility interval 0.50 to 5.77) and celecoxib (1.35;

0.71 to 2.72); for naproxen and diclofenac, evidence was lacking for an increased risk of MI

- For stroke, naproxen, ibuprofen, and diclofenac had risk ratios of 1.3 or greater, but the 95% credibility intervals for naproxen included the value of 1.00 (no difference in risk), and for ibuprofen (RR= 3.36, 95% CI, 1.00 to 11.6) and diclofenac (RR=2.86, 95% CI, 1.09 to 8.36) the credibility intervals were wide
- For stroke, celecoxib did not show an association (RR=1.12, 95% CI, 0.60 to 2.06)
- For cardiovascular death, naproxen (RR=0.98, 95% CI, 0.41 to 2.37) was not associated with increases risk; ibuprofen, diclofenac, and celecoxib had RR of greater than 1.3, but only diclofenac (RR=3.98, 95% CI, 1.48 to 12.70) excluded a RR of 1.0
- For death from all causes, every NSAID had an estimated RR greater than 1.0, but only rofecoxib had an RR whose 95% CI excluded 1.0 (RR=1.56, 1.04 to 2.23)
- The APTC composite outcome had estimated RR greater than 1.0 for all drugs, but only ibuprofen (RR=2.26, 1.11 to 4.89) was greater than 1.30 and had a 95% CI which excluded 1.0

Author's conclusions:

- Naproxen seemed the least harmful of the NSAIDs analyzed in the meta-analysis
- Several other drugs (ibuprofen and diclofenac) are associated with a 30% risk increase for several cardiovascular outcomes
- The event rates in the trials were low, creating imprecision (wide credibility intervals) in the risk estimates
- Absence of statistically robust evidence of harm should not be construed as evidence that a particular drug is safe
- The event rates in the included trials were lower than are expected in routine practice, where patients are typically at moderate to high risk for cardiovascular events; therefore, the harms in routine practice may be greater than in the meta-analyses
- Large scale randomized trials are not available for some commonly used NSAIDs, which is a limitation of the study
- Several trials lacked independent adjudication of events, which is a potential source of bias; however, an analysis which excluded such trials supported the results of the main analysis
- None of the trials looked at intermittent NSAID use; the drugs were used for at least one year in most of the trials
- There was no evidence of a relationship between the selectivity of the drugs for cox-2 and their cardiovascular risk profile; this contrasts with previous claims that this relationship existed
- The results from these randomized trials is consistent with previous notions of NSAID relative toxicity from observational studies

- The choice of drug for chronic musculoskeletal pain is difficult; alternatives to NSAIDs, such as acetaminophen or opioids, have potential hepatotoxicity or habit-forming potential

Comments:

- As the authors point out, the advantage of analyzing randomized trials is that, unlike observational studies, they are less likely to suffer from confounding by indication
- Bayesian meta-analysis was done with “minimally informative prior distributions;” this means that the NSAIDs studied were all considered to have equal safety profiles at the outset (prior information about possible differences in safety from other sources was not used to calculate the posterior probabilities of risk)
- It is possible that if such prior information had been used, the posterior probabilities would have been more in favor of naproxen as compared to diclofenac, celecoxib, and ibuprofen

Assessment: High quality for evidence that naproxen has a more favorable cardiovascular profile than other NSAIDs when used over a long period for chronic pain