National Essential Medicine List Medication Review Process
Adult Hospital Level
Component: Pain

Adverse effects of NSAIDS

Observational data[1],[2] has pointed to differences in the incidence of cardiovascular adverse events associated with various non-steroidal anti-inflammatory agents (NSAIDs). In particular, there are concerns about the risks associated with diclophenac relative to ibuprofen and naproxen. In a pair-wise comparison, the relative risk ratio for naproxen was lower than for ibuprofen (RRR = 0.92, 99% CI 0.87 to 0.99). Diclophenac versus ibuprofen: 1.13 (99% CI 1.03 to 1.24.)

Table 4. Selected pair-wise comparisons of individual drugs.

Drug Tested	Reference Drug in the Comparison				
	Rofecoxib	Diclofenac	Ibuprofen	Naproxen	Celecoxib
Etoricoxib	1.29 (0.86, 1.93), $n=3$ studies	1.36 (0.89, 2.09), $n=3$ studies	**1.68** (1.14, 2.49), $n=3$ studies	**1.75** (1.16, 2.64), $n=3$ studies	
Etodolac		0.95 (0.78, 1.16), $n=5$ studies	1.04 (0.88, 1.24), $n=7$ studies	1.10 (0.96, 1.26), $n=7$ studies	
Diclofenac	1.0 (0.89, 1.12), $n=18$ studies		**1.13** (1.03, 1.24), $n=27$ studies	**1.22** (1.11, 1.35), $n=25$ studies	**1.15** (1.02, 1.30), $n=19$ studies
Naproxen			**0.92** (0.87, 0.99), $n=32$ studies	—	0.96 (0.81, 1.13), $n=23$ studies
Meloxicam				**1.11** (1.0, 1.23), $n=6$ studies	
Indomethacin				**1.23** (1.10, 1.39), $n=15$ studies	

Values are pooled RRRs and 99% CIs. Bold indicates significant difference at $p<0.0033$ (the Bonferroni-adjusted threshold p-value; $n=15$ comparisons; alpha = 0.05).
doi:10.1371/journal.pmed.1001098.t004

Table 5. Results of sensitivity analyses on selected pair-wise comparisons.

Comparison	RRR	RR_{CD}	P_{C1}	P_{C0}	RRR_{adj}	Percent Bias
Etoricoxib versus naproxen	1.75	11.00	0.25	0.10	1.00	75.00
Etoricoxib versus ibuprofen	1.68	9.40	0.25	0.10	1.00	68.48
Indomethacin versus naproxen	1.23	2.80	0.25	0.10	1.00	22.88
Diclofenac versus naproxen	1.22	2.70	0.25	0.10	1.00	21.79
Diclofenac versus celecoxib	1.15	2.10	0.25	0.10	1.00	14.86
Diclofenac versus ibuprofen	1.13	1.95	0.25	0.10	1.00	13.01
Naproxen versus ibuprofen	0.92	0.50	0.25	0.10	1.00	−7.89

RR_{CD} is the association between confounder and disease outcome. P_{C1} is the prevalence of confounder in the exposed. P_{C0} is the prevalence of confounder in the unexposed. RRR_{adj} is the "true", or fully adjusted, RRR. Percent bias is the percentage change to the RRR that would be introduced by a hypothetical confounding variable under the assumptions in the table.
doi:10.1371/journal.pmed.1001098.t005

While these effects are clearly discernible, the problems of biases associated with studies of this nature are well known and always difficult to quantify.

[1] McGettigan P, Henry D (2011) Cardiovascular Risk with Non-Steroidal Anti-Inflammatory Drugs: Systematic Review of Population-Based Controlled Observational Studies. PLoS Med 8(9): e1001098. doi:10.1371/journal.pmed.1001098

[2] McGettigan P, Henry D (2013) Use of nonsteroidal anti-inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle-, and high-income countries. PLoS Med 10: e1001388. doi:10.1371/journal.pmed.1001388

An individual patient meta-analysis[3] assists with this by pooling larger numbers of patients from RCTs, but still suffers from the external validity issues related to careful patient selection. The results of this are best seen in this figure from the report:

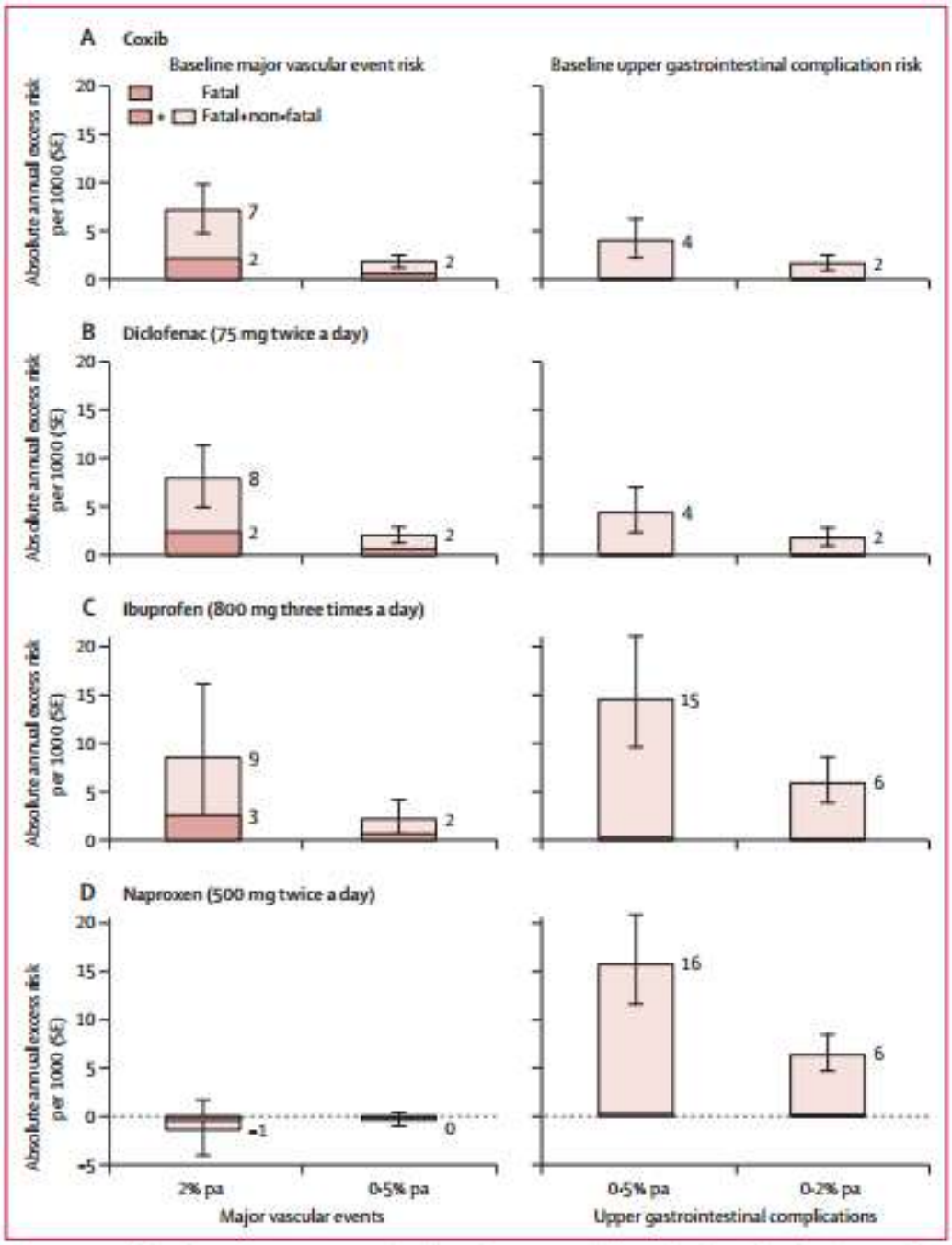

Figure 5: **Annual absolute effects per 1000 of coxibs and tNSAIDs at different baseline risks of major vascular events and upper gastrointestinal complications**

For each category of drug (coxib, diclofenac, ibuprofen, and naproxen), the predicted annual absolute risks of major vascular events (±1 SE) are shown (left) for patients with predicted risk of 2·0% or 0·5% per annum of a major vascular event. For comparison, predicted annual absolute risks of upper gastrointestinal complications (±1 SE) are shown for patients with predicted risks of 0·5% or 0·2% per annum (right). Absolute annual risks for

[3] Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-infl ammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet2013; 382: 769–79.

Although this figure illustrates the balance between CVS and vascular events, it is still not clear what the actual patient impact of a vascular event versus a GIT complication would be; short of translating this into QALYs, this remains difficult to balance.

A further issue concerns duration of therapy; although not formally addressed, it is likely that the CVS effects of short term use are much lower than pertaining to long duration use in high risk patients (e.g. those with rheumatoid arthritis or osteoarthritis.)

Conclusion: It is clear that there are measurable differences in side-effect profiles of NSIADs; whether these are sufficiently large to justify formulary changes is less certain.