

Cardiovascular Risk of COX-2 Selective and Nonselective NSAIDs

Quick take:

- A recent systematic review of observational studies found diclofenac is associated with cardiovascular (CV) risk similar to that of rofecoxib.¹ Diclofenac is a relatively selective cyclooxygenase 2(COX-2) nonsteroidal anti-inflammatory drug (NSAID)
- The results of this review indicate that naproxen appears to carry the safest CV risk profile.

Table 1: Cardiovascular relative risk of cyclooxygenase-2 selective and nonselective nonsteroidal anti-inflammatory drugs*

Drug	# Studies	Relative Risk† (RR)	95 % Confidence Interval
Diclofenac	9	1.40	1.16-1.70
Rofecoxib	11	1.35	1.15-1.59
Meloxicam	3	1.25	1.00-1.55
Indomethacin	6	1.30	1.07-1.60
Ibuprofen	16	1.07	0.97-1.18
Celecoxib	11	1.06	0.90-1.23
Piroxicam	4	1.06	0.70-1.59
Naproxen	15	0.97	0.87-1.07

*Data adapted from McGettigan P, Henry D. JAMA 2006 Sept; 296¹

† Relative risk of serious cardiovascular event; most studies evaluated the outcome of acute myocardial infarction

Key Considerations:

- A weakness of this systematic review is the fact that conclusions are based on observational data.
- The results are reported as relative risk(RR). RR is just that –relative; results can appear much more dramatic. Consider absolute risk (AR) and numbers needed to harm (NNH) of some of the major trials:

Table 2: CV relative risk (RR), absolute risk(AR) and number needed to harm(NNH) of selected trials

Study	Treatment groups	RR	AR(%)	NNH
APPROVE ²	Rofecoxib vs. placebo	Rofecoxib 1.8	1.6	63 over ≈ 2.4 years
CLASS ³	Celecoxib vs NSAID†	NSAID 1.1	0.1	1000 over ≈ 6 months
VIGOR ⁴	Rofecoxib vs. naproxen	Rofecoxib 4	0.3	333 over ≈ 9 months

† NSAID = ibuprofen or diclofenac

- A recent meta-analysis of the CV risk associated with cyclooxygenase-2 (COX-2) selective and nonselective nonsteroidal anti-inflammatory drugs found an increased risk with celecoxib in daily doses of 400mg or above.⁵ Four recent studies have found increased CV risk with celecoxib⁵⁻⁸; further study is required.
- One study found an increased risk of death with ibuprofen in daily doses greater than 1200mg; an increased rate of reinfarction was found regardless of dose.⁷

What does this mean for the patient?

Currently it appears naproxen may have a better CV safety profile than other NSAIDs. Perhaps the bigger implication of this and previous studies is that we still have a lot to learn regarding CV safety of the NSAIDs. Therefore, a shift of focus from the NSAID to the patient may be prudent. Consider the following for patients on NSAIDs:

- Does the patient indeed require NSAID therapy?
- What is the patient’s baseline CV risk? Is the CV risk outweighed by the benefit of the NSAID?
- For a patient currently on NSAID therapy, have the need for therapy and/or CV risk changed?

Until more is known, all NSAIDs should be used with caution, especially among patients with several CV risk factors.

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