Review: Nonselective nonsteroidal antiinflammatory drugs do not increase risk for cardiovascular events

Salpeter SR, Gregor P, Ormiston TM, et al. Meta-analysis: cardiovascular events associated with nonsteroidal anti-inflammatory drugs. Am J Med. 2006;119:552-9.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Cardiology ★★★★★☆☆ Neurology ★★★★☆☆☆ Rheumatology ★★★★★★☆

QUESTIONS

In patients with joint disease or Alzheimer disease, does use of nonselective nonsteroidal antiinflammatory drugs (NSAIDs) increase the risk for cardiovascular events? Does the effect differ between naproxen and other NSAIDs?

METHODS

Data sources: MEDLINE, CINAHL, EMBASE/Excerpta Medica, Cochrane Library databases (July 2005), U.S. Food and Drug Administration files, reference lists, and experts in the field.

Study selection and assessment: Randomized placebo-controlled trials (RCTs) of NSAIDs in joint disease or Alzheimer disease of ≥ 6 weeks duration that reported ≥ 1 outcome of interest. 9 RCTs in joint disease (n = 5645, mean age 55 y, median follow-up 0.4 y, range 0.1 to 2 y) and 4 RCTs in Alzheimer disease (n = 2073, mean age 75 y, median follow-up 0.8 y, range 0.1 to 3 y) met the selection criteria. The NSAIDs studied were naproxen in 8 RCTs; nabumetone in 2 RCTs; and indomethacin, ibuprofen, and diclofenac in 1 RCT each. Methodological quality was based on randomization, blinding, withdrawals, and intention-to-treat analysis.

Outcomes: Cardiovascular events (myocardial infarction, cerebrovascular accident, or death from any cause).

MAIN RESULTS

NSAIDs and placebo did not differ for cardiovascular events for all RCTs combined or in the analyses subdivided by indication (Table). Effect did not differ between naproxen and nonnaproxen agents in either Alzheimer disease or joint disease trials (Table).

CONCLUSIONS

In patients with joint disease or Alzheimer disease, nonselective nonsteroidal antiinflammatory drugs (NSAIDs) do not increasethe risk for cardiovascular events or death more than does placebo. There is no evidence that the effect of naproxen on cardiovascular risk differs from that of other NSAIDs.

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Risk for cardiovascular events or death with nonsteroidal antiinflammatory drugs (NSAIDs) vs placebo at 0.1 to 3 years*

Type of trial	Type of NSAID	Number of trials (n)	Weighted event rates		RRI (95% CI)	NNH
			NSAIDs	Placebo		
All	All	13 (7718)	1.1%	0.8%	28% (–19 to 104)	Not significant
Alzheimer disease	All	4 (2073)	3.4%	2.2%	57% (–7 to 164)	Not significant
Naproxen	2 (1988)	3.3%	2.1%	53% (–11 to 164)	Not significant	
Nonnaproxen	2 (85)	5.3%	2.6%	106% (–68 to 1233)	Not significant	
					RRR (CI)	NNT
Joint disease	All	9 (5645)	0.17%	0.28%	41% (–65 to 79)	Not significant
Naproxen	6 (4149)	0.15%	0.22%	31% (–145 to 81)	Not significant	
Nonnaproxen	3 (1496)	0.19%	0.42%	56% (–151 to 92)	Not significant	

*Abbreviations defined in Glossary; weighted event rates, RRI, RRR, NNH, NNT, and CI calculated from data in article using a random-effects model.

COMMENTARY

The recognition that such traditional "nonselective" NSAIDs as ibuprofen, diclofenac, and others exhibit varying effects on the cyclooxygenase 2 (COX-2) isoform has raised legitimate questions about whether these drugs might increase cardiovascular risk in a manner similar to the COX-2–selective NSAIDs.

Observational studies of this issue have come to differing conclusions but are fraught with methodological challenges that make subtle drug effects difficult to detect and causality even harder to assign. RCTs are limited by their tendency to exclude patients at increased risk for toxicity and by their lack of sufficient power to detect infrequent adverse events. The pooling of individual trials, as done by Salpeter and colleagues, is a logical way to try to overcome this limitation.

What can we learn from the results of this meta-analysis? Regrettably, not very much. The included trials were mostly small and of short duration, and the total number of events was low despite pooling, making it virtually impossible to draw meaningful inferences about individual NSAIDs. Furthermore, the overall results were largely driven by the Alzheimer's Disease Anti-inflammatory Prevention Trial (1). This fact raises legitimate questions about the generalizability, and perhaps even the novelty, of the conclusions of the meta-analysis itself. A much larger meta-analysis of published and unpublished RCTs (2) and another of observational studies (3) suggest that various nonselective NSAIDs confer different degrees of cardiovascular risk. These observations are statistically and methodologically robust and pharmacologically intuitive.

In summary, despite the findings of Salpeter and colleagues, converging lines of evidence now suggest that many NSAIDs can modestly increase the risk for cardiovascular events. Other than the timeless advice of limiting the dose and duration of NSAID therapy, based on current evidence, we suggest that naproxen may be the safest NSAID for patients at increased risk for cardiovascular events.

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References

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3. **McGettigan P, Henry D.** JAMA. 2006;296:1633-44.