Review: Selective COX-2 inhibitors increase vascular events more than placebo and naproxen, but not more than other NSAIDs

Kearney PM, Baigent C, Godwin J, et al. **Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials.** BMJ. 2006;332:1302-8.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Hemato/Thrombo ★★★★☆☆☆ Rheumatology ★★★★★★☆

QUESTION

Do selective cyclooxygenase-2 (COX-2) inhibitors increase risk for serious vascular events more than placebo or traditional nonsteroidal antiinflammatory drugs (NSAIDs)?

METHODS

Data sources: MEDLINE and EMBASE/Excerpta Medica (1966 to April 2005), U.S. Food and Drug Administration Web site, and drug manufacturers.

Study selection and assessment: Randomized controlled trials (RCTs) ≥ 4 weeks in duration that compared a selective COX-2 inhibitor with placebo or a traditional NSAID. 138 RCTs (n = 145 373) met the selection criteria. Investigators and manufacturers provided details on the number of vascular events and person-time at risk.

Outcomes: Myocardial infarction (MI), stroke, and vascular death, and a composite endpoint of all vascular events.

MAIN RESULTS

Selective COX-2 inhibitors increased risk for all vascular events and MI, but not stroke or vascular death, more than placebo and naproxen (Table). COX-2 inhibitors and nonnaproxen NSAIDs did not differ for all vascular events, MI, or vascular death; risk for stroke was lower with COX-2 inhibitors (Table). When data from indirect and direct comparisons were used, the rate ratios for all vascular events of traditional NSAIDs compared with placebo were 0.9 (95% CI 0.7 to 1.3) for naproxen, 1.5 (CI 1.0 to 2.4) for ibuprofen, and 1.6 (CI 1.1 to 2.4) for diclofenac.

CONCLUSION

Selective cyclooxygenase-2 inhibitors increase risk for serious vascular events more than placebo and naproxen, but not more than nonnaproxen traditional nonsteroidal antiinflammatory drugs.

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Risk for vascular events with selective cyclooxygenase-2 (COX-2) inhibitors vs placebo, naproxen, or other traditional nonsteroidal antiinflammatory drugs (NSAIDs) at 4 to 208 weeks*

Comparisons	Number of trials (person-y)	Outcomes	Weighted event rates per person-y	RRI (95% CI)	NNH (CI)
COX-2 vs placebo	121 (31 129)	Myocardial infarction	0.6% vs 0.3%	86% (33 to 159)	351 (190 to 913)
		All vascular events	1.3% vs 0.9%	42% (13 to 78)	269 (145 to 869)
		Stroke	0.4% vs 0.4%	2% (–29 to 47)	Not significant
		Vascular death	0.4% vs 0.2%	49% (–3 to 129)	Not significant
COX-2 vs naproxen	42 (27 338)	Myocardial infarction	0.6% vs 0.3%	104% (41 to 196)	353 (187 to 894)
		All vascular events	1.2% vs 0.7%	57% (21 to 103)	238 (132 to 646)
		Stroke	0.4% vs 0.4%	10% (–27 to 65)	Not significant
		Vascular death	0.3% vs 0.2%	47% (–10 to 140)	Not significant
COX-2 vs other NSAIDs	51 (29 247)	Myocardial infarction	0.5% vs 0.4%	20% (–15 to 68)	Not significant
				RRR (CI)	NNT (CI)
		All vascular events	0.9% vs 1.1%	12% (–12 to 31)	Not significant
		Stroke	0.2% vs 0.4%	38% (5 to 59)	663 (427 to 5038)
		Vascular death	0.2% vs 0.3%	33% (–6 to 57)	Not significant

*Abbreviations defined in Glossary; weighted event rates, RRI, RRR, NNH, NNT, and CI calculated from control rates and rate ratios in article using the Peto 1-step approximation method.

COMMENTARY

The review by Kearney and colleagues is the most extensive and methodologically sound systematic review of the cardiovascular effects of selective COX-2 inhibitors yet published. Not surprisingly, it found that COX-2 inhibitors increase risk for "all vascular events" (regardless of whether patients were taking aspirin at the same time), mainly because of an increase in the incidence of MI, but it did not find evidence of any difference among the individual COX-2 inhibitors. An even more important contribution of this review is that it shows that traditional NSAIDs, with the exception of aspirin and possibly naproxen, cause an increase in vascular events that seems similar to that of COX-2 inhibitors.

What are the clinical implications of these findings? They reinforce that when both traditional and selective NSAIDs are prescribed, 3 factors must be considered—the likelihood that the patient will benefit symptomatically compared with more conservative measures, the patient's chance of a serious gastrointestinal complication from NSAID treatment (not evaluated in this review), and the patient's risk factors for cardiovascular disease. All patients should be fully informed about these factors and encouraged to take the drug for the shortest possible period.

A number of clinically important questions about the cardiovascular effects of selective COX-2 inhibitors could not be answered by the review by Kearney and colleagues because of the (thankfully!) low prevalence of vascular events. These questions include the risk for vascular events with low versus high drug doses and how soon after the drugs are started that cardiovascular risk increases. Studies of intravenous administration of selective COX-2 inhibitors in patients after coronary artery bypass surgery have shown increased risk for vascular events within days (1), suggesting that the risk with oral medications may also increase rapidly. An individual-patient meta-analysis planned by the same authors, which may address some of these issues, is anticipated with interest.

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Reference

1. **Nussmeier NA, Whelton AA, Brown MT, et al.** N Engl J Med. 2005; 352:1081-91.