Review: Risk for cardiovascular events is increased with rofecoxib, diclofenac, and indomethacin, but not celecoxib

McGettigan P, Henry D. **Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2.** JAMA. 2006;296:1633-44.

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

QUESTION

What are the risks for cardiovascular (CV) events in patients using cyclooxygenase 2 (COX-2) inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs)?

METHODS

Data sources: MEDLINE and EMBASE/Excerpta Medica (1985 to January 2006), Cochrane Library, Google Scholar, epidemiological research Web sites, abstracts of scientific meetings, and bibliographies of relevant studies.

Study selection and assessment: Case-control or cohort studies that reported CV risks associated with use of selective COX-2 inhibitors and conventional NSAIDs with nonuse or remote exposure as the reference exposure. 17 case-control (8 nested) and 6 cohort studies (n = 1 659 288) met the selection criteria. Methodological quality of the individual studies was assessed with the Newcastle-Ottawa Scale. All studies scored from 7 to 8 out of 9 points.

Outcomes: CV events (included fatal or nonfatal acute myocardial infarction, CV death, coronary heart disease death, sudden cardiac death, unstable angina pectoris, thromboembolic CV event, and ischemic stroke).

MAIN RESULTS

COX-2 inhibitors studied were celecoxib (11 studies), rofecoxib (11 studies), and meloxicam (3 studies); NSAIDs studied were naproxen (15 studies), diclofenac (9 studies), ibuprofen (13 studies), indomethacin (6 studies), and piroxicam (4 studies). Point estimates were pooled using a random-effects model. Results are in the Table. Among COX-2 inhibitors, an increase in CV events was seen with rofecoxib, particularly at doses > 25 mg/d. Celecoxib, at the doses used in these studies, did not increase risk for CV events. Among NSAIDs, case-control studies showed increased risk with diclofenac and indomethacin.

CONCLUSIONS

A dose-related increased risk for cardiovascular events exists with rofecoxib. An increased risk could not be excluded with doses of celecoxib > 200 mg/d. Among nonsteroidal anti-inflammatory drugs, diclofenac and indomethacin had risks comparable to that seen with rofecoxib.

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Risk for cardiovascular events with cyclooxygenase 2 inhibitors and nonsteroidal antiinflammatory drugs*

Drug	Case-control studies		Cohort studies		Case-control and cohort combined RR (CI)
	Number of studies	RR (95% CI)	Number of studies	RR (CI)	
Celecoxib	8	1.01 (0.90 to 1.13)†	3	1.22 (0.69 to 2.16)†	1.06 (0.91 to 1.23)†
Rofecoxib	9	1.31 (1.18 to 1.46)	2	1.53 (0.68 to 3.44)†	1.35 (1.15 to 1.59)
Rofecoxib > 25 mg/d	4	1.89 (1.43 to 2.51)	2	2.46 (1.29 to 4.71)	2.19 (1.64 to 2.91)
Meloxicam	3	1.25 (1.00 to 1.55)	0	-	1.25 (1.00 to 1.55)
Naproxen	12	0.96 (0.84 to 1.10)†	3	0.94 (0.85 to 1.04)†	0.97 (0.87 to 1.07)†
Diclofenac	7	1.36 (1.21 to 1.54)	2	1.36 (0.51 to 3.65)†	1.40 (1.16 to 1.70)
Ibuprofen	11	1.06 (0.95 to 1.18)†	5	1.12 (0.90 to 1.38)†	1.07 (0.97 to 1.18)†
Indomethacin	6	1.30 (1.07 to 1.60)	0	-	1.30 (1.07 to 1.60)
Piroxicam	4	1.06 (0.70 to 1.59)†	0	-	1.06 (0.70 to 1.59)†

*RR = relative risk; CI defined in Glossary. A random-effects model was used.
†Not significant.

COMMENTARY

Ever since the sudden withdrawal of rofecoxib in 2004, the cardiovascular safety of all COX-2 selective NSAIDs has been called into question, and even older nonselective NSAIDs are being drawn into the fray. We urgently need to know which, if any, of these drugs is safe to use.

The review by McGettigan and Henry seems to provide some reasonably clear answers, implying that rofecoxib is definitely out (at any dose), and that low-dose celecoxib is possibly safe, as are naproxen and ibuprofen. However, notwithstanding the use of a quality yardstick for observational studies, these conclusions are based entirely on observational studies that are intrinsically weaker than randomized controlled trials. Observational studies are relied on heavily in drug safety research, but this is mainly because sufficient numbers of large randomized trials are often not available. This is not particularly true for COX-2 inhibitors.

Kearney and colleagues (1) did a meta-analysis of COX-2 inhibitor trials looking specifically at cardiovascular risk. They concluded that there is an increased cardiovascular risk for all COX-2 inhibitors and, indeed, for many of the older NSAIDs too. McGettigan and Henry point out that a dose-response relation was noted for celecoxib, with lower doses seeming to be safer in the Kearney and colleagues review. The emerging picture, as Sánchez-Delgano highlights (2), is consistent with the risks and benefits of NSAIDs being more related to dose and potency than to COX selectivity. The debate about whether cardiovascular risk is or is not related to COX-2 selectivity may be academic. All NSAIDs are problematic, with cardiovascular risk likely increasing with potency, dose, and duration of treatment, with the possible exception of naproxen (1).

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References

1. **Kearney PM, Baigent C, Godwin J, et al.** BMJ. 2006;332:1302-8.
2. **Sánchez-Delgado EJ.** BMJ. 2006;332:1451-2.