Celecoxib for colorectal adenomas increased CV events

Solomon SD, McMurray JJ, Pfeffer MA, *et al*. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;**352**:1071–80

Clinical impact ratings GP/FP/Primary care ★★★★★★☆ IM/Ambulatory care ★★★★★★☆ Oncology ★★★★★☆☆ Gastroenterology ★★★★★☆☆ Cardiology ★★★★★☆☆

Q In patients with a history of colorectal neoplasia who are at risk of recurrent adenomatous polyps, how safe is celecoxib with respect to cardiovascular (CV) events?

METHODS

Design: randomised placebo controlled trial (Adenoma Prevention with Celecoxib [APC] Study).

Allocation: unclear allocation concealment.*

Blinding: blinded (clinicians, patients, judicial assessors of outcomes, and monitoring committee).*

Follow up period: 2.8–3.1 years.

Setting: 91 sites in the US, Canada, Australia, and the UK.

Patients: 2035 patients 32–88 years of age (mean age 60y, 68% men) who had had endoscopic polypectomy to remove colorectal adenomas.

Intervention: twice daily celecoxib, 200 mg (n = 685); celecoxib, 400 mg (n = 671); or placebo (n = 679). Patients were stratified by centre and use or non-use of aspirin for CV prophylaxis.

Outcomes: composite endpoint of death from CV causes, myocardial infarction (MI), stroke, or heart failure. Secondary composite endpoints included the addition of angina and need for a CV procedure.

Patient follow up: all patients completed at least 2.8–3.1 years of follow up (intention to treat analysis).

*See glossary.

MAIN RESULTS

The trial was stopped early with a 77% completion rate. 800 mg/day of celecoxib led to a greater risk of the CV composite endpoint than did placebo (table). The risk decreased slightly when angina (hazard ratio [HR] 2.3, 95% CI 1.1 to 4.7) and need for a CV procedure (HR 1.9, CI 1.0 to 3.3) were added to the composite endpoint. Compared with placebo, 800 mg/day of celecoxib increased CV death or non-fatal MI (HR 3.8, CI 1.3 to 11.5) and CV death, non-fatal MI, or stroke (HR 3.4, CI 1.4 to 8.5), regardless of whether patients took low doses of aspirin. Risks of CV events were increased with 400 mg/day of celecoxib, but only reached borderline statistical significance for CV death or non-fatal MI (HR 3.0, CI 1.0 to 9.3) and CV death, non-fatal MI, or stroke (HR 2.5, CI 1.0 to 6.4).

CONCLUSION

In patients with a history of colorectal neoplasia who were at risk of recurrent adenomatous polyps, celecoxib led to a dose related increase in cardiovascular events.

Abstract and commentary also appear in ACP Journal Club.

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Other more meaningful questions arise naturally from these 2 studies. Why did it take so long to clearly establish this association? Part of the answer rests in the high background incidence and "expectedness" of CV events, especially in older patients treated with COX 2 inhibitors, and the complex "web of causation" that makes it virtually impossible to definitively attribute even a single CV event to these drugs. Another explanation stems from the challenges of observational epidemiology. Foremost among these is the fact that patients treated with COX 2 inhibitors were often older and "sicker" than patients given traditional NSAIDs, making it difficult to ferret out the modifying influences of bias and confounding on CV outcomes.

A more difficult and sensitive question relates to the toll exacted by COX 2 inhibitors at the population level. The true magnitude is unknowable, but given the popularity of these drugs and the absolute risk estimates of Bresalier *et al* and Solomon *et al* (notably, estimates derived from relatively "well" patients), it is likely that COX 2 inhibitors have caused many excess deaths from MI, heart failure, and stroke.

While science and the courts look into the rearview mirror, clinicians and patients wonder how best to use these drugs in the future. Rofecoxib has been removed from the market, but celecoxib and other COX 2 inhibitors remain available. Although a considerable body of evidence suggests that celecoxib may be safer than rofecoxib, it is clearly not risk free. In light of celecoxib's mediocre track record as an anti-inflammatory, it seems reasonable to ask whether it or COX 2 inhibitors should be used at all. Clinicians may have differing opinions on this. Recognising that no drug is completely free of risk, it seems sensible to restrict the use of COX 2 inhibitors to a small minority of patients without overt vascular disease who require an anti-inflammatory but are at high risk of gastrointestinal haemorrhage or are intolerant of other NSAIDs. These patients should be apprised of the possible risks and if they consent to treatment, both the dose and duration of therapy should be minimised.

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1 FitzGerald GA, Patrono C. *N Engl J Med* 2001;**345**:433–42.
2 Bombardier C, Laine L, Reicin A, *et al*. *N Engl J Med* 2000;**343**:1520–8.

Cardiovascular (CV) safety of 400 and 800 mg/day of celecoxib for colorectal adenomas at 2.8–3.1 years*

Outcome	Comparisons	Event rates	RRI (95% CI)	NNH (CI)
CV death, non-fatal MI, stroke, or heart failure†	Celecoxib 800 *v* placebo	3.4% *v* 1.0%	236% (40 to 654)	43 (16 to 252)
	Celecoxib 400 *v* placebo	2.3% *v* 1.0%	129% (−10 to 438)	Not significant

*MI = myocardial infarction. Other abbreviations defined in glossary; RRI, NNH, and CI calculated from hazard ratios in article. †Primary composite endpoint.