

Rofecoxib for colorectal adenomas increased thrombotic events

Bresalier RS, Sandler RS, Quan H, *et al*. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;**352**:1092–102.

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

Q In patients with colorectal adenomas who are at risk of recurrent adenomatous polyps, how safe is rofecoxib with respect to thrombotic events?

METHODS

Design: randomised placebo controlled trial (Adenomatous Polyp Prevention on Vioxx [APPROVe] Trial).

Allocation: unclear concealment.*

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

Follow up period: 3 years.

Setting: 108 centres in 29 countries.

Patients: 2586 patients ≥40 years of age (mean age 59 y, 62% men) who had ≥1 histologically confirmed large bowel adenoma removed within 12 weeks of study entry and did not require long term non-steroidal anti-inflammatory drug (NSAID) therapy. Exclusion criteria: uncontrolled hypertension; angina or congestive heart failure; myocardial infarction (MI), coronary angioplasty, or coronary artery bypass grafting in the previous year; or stroke or transient ischaemic attack (TIA) in the previous 2 years.

Intervention: rofecoxib, 25 mg/day (n = 1287), or placebo (n = 1299) for 3 years.

Outcomes: thrombotic events (fatal and nonfatal MI, unstable angina, sudden death from cardiac causes, fatal and non-fatal ischaemic stroke, TIA, peripheral arterial thrombosis, peripheral venous thrombosis, and pulmonary embolism). The endpoint of the Antiplatelet Trialists' Collaboration (APTC) study was also analysed (combined incidence of death from cardiovascular, haemorrhagic, and unknown causes; non-fatal MI; and non-fatal ischaemic and haemorrhagic stroke).

Patient follow up: all patients were included in the safety analysis. 72% completed 3 years of treatment.

*See glossary.

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MAIN RESULTS

The study was terminated 2 months before the planned date of completion. More patients in the rofecoxib group than the placebo group had thrombotic events, primarily caused by increased MI and stroke in the rofecoxib group (table). Results for the APTC endpoint were similar (table).

CONCLUSION

In patients with colorectal adenomas at risk of recurrent adenomatous polyps, rofecoxib increased thrombotic events.

Abstract and commentary also appear in *ACP Journal Club*.

Commentary

It seemed like a good idea at the time: drugs that selectively inhibited cyclooxygenase 2 (COX 2) would inhibit the synthesis of prostaglandins responsible for pain and inflammation, without interfering with the important "housekeeping" functions of COX 1, such as maintenance of gastric mucosal integrity.¹ It soon became apparent, however, that the COX 2 inhibitors (led by celecoxib and rofecoxib) were not wonder drugs at all. Efficacy was similar to their non-selective counterparts, but they were considerably more expensive and conferred only a slight gastrointestinal safety advantage. Nevertheless, these drugs became pharmaceutical juggernauts used by tens of millions of patients worldwide.

The possibility that COX 2 inhibitors might increase risk of CV events was first raised in a large trial of rofecoxib.² The 5 fold higher incidence of MI with rofecoxib, 50 mg/day was initially attributed to a cardioprotective effect of naproxen, the active comparator. Despite its rather thin biological plausibility, this assertion could not be refuted given the absence of a placebo group. Subsequent observational studies and other randomised trials of COX 2 inhibitors reached inconsistent conclusions, particularly on the hazards of celecoxib. However, the trials of Bresalier *et al* and Solomon *et al* provide new evidence that COX 2 inhibitors, as a class, increase risk of CV events in a dose dependent fashion.

Why? The most widely held hypothesis is that unlike traditional NSAIDs, COX 2 inhibitors selectively inhibit endothelial prostacyclin synthesis without blocking the synthesis of thromboxane A2 in platelets, resulting in platelet aggregation and vasoconstriction. If this is the case, it is reasonable to ask why low dose aspirin did not seem protective in the APPROVE trial. In fact, it probably was. By virtue of being treated with aspirin, these patients (who were initially excluded from the trial) were almost certainly at increased risk of CV events *a priori*, and the concomitant use of aspirin probably attenuated the observed association between rofecoxib and CV events.

Commentary continued on next page.

Thrombotic safety of rofecoxib v placebo for colorectal adenomas at 3 years*

Outcomes	Rofecoxib		Placebo		RRI (95% CI)	NNH (CI)
	Event rates	Patient years at risk	Event rates	Patient years at risk		
Thrombotic events	3.6%	3059	2.0%	3327	92% (19 to 211)	55 (24 to 264)
APTC combined endpoint	2.6%	3070	1.4%	3334	106% (16 to 264)	68 (28 to 447)

*APTC = Antiplatelet Trialists' Collaboration. Other abbreviations defined in glossary; RRI, NNH, and CI calculated from relative risks in article.