THERAPEUTICS

Rofecoxib increased thrombotic events in patients with colorectal adenomas

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: GIM/FP/GP ★★★★★☆☆ Cardiology ★★★★★★☆ Gastroenterology ★★★★☆☆☆ Oncology ★★★★★★☆

QUESTION

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

METHODS

Design: Randomized placebo-controlled trial (Adenomatous Polyp Prevention on Vioxx [APPROVe] Trial).
Allocation: Unclear allocation concealment.*
Blinding: Blinded (clinicians, patients, judicial assessors of outcomes, and monitoring committee).*
Follow-up period: 3 years.
Setting: 108 centers 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 nonsteroidal anti-inflammatory drug (NSAID) therapy. Exclusion criteria were 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 ischemic attack (TIA) in the previous 2 years.
Intervention: Rofecoxib, 25 mg/d (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 nonfatal ischemic stroke, TIA, peripheral arterial thrombosis, peripheral venous thrombosis, and pulmonary embolism). The endpoint of the Antiplatelet Trialists' Collaboration (APTC) study was also analyzed (combined incidence of death from cardiovascular, hemorrhagic, and unknown causes; nonfatal MI; and nonfatal ischemic and hemorrhagic stroke).
Patient follow-up: All patients were included in the safety analysis.

MAIN RESULTS

The study was terminated 2 months before the planned date of completion, with 1857 patients (72%) completing 3 years of treatment. 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 for recurrent adenomatous polyps, rofecoxib was associated with increased thrombotic events.

Source of funding: Merck Research Laboratories.

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*See Glossary.

Thrombotic safety of rofecoxib vs placebo for colorectal adenomas at 3 years†

Outcomes	Rofecoxib		Placebo		RRI (95% CI)	NNH (CI)
	Event rates	Patient-y at risk	Event rates	Patient-y at risk		
Adjudicated 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.

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 nonselective 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 for CV events was first raised in a large trial of rofecoxib (2). The 5-fold higher incidence of MI with rofecoxib 50 mg/d was initially attributed to a cardioprotective effect of naproxen, the active comparator. Despite its rather thin biologic plausibility, this assertion could not be refuted given the absence of a placebo group. Subsequent observational studies and other randomized trials of COX-2 inhibitors reached inconsistent conclusions, particularly regarding the hazards of celecoxib. However, the trials of Bresalier and Solomon and their colleagues provide new evidence that COX-2 inhibitors, as a class, increase risk for 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 A_2 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 for CV events a priori, and the concomitant use of aspirin probably attenuated the observed association between rofecoxib and CV events.

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 inhibi-

(continued on page 3)

Celecoxib increased cardiovascular events in patients with colorectal adenomas

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: GIM/FP/GP ★★★★★★☆ Cardiology ★★★★★☆☆ Gastroenterology ★★★★★☆☆ Oncology ★★★★★★☆

QUESTION

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

METHODS

Design: Randomized 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 to 3.1 years.

Setting: 91 sites in the United States, Canada, Australia, and the United Kingdom.

Patients: 2035 patients 32 to 88 years of age (mean age 60 y, 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 center and use or nonuse 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 to 3.1 years of follow-up (intention-to-treat analysis).

MAIN RESULTS

The trial was stopped early on the recommendation of the CV safety committee, with a 77% completion rate. Patients who received 800 mg/d of celecoxib had a greater risk for the CV composite endpoint than did patients who received 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/d of celecoxib was also associated with increased CV death or nonfatal MI (HR 3.8, CI 1.3 to 11.5) and CV death, nonfatal MI, or stroke (HR 3.4, CI 1.4 to 8.5), regardless of whether patients took low doses of aspirin. Risks for CV events were increased with 400 mg/d of celecoxib, but only reached borderline statistical significance for CV death or nonfatal MI (HR 3.0, CI 1.0 to 9.3) and CV death, nonfatal 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 for recurrent adenomatous polyps, celecoxib led to a dose-related increase in cardiovascular events.

Sources of funding: National Cancer Institute and Pfizer.

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*See Glossary.

Cardiovascular (CV) safety of 400 and 800 mg/d of celecoxib for colorectal adenomas at 2.8 to 3.1 years†

Outcome	Comparisons	Event rates	RRI (95% CI)	NNH (CI)
CV death, nonfatal MI, stroke, or heart failure‡	Celecoxib 800 vs placebo	3.4% vs 1.0%	236% (40 to 654)	43 (16 to 252)
	Celecoxib 400 vs placebo	2.3% vs 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.

COMMENTARY

(continued from page 2)

tors, 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 and Solomon and colleagues (notably, these estimates were 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 antiinflammatory, it seems reasonable to ask whether it or COX-2 inhibitors should be used at all. Clinicians may have differing opinions on this. Recognizing 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 antiinflammatory but are at high risk for gastrointestinal hemorrhage 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 minimized.

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