

# Clinical Questions #6

*Editor's note: This is the sixth installment in a series of "Clinical Questions." Readers are presented with a case and clinical question. An evidence-based answer is provided on a later page. The answer includes how the evidence was found and evaluated.*

## **Does celecoxib increase cardiovascular risk?**

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### **Patient**

A 50-year-old woman with no coronary risk factors and a history of peptic ulcer disease is taking rofecoxib for osteoarthritis. She has tried acetaminophen and did not receive as much relief for her pain as she does with the rofecoxib. Since rofecoxib was voluntarily withdrawn from the market for increased cardiovascular events, she wants to know if her cardiovascular risk would be increased if she switched to celecoxib.

### **Clinical Question**

In low-risk patients does celecoxib increase the risk of cardiovascular events?

How and where could you locate evidence to answer this question?

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How would you treat this patient?

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*Turn the page for one possible approach.*

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## Suggested Approach for Clinical Question #6

### Search Strategy

- EBM search of ACP Journal Club, DARE, and Cochrane Database of Systematic Reviews using the OVID interface May 2005 week 2:
  - “cox2 or cyclooxygenase or celebrex or celecoxib or vioxx or rofecoxib”
  - “MI or Myocardial Infarction or thrombosis or CVA or stroke or CAD or Cardiovascular”
  - Combine [A] and [B]
  - 30 Reviews—none of which specifically addressed our clinical question
- Recent Medline (1996 to present May 2005 week 2) using OVID interface
  - “Celebrex or celecoxib or vioxx or rofecoxib or cox2”
  - “Exp Cardiovascular Diseases” (exploded MeSH heading)
  - Combine [A] and [B] limit to human and English
  - Limit [C] to “therapy (specificity)” under Clinical Queries
  - 23 studies—one of which pertained to our clinical question
    - Solomon SD, et al. Cardiovascular Risk associated with Celocoxib in a Clinical Trial For Colorectal Adenoma Prevention.

### Study Characteristics

- 2035 patients at 91 different sites
- Age 32-88
- Patients with a history of colonic polyps
- Patients randomized into 3 groups
  - Placebo
  - Celocoxib 200 mg twice daily
  - Celocoxib 400 mg twice daily
- Main outcome was a composite endpoint of death from CV causes, myocardial infarction, stroke, or heart failure

### Validity of Evidence

- Properly randomized trial
- Baseline risk factors for cardiovascular disease prospectively recorded
- Appropriately blinded
- 3-year follow up seemed short for cardiovascular events
- All patients completed 2.8-3.1 years of follow up
- Intention to treat analysis
- Study not specifically designed to detect cardiovascular events
- Retrospective attempt to evaluate safety
- Overall this study is of moderate methodological quality due to the retrospective evaluation of cardiac endpoints.

### Results

- Trial was stopped early by the cardiovascular safety committee
- Composite endpoint of cardiovascular death, nonfatal MI, stroke, or heart failure were increased in both Celecoxib groups

- Hazard ratios (HR)
  - 200mg bid
    - HR 2.3, 95% CI 0.9 to 5.5
  - 400mg bid
    - HR 3.4, 95% CI 1.4 to 7.8
- Number Needed to Harm (NNH)
  - 200mg twice daily not significant
  - 400mg twice daily
    - NNH 43, 95% CI 16 to 252
- No individual endpoint reached statistical significance

### Applying the Evidence to the Patient

- Patient is similar to those in the study.
- Celecoxib is a feasible intervention.
- Our patient's cardiovascular risk is 1% over 10 years.
  - Calculated using the National Cholesterol Education Program's cardiovascular risk calculator.
- Worst case scenario is that, using the high end of the confidence interval, our patient's risk would increase to 5.5% over 10 years.

### Summary

This is a good quality study that demonstrates increased risk for a composite endpoint of cardiovascular events. These results are consistent with the APPROVe trial that led to Vioxx being voluntarily taken off the market. Our patient had a very low baseline cardiovascular risk. Even with the increased risk of taking Celecoxib, her overall risk of cardiovascular events in the next 10 years remains relatively low. After a discussion about the potential risks, our patient ultimately chose not to use this medication since her insurance provider would not cover it.

### Conclusion

Celecoxib increases the risk of cardiovascular events. The patient's baseline risk should be taken into account when prescribing this medication. Before prescribing Celecoxib, an informed discussion should be held with the patient about the risks, benefits and alternatives, especially as this medication has not been shown to be more effective than other NSAIDs.

### References:

- Solomon SD, McMurray JJV, Pfeffer MA, Wittes J, et al. Cardiovascular risk associated with Celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med.* 2005; 352:1071-1080.
- Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med.* 2005; 352:1092-1102.
- Risk Assessment Tool for Estimating Your 10-year Risk of Having a Heart Attack. NCEP Web site. Available at: <http://hin.nhlbi.nih.gov/atp/iii/calculator.asp>. Accessed October 25, 2005.

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