We thank Dr. Lipani for his thoughtful discussion of our article on COX-2 inhibitors and for raising several concerns and issues. We readily admit that our study had limitations, like all retrospective studies. Nevertheless, we believe that our hypothesis is plausible, our methods were valid, and our conclusions—that further study is warranted and caution should be exercised in prescribing COX-2 inhibitors—are sound.


Our hypothesis is plausible

COX-2 inhibitors decrease vascular prostacyclin production and may affect the balance between prothrombotic and antithrombotic eicosanoids, thereby shifting the balance to a thrombotic state. In contrast, the non-selective NSAIDs inhibit platelet aggregation.

The prothrombotic potential of COX-2 inhibitors is supported by basic research:

- Shinmura et al demonstrated that COX-2 mediates the cardioprotective effects of the late phase of ischemic preconditioning—the ability of myocytes to survive ischemia if previously exposed to mild ischemia.
- Hennan et al showed that celecoxib abolished aspirin’s effect of increasing the time to occlusion in a canine model of coronary thrombosis.
- Dowd et al recently demonstrated that inhibition of COX-2 aggravates doxorubicin-mediated cardiac injury in vivo, suggesting that COX-2 has salutary effects in the heart.

We defend our methods

Although cardiovascular events were not prespecified as end points in the design of the VIGOR trial, an excess of cardiovascular events was recognized during an interim analysis, and these events were specified and adjudicated from that point on. This was done in a blinded fashion, without knowledge of the particular drug being given.

Comparing the treatment groups in the VIGOR trial, we calculated that the relative risk of cardiovascular events with rofecoxib vs naproxen was 2.38, which was statistically significant (95% CI 1.39–4.00, $P < .002$).

In addition, the relative risk might be even higher for patients with preexisting coronary disease. Although aspirin use was not permitted in the VIGOR trial, a subgroup analysis was performed in patients for whom aspirin was indicated, ie, who had a past medical history of stroke, transient ischemic attack, myocardial infarction, unstable angina, angina pectoris, coronary artery bypass graft surgery, or percutaneous coronary interventions. The relative risk of a serious cardiovascular event in “aspirin indicated” patients taking rofecoxib compared with naproxen was 4.89 (95% CI 1.41–16.88, $P = .01$).

Dr. Lipani correctly points out that rheumatoid arthritis increases the risk of cardiovascular events, but even so, one is still faced with the difference in cardiovascular events between rofecoxib and naproxen in the VIGOR trial, in which all the patients had rheumatoid arthritis. Since rofecoxib was associated with increased cardiovascular events in patients with rheumatoid arthritis, one could extend this argument and say that any patient with other cardiac risk factors remains at risk with these agents.

In contrast to the VIGOR study, the CLASS study did not show a significant increase in cardiovascular event rates with a COX-2 inhibitor (celecoxib) compared with NSAIDs. One explanation is that the use of low-dose aspirin was allowed in the CLASS trial, but not in the VIGOR trial.

In addition, the two trials used different NSAIDs as...
controls. Diclofenac and ibuprofen (used in CLASS) have significantly less antiplatelet effect than does naproxen (used in VIGOR). To have a vascular protective effect, near-complete inhibition of thromboxane over time is needed, and the degree of thromboxane inhibition with diclofenac and ibuprofen may not afford any cardioprotection.

Furthermore, diclofenac has more effect on prostacyclin inhibition than naproxen. Van Hecken et al demonstrated that diclofenac 50 mg three times a day inhibits COX-2 by 94%, compared with 71% for naproxen 550 mg twice a day. Thus, diclofenac has not only less of an antiplatelet effect, but may have some intrinsic prothrombotic effect due to inhibition of vasodilatory prostacyclin, and this may have masked any increase in event rates with celecoxib.

Two ongoing phase III trials are evaluating the role of COX-2 inhibitors in Alzheimer disease, but neither of them have cardiovascular events as their primary end point and neither of them has formally reported their findings.

Of note, in the CLASS trial there was no significant difference between the groups in the incidence of the primary end point of ulcer perforation, gastric-outlet obstruction, or upper gastrointestinal bleeding (0.8% in the celecoxib group vs 1.5% in the two NSAID groups, \( P = .09 \)).

**NEED FOR FURTHER STUDY**

Together, the clinical and basic data raise several important questions:

- Are COX-2 inhibitors prothrombotic?
- Can aspirin offset the potential prothrombotic risk?
- Does aspirin negate the gastrointestinal safety of COX-2 inhibitors?
- Should COX-2 drugs be avoided in patients with coronary artery disease or its equivalents? Should they be avoided in patients at high risk for coronary artery disease?
- Do these agents have any potential beneficial effects on atherosclerosis in view of their anti-inflammatory effects?

The available data point to an increase in cardiovascular event rates for the currently available COX-2 inhibitors. The only way to definitively answer this question would be to do a prospective randomized clinical trial with cardiovascular events as the primary end point. Given the immense popularity of this new class of medications, it is imperative to conduct such a trial. Until a cause-and-effect relationship between COX-2 inhibitors and cardiovascular events can be ruled out, we should exercise caution in prescribing these agents to patients at risk for cardiovascular morbidity.

**REFERENCES**


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