

ALTERNATIVE VIEWPOINTS

More on NSAIDs and Cardiovascular Risk

B. Daniel Lucas, Jr., Pharm.D., Kristy H. Lucas, Pharm.D., and Bernardo J. Reyes, M.D.

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We are disappointed that we were unable to convince Dr. Stacy and his colleagues of the limitations of their appreciated contribution.¹ As we review their position, we are concerned that readers will take a misguided clinical approach if the issue of NSAID use is not examined more comprehensively.

Although worrisome primarily because it is a factual error, the last sentence of the first paragraph in their reply is incorrect. That is, it states that mortality was the endpoint of both the observational and randomized studies, whereas, the endpoint most readily employed was a combined CV endpoint, which, at times, incorporated mortality.

Their conviction that “product-specific decisions be made rather than by drug class” is exactly the point with which we disagree. Certainly, they have a right to their opinion; yet, their citation of support from the FDA is incorrect. As stated, the FDA did not “remove all COX-2 inhibitors from the market.” Technically, the FDA did not remove any COX-2 inhibitor from the market (rofecoxib and valdecoxib were voluntarily withdrawn with the latter agent’s sponsor providing “respectful” disagreement with the FDA). More importantly, the FDA did make a drug class decision, which is quite obvious, even to those not following the details

of this issue. That is, product labeling changed for all NSAIDs, whether selective or not. Lastly, it is ironic that the additional evidence cited indicates that there is risk with diclofenac, meloxicam and indomethacin (nonselective NSAIDs), a point that they exclude.³

Although it would make our conundrum more simplistic, the COX-1/COX-2 ratio is unable to fully explain the CV toxicity. Disparate clinical findings support this contention that is reiterated in an American Heart Association Advisory.⁴

In their reply, Dr. Stacy and his colleagues continue to advocate for a nonselective inhibitor and PPI. They cite studies supporting the GI protective effect,^{5, 6} yet these studies are essentially equivalent to those produced by celecoxib (mostly endoscopy-related endpoints), therefore making it difficult to accept their position of superiority. Moreover, the FDA has not “endorsed a combination nonselective NSAID and PPI/misoprostol” as incorrectly stated in their reply.

We are again misquoted in the final paragraph of the reply by Dr. Stacy and his colleagues. We do not say that “the cardiovascular risks of selective COX-2 inhibitors and NS-NSAIDs are similar.” We do say that the *relative* CV risk of selective COX-2 inhibitors and NS-NSAIDs is largely unknown (i.e., comparing COX-2 to NS-NSAID), which is why we vehemently disagree with their proposition of a market shift. Their recommendation is not supported by existing evidence. Further, the FDA has taken a class approach in labeling changes (important for the practicing clinician to know) and suggests further study is necessary before “product specific decisions may be made.”

We believe that the approach advocated by Dr.

From the Charleston Area Medical Center - Health Education and Research Institute, Charleston, West Virginia (Drs. B. Daniel Lucas and Bernardo J. Reyes) and West Virginia University-Charleston Division, Schools of Pharmacy and Medicine, Charleston, West Virginia (Dr. Kristy Lucas).

Address reprint requests to B. Daniel Lucas, Pharm.D., Charleston Area Medical Center - Health Education and Research Institute, 3200 MacCorkle Avenue, SE Charleston West Virginia 25304; email: dan.lucas@camc.org.

Stacy and his colleagues is rash. That is, they appear to desire steering patients from one compound to another under the guise of escaping cardiovascular toxicity when we truly do not know if this is better or worse. This ill-conceived advice is, at a minimum, damaging to clinician's credibility (granting false sense of security to patients), and at worse, advocating what may turn out to be a more CV-toxic compound than the original drug. We reiterate that clinicians should employ the FDA's conservative guidance in this matter.

References

1. Stacy ZA, Dobesh PP, Trujillo TC. Cardiovascular risks of cyclooxygenase inhibition. *Pharmacotherapy* 2006;26(7):919-938.
2. Lucas Jr. BD, Lucas KH, Reyes BJ. Cardiovascular risks of cyclooxygenase inhibition. *Pharmacotherapy* 2006;26:e125-e128.
3. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006;296:1633-1644.
4. Bennett JS, Daugherty A, Herrington D, Greenland P, Roberts H, Taubert KA. The use of nonsteroidal anti-inflammatory drugs (NSAIDs): a science advisory from the American Heart Association. *Circulation* 2005;111(13):1713-1716.
5. Lai KC, Chu KM, Hui WM et al. Celecoxib compared with lansoprazole and naproxen to prevent gastrointestinal ulcer complications. *Am J Med* 2005;118(11):1271-1278.
6. Scheiman JM, Yeomans ND, Talley NJ et al. Prevention of ulcers by esomeprazole in at-risk patients using non-selective NSAIDs and COX-2 inhibitors. *Am J Gastroenterol* 2006;101:701-710.