

ALTERNATIVE VIEWPOINTS

Cardiovascular Risks of Cyclooxygenase Inhibition

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Dr. Stacy and colleagues' review is timely in a period of considerable uncertainty regarding the appropriate therapeutic approach to utilizing selective and nonselective cyclooxygenase inhibitors.¹ We would like to emphasize points briefly mentioned in the manuscript, implications thereof and share with readers an omitted prospectively designed trial destined to add valuable insight into this morass.

According to the Centers for Disease Control and Prevention, arthritis is the leading cause of disability in the United States with a reported prevalence ranging from 19% in the 18–44 year-old age group to 59% in those ≥ 65 years of age, which legitimizes the significance of the toxicities associated with symptom relief.² Nonselective, nonaspirin, nonsteroidal anti-inflammatory drugs (NS-NSAIDs) are effective analgesic, anti-inflammatory and antipyretic agents, but associated gastrointestinal (GI) toxicity led to the development and widespread use of selective cyclooxygenase-2 (COX-2) inhibitors. Despite the associated GI and recently accentuated cardiovascular (CV) toxicities, the graying of America is expected to increase the demand for symptom relief from this disabling condition.

We are in agreement with the authors' assertion that "without adequate randomized, placebo-controlled studies, it is difficult to make a definitive statement regarding the overall effect

on CV risks with NS-NSAID therapy." Furthermore, the limitations of observational studies towards reaching definitive conclusions are acknowledged. Counterintuitively, the authors then proffer the following therapeutic advice. "It seems reasonable that celecoxib be *reserved* for patients who have significant risks for GI bleeding with NS-NSAIDs. The FDA urges clinicians to consider using the combination of naproxen and a proton pump inhibitor in those patients with GI risk factors." Available evidence does not lend itself to preferential use of nonselective over selective NSAIDs. Moreover, we are unaware of the FDA preferentially "urging clinicians towards naproxen and a proton pump inhibitor in the setting of GI risk factors."

Previous research has demonstrated an increased risk for myocardial infarction (MI) with rofecoxib, celecoxib, *naproxen* and other traditional NS-NSAIDs. As shared in their review, studies of NS-NSAIDs, largely observational, have shown decreases, increases, or no effects on the risk of CV events.¹ Unlike the situation with COX-2-selective agents, large long-term, placebo-controlled clinical trials with NS-NSAIDs have not been conducted to evaluate long-term risks including CV risks. Therefore, whether COX-2 inhibitors have similar or different CV toxicities remains unknown.

Most of the presently available NS-NSAIDs were approved many years ago, and as a result, databases reflected in their approval are paltry in comparison to the accumulated evidence regarding efficacy and safety of the COX-2 selective drugs. Therefore, it is not surprising that, when studied with more contemporary approaches, more issues of safety arise with COX-2 inhibitors.

Additional uncited evidence in support of the

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position of the present inability to recommend a nonselective over a selective agent is the recently reported retrospective cohort study in patients with congestive heart failure (CHF). The risk of death and recurrent CHF combined was lower in patients prescribed celecoxib than in those prescribed NS-NSAIDs or rofecoxib.³ In patients with a prior MI taking either COX-2 inhibitors or NS-NSAIDs, a number needed to harm (NNH) for *both* was more significant than was demonstrated in the Adenoma Prevention with Celecoxib (APC) trial, likely due to the high risk population studied.⁴ Again, as the authors have conceded, observational studies cannot test definitively whether there are small to moderate risks or benefits of a class of drugs when the factors associated are difficult or impossible to control or are unknown. Recently announced at the April 2006 meeting of the American Association for Cancer Research, celecoxib prevented precancerous lesions in patients at high risk for developing colorectal cancer. Investigation also continues in this area of concern to clarify the risk to benefit ratio of therapy, and further reminds us that we must not abandon this class of medications hastily. The totality of findings, including the absence of any long-term placebo- or active-controlled clinical trials of most of the NS-NSAIDs, make it difficult to conclude that the COX-2 selective drugs as a class have greater CV risks than NS-NSAIDs.

Although a change in the *class* labeling is mentioned in the manuscript, we believe it is noteworthy enough to emphasize in their review's conclusion. The incongruence in the existing data and absence of definitive data lead the FDA to what Dr. Stacy and colleagues describe as a "conservative approach" when calling for a *class* label change; whereas, we believe in light of evidence and lack thereof, this decision was the most prudent.

Briefly, April 2005, the FDA made the following decisions in the wake of the NSAID safety scare: All marketed prescription NSAIDs (with the exception of aspirin), including COX-2 inhibitors, must include a black-box warning on their labels. The label was to warn about the potential for increased risk for CV events and serious and severe, potential life-threatening GI bleeding associated with their use. The black-box warning must also describe early symptoms of Stevens-Johnson Syndrome, which has been linked to use of certain NSAIDs. In addition, a medication guide, written in lay language, as part of the labeling, was required to be given at the

time the drug is dispensed to inform patients of the potential risks. Beyond the prescription NSAIDs, the FDA said warning labels on over-the-counter (OTC) medications containing ingredients such as generic ibuprofen, ketoprofen or naproxen must also inform patients about the increased risks of CV side effects, GI bleeding and serious skin reactions, and to remind people only to use the recommended dosage for the recommended duration of treatment. In June 2005, the FDA published the requirements for the new warnings for all NS-NSAIDs and the available COX-2 selective inhibitors within the US, stressing the importance of limiting the use of NSAIDs to the lowest effective dose for the shortest possible duration.

Underpinning the announcement of April 7, 2005 was an informative memorandum (Analysis and recommendations for agency action regarding nonsteroidal anti-inflammatory drugs and CV risk) issued on April 6 from John K. Jenkins, M.D. (Director, Office of New Drugs) and Paul J. Seligman, M.D., M.P.H. (Director, Office of Pharmacoeconomics and Statistical Science) to NDA files 20-998, 21-156, 21-341 and 21-042. The comprehensive review of published and unpublished data from FDA files, some of which was proprietary, concluded that available data are best interpreted as consistent with a *class effect of all NSAIDs*, justifying substantial concern, and a black-box warning. Key points taken from this report include: 1) COX-2 selective NSAIDs are associated with an increased risk of serious adverse CV events compared to placebo. 2) Data from large long-term controlled clinical trials that have included a comparison of COX-2 selective and NS-NSAIDs do not clearly demonstrate that the COX-2 selective agents confer a greater risk of serious adverse CV events than NS-NSAIDs. 3) Long-term placebo-controlled clinical trial data are not available to adequately assess the potential for the NS-NSAIDs to increase the risk of serious adverse CV events. 4) Pending the availability of additional long-term controlled clinical trial data, the available data are best interpreted as being consistent with a class effect of an increased risk of serious adverse CV events for COX-2 selective and NS-NSAIDs. 5) COX-2 selective drugs reduce the incidence of GI ulcers visualized at endoscopy compared to certain NS-NSAIDs. However, the benefit of COX-2 selective drugs in reducing the risk of serious GI bleeding remains uncertain, as does the comparative effectiveness of other strategies for reducing the risk of GI

bleeding such as Dr. Stacy and colleagues' recommended concomitant use of a NS-NSAID and a proton pump inhibitor.

Importantly, the report cites that long marketing history of many of the NS-NSAIDs cannot be taken as evidence that they are not associated with an increased risk of serious adverse CV events since CV events occur fairly commonly in the general population and small increases in common adverse events are impossible to detect from spontaneous reporting systems. The adverse CV risk signal for the COX-2 selective drugs became apparent only from large long-term controlled clinical trials and large retrospective cohort studies. They conclude that similar clinical trials are needed to assess the potential risks of the NS-NSAIDs.

Finally, the authors of this FDA memorandum state that their interpretation of the data will serve to promote public health by alerting physicians and patients to this *class* concern and will make it clear that switching from a COX-2 selective agent to a NS-NSAID does not mean that the potential for increased risk of serious adverse CV events has been fully, or even partially, mitigated. Disconcerting is evidence to suggest that a "market shift" in prescribing patterns has occurred, likely with practitioners and patients believing they are trading a more CV risky drug (i.e., selective COX-2 inhibitor) for one with fewer CV risks (i.e., NS-NSAIDs). Improved GI tolerability of NSAIDs is an important issue for an individual patient and public health perspective and is a rationale for maintaining a range of options in the NSAID class from which clinicians and patients may choose. The aforementioned interpretation is consistent with the Joint Meeting of the Arthritis Advisory and the Drug Safety and Risk Management Advisory Committees' conclusions from their February 16-18th 2005 meeting.

Due to the dearth of knowledge regarding the relative safety of these drugs and at the FDA's request, the manufacturer of celecoxib has recently announced that they plan to fund a major 20,000-person clinical trial, PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen) comparing celecoxib 200 mg with ibuprofen 2400 mg and naproxen 1000 mg in a blinded randomized fashion. Though the manufacturer is funding the work with costs projected to be upwards of a hundred million dollars, the Cleveland Clinic will maintain and share the data with the NIH. CV safety will be

the primary endpoint in this high-risk population with preexisting or significant risk for CV disease. The trial's endpoint of 715 CV events (Antiplatelet Trialists' Collaboration end point: nonfatal MI, nonfatal stroke, or vascular death) is expected to take approximately four years. Although the study will be a landmark in the setting of a drug class where regulatory approval rigor is less than what one would expect when a drug is likely to be taken for a third or more of one's lifetime, there are criticisms that have been put forth. The most salient of which is the lack of placebo, justified by the ethical dilemma of untreated pain. Yet, ample consideration could be given to a placebo study arm with a "safety net" provided for breakthrough pain. Another pertinent criticism is that it will prove challenging to extrapolate the findings to patients free of CV disease and its risk factors. Moreover, it does not address the widespread short-term treatment, compounded by OTC availability. Independent of these criticisms, the study will provide a better relative understanding of the selective and nonselective cyclooxygenase inhibitors' place in therapy.

Until further conclusive data become available better elucidating the relative CV and GI risks, an evidence-based approach to the use of NSAIDs eludes us. Importantly, it is imperative that we do not give false reassurance that there is no CV problem with the NS-NSAIDs. We agree with Dr. Stacy and colleagues' comment, "selecting an appropriate agent must include a multifaceted approach, integrating rheumatoid, GI, and CV perspectives." Prudent advice now entails using the lowest effective dose for the shortest duration with whatever agent is chosen. Caution is in order when considering treatment in a patient with CV history as the risk of thrombosis is significant. Initially prescribing drugs with the lowest risk of thrombosis (aspirin, acetaminophen) in such a patient with low GI risk seems rational. As Dr. Stacy and colleagues imply, it is quite reasonable to consider a COX-2 selective agent as an alternative in patients with a high GI risk. Lastly, in patients who are not otherwise high risk for CV or GI complications, current evidence does not compel use of a NS-NSAID over a COX-2 inhibitor.

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Authors' Reply

The comments by Dr. Lucas and his colleagues on the cardiovascular risks of cyclooxygenase (COX) inhibition highlight several clinical challenges. We agree that large, randomized, conclusive trials designed to compare the cardiotoxicity of non-selective non-steroidal anti-inflammatory drugs (NS-NSAIDs) and COX-2 inhibitors are unavailable; however, we feel that stating the cardiovascular (CV) risks of COX-2 inhibitors as unknown is inaccurate. Several investigations have documented increased cardiovascular risks associated with selective COX-2 inhibition. While these investigations have study designs that lack the scientific rigor of randomized, double-blind, placebo-controlled trials, the signal of CV risk has been duplicated in several trials and meta-analyses. Regardless of the age, source, or quality of the data, a hard endpoint such as mortality is difficult to refute in these studies.

A clinical decision based on the totality of the data is made more difficult when COX-2 inhibitors and NS-NSAIDs are evaluated as classes rather than individual agents. A recent review has provided additional evidence that within the class of NS-NSAIDs, significant CV risk differences may exist.¹ Had the FDA made a drug class-based decision, all of the COX-2 inhibitors would have been removed from the market. We are suggesting that independent product-specific decisions be made rather than by drug class.

Additionally, the gastrointestinal (GI) protection afforded by selective inhibition of COX-2 is controversial. Only rofecoxib has

demonstrated significant reductions in clinically relevant endpoints such as GI bleeding.² Subsequent investigations with alternative COX-2 inhibitors have only shown reductions in the incidence of endoscopically confirmed GI ulcers. Similar to the CV toxicity, the COX-1/COX-2 ratios can be used to explain these efficacy endpoints.¹

Recent investigations have confirmed the effectiveness of combination therapy with a proton pump inhibitor and NS-NSAID therapy.^{3,4} Combination therapy provided similar GI protection in moderate- to high-risk patients receiving various NS-NSAIDs. The Food and Drug Administration continues to endorse consideration of a NS-NSAID in combination with a proton pump inhibitor or misoprostol.⁵

In summary, minimal clinically significant gastrointestinal protection has been documented with the selective COX-2 agents when compared to NS-NSAID therapy. If the cardiovascular risks of selective COX-2 inhibitors and NS-NSAIDs are similar, as Lucas proposes, we feel it is irresponsible to recommend a COX-2 inhibitor because of cost disparities and a market shift in prescribing patterns may be justified.

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