

# Circulation

**N/A**

Gail Cawkwell and George H Sands  
CIRCULATIONAHA/2007/702423

**This information is current as of March 13, 2007**

Disclaimer: The contents of this manuscript are confidential and intended for review purposes only. Downloaded from <http://submit-circ.ahajournals.org> on March 13, 2007

## Author Disclosures

**Gail Cawkwell:**

Other:

I am a full time employee of Pfizer Inc, working on the COX-2 global medical team, Amount:  
>= \$10,000

**George H Sands:**

Other:

I am a full time employee of Pfizer Inc, working on the COX-2 global medical team, Amount:  
>= \$10,000

Letter to editor re: Antman et al, Use of Nonsteroidal Antiinflammatory Drugs, An Update for Clinicians, A Science Advisory from the American Heart Association Circulation. 2007;115

To the editor:

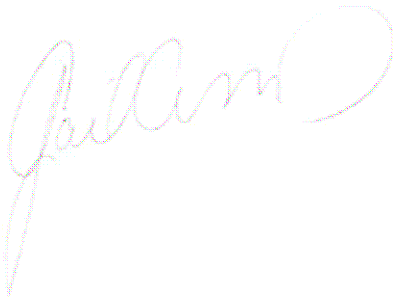
Antman et al<sup>1</sup> present a review of the science and recent history around the cardiovascular (CV) safety of nonsteroidal anti-inflammatory drugs (NSAIDs), medicines used by millions of patients to treat pain and inflammation. While we understand their efforts to develop a clinical advisory, any treatment recommendations must be based on the evaluation of rigorously obtained, clinically meaningful data. All potential risks and benefits, cardiovascular and others, must be considered thoroughly.

The stepped-care approach Antman et al advocate for patients with CV risk is based on some clinical data, and a controversial mechanistic hypothesis. The authors' suggestion that the greater the degree of COX-2 specificity, the greater the CV risk, is not supported by the data included in their table, nor is it consistent with their own conclusions. In fact, the FDA<sup>2</sup> required that all prescription non-aspirin NSAIDs contain the same boxed warnings about potential CV risks. Additionally, a recent review has concluded that the degree of COX-2 specificity is unrelated to CV risk.<sup>3</sup>

Pain is a serious medical problem, requiring adequate and appropriate treatment. Higher pain scores are associated with increased levels of cardiac disease and higher mortality rates in osteoarthritis patients.<sup>4</sup> Some of the medicines recommended as safe by Antman et al have either not been studied from a CV viewpoint or are associated with non-CV risks that must also be considered. Acetaminophen-related hepatotoxicity is well recognized; even intermittent acetaminophen usage has been associated with hypertension, suggesting potential CV risk.<sup>5</sup> Opioids increase the risk of falls, especially amongst patients – like many arthritis patients – with borderline mobility capabilities.

We agree with the authors that additional prospective data are needed to address the long-term CV safety of NSAIDs, at commonly used doses, in arthritis patients. To address this need, Pfizer is sponsoring, and the Cleveland Clinic is conducting, the ongoing PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen) study in osteoarthritis and rheumatoid arthritis patients with cardiovascular disease (CVD) or at high risk for developing CVD.

Recommendations based on all available data should be developed transparently and with input from a broad group of representatives, including patient groups and practitioners. Antman et al's recommendations, unfortunately, may not lead to the most informed treatment decisions.



Gail Cawkwell, MD, PhD  
Senior Medical Director  
Neuroscience, Pain & Inflammation  
COX-2 Global Medical Team Lead  
Pfizer Inc, New York, NY



George Sands, MD, FAAN, FAHA  
Medical Director  
Neuroscience, Pain & Inflammation  
COX-2 Global Medical Team  
Pfizer Inc, New York, NY

1. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of Nonsteroidal Antiinflammatory Drugs. An Update for Clinicians. A Scientific Statement From the American Heart Association. *Circulation*. 2007;115.
2. Jenkins JK, Seligman PJ. Analysis and recommendations for Agency action regarding non-steroidal anti-inflammatory drugs and cardiovascular risk. April 6, 2005. FDA. Available at: <http://www.fda.gov/cder/drug/infopage/cox2/nsaiddecisionmemo.pdf>
3. Flavahan NA. Balancing prostanoid activity in the human vascular system. *Trends Pharmacol Sci*. 2007;28:106-10.
4. Pincus T, Sokka T. People with Osteoarthritis in the General Population Who Report Pain Scores >40/100 Also Have Increased Levels of Cardiac Disease and Higher Mortality Rates Over the Next 5 Years. *Arthritis Rheum*. 2005;52(9 Suppl):S514-5.
5. Forman JP, Rimm EB, Curhan GC. Frequency of Analgesic Use and Risk of Hypertension Among Men. *Arch Intern Med*. 2007;167:394-9.

## Response to Pfizer

Cawkwell and Sands, writing on behalf of the Neuroscience, Pain & Inflammation division of Pfizer, Inc question the stepped care approach in the AHA's Scientific Statement on Use of NSAIDs. (1) They argue that the data in the Table in the statement do not support the contention that the degree of COX-2 selectivity is related to CV risk. They also argue against the mechanistic hypothesis that an imbalance between thromboxane A2 and prostacyclin contributes to the risk of thrombosis in patients treated with NSAIDs and coxibs in particular.

We disagree with the position espoused by Cawkwell and Sands. On the basis of the available data in the Table in the Scientific Statement one may conclude that compared to placebo naproxen appears to be neutral with respect to CV risk but other NSAIDs with increasing degrees of COX-2 selectivity (ibuprofen and diclofenac) are associated with progressively greater degrees of risk versus placebo, although the 95 CI's cross unity, preventing a definitive conclusion. In contrast, the data on the risk of coxibs are statistically significant with respect to evidence of increased CV risk compared to placebo. Thus, the argument put forward by Flavahan (2) (a consultant to Merck) and cited by Cawkwell and Sands is inconsistent with the accumulated data from randomized trials, registries, and observational studies cited in the Scientific Statement and recently presented to the FDA regarding comparison of the highly COX-2 selective agent etoricoxib with other NSAIDs ([http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1\\_31\\_AA-FDA-Tab-T.pdf](http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_31_AA-FDA-Tab-T.pdf)). The prothrombotic hypothesis coupled with the increased risk of hypertension, edema, and heart failure seen to a greater extent with drugs having greater degrees of COX-2 selectivity is the most likely explanation for the clinical data.

We agree that pain is a serious medical problem and that higher pain scores are associated with increased risk of CV events. Indeed it is reduction of the risk of such events that served as the impetus for the AHA to update its position on NSAIDs. While it is correct that the FDA currently requires that all NSAIDs have the same black boxed warning, that does not preclude the fact that there appears to be a gradient of risk with the available agents. The AHA Scientific Statement acknowledges that even a relative lack of COX-2 selectivity does not completely eliminate the risk of CV events---considering the degree of COX-2 selectivity is an important fact when contemplating therapy. (1)The Scientific Statement also cautions clinicians about the appropriate selection of patients who might be candidates for short term use of narcotics for pain relief. We would argue that the approach taken by Cawkwell and Sands and in a recently launched advertising campaign for celecoxib (<http://www.celebrex.com/content/index.jsp>) that downplays the available evidence and portrays the relative risk of the coxibs as similar to other NSAID choices is not in the best interest of patients.

Since the implications for CV health are quite profound, patients and clinicians need practical advice now. The focus of the AHA Scientific Statement is to provide such advice to clinicians who are faced with the task of treating musculoskeletal symptoms in patients with heart disease or who are at risk of ischemic heart disease, but striking the critical balance so that such treatment does not increase the risk of CV events. We believe the stepped care approach outlined in Figure 7 of the Scientific Statement, which places

coxibs as the last resort to be tried is the best advice to the clinical community at the present time.

#### References

1. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of Nonsteroidal Antiinflammatory Drugs an Update for Clinicians- a Science Advisory from the American Heart Association. *Circulation* 2007;115: 1634-1642.
2. Flavahan NA. Balancing prostanoid activity in the human vascular system. *Trends Pharmacol Sci.* 2007;28:106-10.