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Joseph Loscalzo MD, PhD
Editor, ***Circulation***
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Dear Editor,

Antman EM, et al. in the article 'Use of Nonsteroidal Antiinflammatory Drugs an Update for Clinicians- a Science Advisory from the American Heart Association"[1] provide an excellent review of the published studies relating to cardiovascular (CV) risk associated with both the selective and nonselective cyclooxegenase (COX) inhibitor nonsteroidal anti-inflammatory drugs (NSAIDs). The authors also describe the current deficiencies in our understanding of the CV risk of NSAIDS and the currently active or planned studies to address these issues. Nevertheless, it is important to emphasize that increasing COX-2 selectivity creating greater CV risk is not a data driven concept, and data from large trials does not convincingly support superior CV safety for non-Naproxen NSAIDs.

However, as the current President and members of the Drug Safety Committee of the American College of Rheumatology, we feel that the "stepped-care approach to management of musculoskeletal symptoms" in this article very much over simplifies the management of patients with rheumatic diseases. In many of the acute and chronic musculoskeletal disorders the clinical manifestations, and more importantly, the pathophysiologic mechanisms and complications are a direct result of inflammation in the target tissues. In these inflammatory conditions (such as arthritis, bursitis and tendonitis) NSAIDs have been shown in both experimental and clinical studies to specifically suppress the inflammatory process. These agents not only improve symptoms but also minimize or avoid tissue complications associated with progression of the inflammatory processes. Use of the proposed stepped-care approach with emphasis on nonpharmacologic treatments plus acetaminophen or aspirin is not sufficient to treat inflammatory arthritis. Many randomized placebo and active controlled clinical trials that have established the efficacy of NSAIDs over and above the use of analgesic agents. Moreover, to be effective in suppressing the inflammatory process, these NSAIDS need to be used in the pharmacologic doses and dosing duration found to suppress the COX mediated inflammatory process.

Rheumatoid arthritis, the spondyloarthropathies, psoriatic arthritis and osteoarthritis have been shown to cause early death, chronic disability, and significant negative impact on overall all quality of life[2]. While we appreciate the substantial CV toxicity associated

with selective and non-selective NSAIDs, the current AHA statement does not reflect the proven benefits of these agents in patients with arthritis and other chronic inflammatory conditions. Just as collaborative treatment plans for a given patient result in improved care, we would urge the cardiology community to engage their rheumatology colleagues in formulating optimal recommendations for the use of NSAIDs.

Respectfully submitted,

Neal S. Birnbaum, MD
President, American College of Rheumatology

Daniel J. Lovell, MD, MPH and Daniel H. Solomon, MD, MPH for the members of the American College of Rheumatology Drug Safety Committee

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: xx-xx.

2. Callahan LF, Pincus T. Mortality in the rheumatic diseases. Arthritis Care Res 1995; 8:229-41.

Response to Drs. Birnbaum,Lovell,and Solomon

We appreciate the comments of Drs. Birnbaum, Lovell, and Solomon who wrote on behalf of the American College of Rheumatology in followup to the AHA Scientific Statement on the use of NSAIDs. (1) The major concerns outlined are noted below along with our responses.

1. **Increasing COX-2 selectivity creating greater CV risk is not a data driven concept and data from large trials do not convincingly support superior CV safety for non-naproxen NSAIDs.**

   We agree that the database on which to judge the relative merits of the various NSAIDs that might be prescribed for management of musculoskeletal symptoms is incomplete, with particularly notable deficiencies comparing the non-naproxen NSAIDs with the coxibs. However, we wish to reiterate that the focus of the AHA's Scientific Statement was on the factors that should be considered when selecting medications for pain relief in patients with heart disease or who are at risk for ischemic heart disease. The Scientific Statement should be read in its entirety, including the details in the text as well as the stepped care recommendations in Figure 7. The data summarized in the Table and Figure 1 are consistent with a progressive increase in risk of cardiovascular events with NSAIDs exhibiting a progressively greater ability to inhibit COX-2 compared to COX-1; this is especially true for myocardial infarction.

   While issues such as dose, duration of exposure, and the underlying risk of the patient are likely to contribute to the actual risk observed in an individual case, when considering the totality of the evidence (the basic science discussed in the Scientific Statement, the established benefits of low dose aspirin, the probable neutral effect of naproxen, and the directionality of the data with more COX-2 selective drugs), we feel that patients with known heart disease or who are at risk for ischemic heart disease should be managed according to the stepped care approach shown in Figure 7. It should be noted that we underscore the potential risk of virtually all the NSAIDs by the introduction of the horizontal black line in Figure 7, indicating that effective pain relief may come at the cost of a small but real increase in risk for cardiovascular or cerebrovascular complications. As mentioned in the Scientific Statement, we welcome additional data such as that which likely to be forthcoming from the PRECISION trial.

2. **The stepped care approach oversimplifies the management of patients with rheumatic diseases and does not adequately address the anti-inflammatory benefits of NSAIDs.**

   We are in complete agreement with the ACR that specific suppression of the inflammatory processes is central to the management of arthritis, not only to improve symptoms but also to avoid tissue complications. We fully acknowledge the established expertise of rheumatologists in evaluation and management of patients with arthritis and sought, within the limitations of the space allocated for the Scientific Statement, to reference as much as possible the more global management strategies recommended by the ACR. For example, in the Scientific Statement we cite

an ACR guideline (2), and in the text of our statement emphasize the importance of categorizing patients into those with tendonitis/bursitis, degenerative joint problems, and inflammatory joint problems. Our statement that initial treatment should focus on nonpharmacologic approaches is consistent with prior publications by rheumatologists but does not diminish the importance of disease modifying treatments in patients with inflammatory arthritis or the well-recognized benefits of anti-inflammatory treatments. Rather, we sought to provide a cardiovascular perspective on the pharmacologic treatment options for management of musculoskeletal symptoms in patients with known heart disease or who are at risk of ischemic heart disease.

The American Heart Association wholeheartedly endorses collaboration between rheumatologists and cardiologists. Given the number of patients with arthritis and cardiovascular disease and the potential health consequences of the number of prescriptions written annually for the medications listed in our Figure 7, a rigorous weighing of the benefits and risks from both a rheumatologic and cardiovascular perspective is needed for optimum patient care.

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. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for the initial evaluation of the adult patient with acute musculoskeletal symptoms. *Arthritis Rheum.* 1996;39:1– 8.

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