Letter of Response to Antman et al AHA scientific statement

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The AHA recently published a position statement on the increased cardiovascular (CV) risk associated with nonsteroidal anti-inflammatory drugs (NSAIDs).[1] This statement made a distinction between traditional nonselective NSAIDs and COX-2 selective inhibitors, indicating that greater COX-2 selectivity is associated with greater CV risk.[1] A recent meta-analysis of randomized placebo-controlled trials of COX-2 selective inhibitors, however, did not support this alleged distinction[2]. No evidence of a significant difference in risk of antiplatelet trialists' collaboration (APTC) events between COX-2 selective inhibitors and non-naproxen NSAIDs was found. Furthermore, a significant dose-response relationship was shown for celecoxib and risk of APTC events, suggesting that low-dose celecoxib (200 mg/day, the recommended dose for osteoarthritis [OA]) was not associated with increased risk.[2] Moreover, among observational studies, no increased risk for celecoxib compared with non-use of NSAIDs for MI has been found.[3] These studies fail to show that COX-2 selective inhibitors differ from non-naproxen NSAIDs in CV risk.

In addition, the AHA statement does not consider the findings of the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), a large (n=18,325) 1-year outcomes study in OA patients which demonstrated that prespecified MI risk and incidence of APTC endpoint were not significantly different in patients treated with lumiracoxib 400 mg (4 x recommended dose in OA) compared to patients treated with naproxen 500 mg bid or ibuprofen 800 mg tid (numerical trend favoring naproxen over lumiracoxib and favoring lumiracoxib over ibuprofen; no formal non-inferiority testing performed).[4] Given that lumiracoxib is the most selective COX-2 inhibitor, these findings are contrary to the hypothesis from the AHA statement that increasing COX-2 selectivity is associated with greater CV risk.

The AHA statement also added that NSAIDs, and COX-2 selective inhibitors in particular, can elevate blood pressure and attenuate the benefit of antihypertensives.[1] Evidence again suggests that NSAIDs, as a class, affect salt and water retention and increase blood pressure, and that COX-2 selectivity does not determine their pressor effects. Indeed, lumiracoxib is associated with a lower BP compared with nonselective NSAIDs.[4]

Thus, NSAIDs, including COX-2 selective inhibitors, have a positive risk-benefit profile and are often a treatment option used for patients with arthritis pain as they provide more effective pain relief than acetaminophen, and opioid analgesics are limited to short-term use due to their deleterious side effects.[5] Treatment with both non-selective NSAIDs and COX-2 selective inhibitors should be individualized and used in adherence to current clinical and regulatory guidelines.

References

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Response to Schnitzer et al

We disagree with the contention by Schnitzer et al that NSAIDs, including COX-2 selective inhibitors have a positive risk-benefit profile. It is important to note that the AHA Scientific Statement on NSAIDs provided an analysis of the available data and recommendations for management of patients with known cardiovascular disease or who are at risk for ischemic heart disease. With this perspective in mind the TARGET trial comparing the highly COX-2 selective inhibitor lumiracoxib with naproxen or ibuprofen contributes relatively little relevant information.[1] Of the 18,532 with osteoarthritis enrolled in the TARGET only 24% were male and only 12-13% were judged to be at high cardiovascular risk. The trial design specifically excluded patients with a history of MI, stroke, CABG surgery, invasive coronary revascularization, or new-onset angina within the prior 6 months. Also excluded were patients with ECG evidence of a recent silent MI and those with NYHA class III-IV symptoms of heart failure. Not unexpectedly, the relatively low risk population enrolled in TARGET yielded only 109 cardiovascular endpoints (59 in the lumiracoxib group [0.65%] and 50 in the NSAID group [0.55%] through one year of followup. Even with this low event rate the hazard ratio of 1.14 is consistent with an increased risk of cardiovascular events with lumiracoxib and the upper bound of the 95% CI extends to 1.66.

It is misleading to cite the results of studies on such low risk patients and infer that NSAIDs in general and in particular lumiracoxib is safe in patients with heart disease. We stand by our recommendations for a stepped care approach as shown in Figure 7 of our Scientific Statement. Additionally, we refer Schnitzer et al to a previously published review in this area that emphasizes the strengths and weaknesses of various study designs with respect to the ability to detect a signal of harm with COX-2 inhibitors in randomized trials. [2]

1. Farkouh M et al Lancet 364: 675, 2004

2. Antman E et al Circulation 112: 759, 2005