



## What Effects Do NSAIDs and Dietary Supplements Have on Cardiovascular Risk?

An attendee of Updates in Cardiology Chicago posed the following challenge to Peter Libby, MD, Chief of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA. Following is the challenge and Dr Libby's response. *Please note that this activity is not certified for continuing medical education credit.*

### Q. Please comment on the utility of using NSAIDs, glucosamine chondroitin sulfate or folic acid to reduce risk of cardiovascular disease.

A. The implication of the question seems to be, since atherosclerosis is an inflammatory disease, could anti-inflammatory drugs reduce its incidence? For example, could corticosteroids or NSAIDs attenuate the severity of the underlying inflammation of atherosclerosis? The problem with the use of these types of global anti-inflammatory drugs is that they are too nonspecific to affect only the inflammatory processes of atherosclerosis and, therefore, are likely to produce other unwanted effects. For example, the corticosteroids can cause insulin resistance and/or high triglycerides. In fact, corticosteroids are actually associated with accelerated atherosclerosis<sup>1</sup> and have been shown in clinical trials to have adverse effects or neutral effects on patients who survive acute infarction.<sup>2</sup> In essence, although corticosteroids are great anti-inflammatory drugs they are too blunt a tool for use in treatment of atherosclerosis.

The NSAIDs, likewise, are very ambiguous kinds of agents for cardiovascular indications. NSAIDs tend to have deleterious renal effects. They can cause hypertension. Almost all of the NSAIDs that have been studied sufficiently have been shown, at least in observational data collections, to be associated with a slightly increased risk of adverse cardiac outcomes.<sup>3</sup> Although these studies reveal that the hazards of using NSAIDs on cardiovascular disease may be quite small, the population attributable harm may be much greater. For example, a few millimeters of increase in blood pressure over years in a large population of individuals who are exposed to NSAIDs can cause considerable morbidity.

Furthermore, the COX-2 inhibitors appear to have a thrombotic diathesis, perhaps because they selectively block the production of prostacyclin through COX-2 inhibition. Remember, prostacyclin is the "good guy prostaglandin." Prostacyclin's actions are vasodilatory and anti-aggregatory for platelets. The COX-2 inhibitors, however, don't block thromboxane, which is the "bad guy prostaglandin" that causes platelet aggregation and vasoconstriction. So, there may be an imbalance when you selectively block COX-2 that makes these selective NSAIDs even more hazardous to the cardiovascular system. However, we definitely need to have more information about the safety of the NSAIDs because many of our patients who have both cardiac disease, or risk factors for cardiovascular disease, and arthritis, find drugs of the COX-2 class very useful for managing their arthritis pain. There is a clinical trial ramping up now that will look at safety issues of celecoxib in patients who are at fairly high risk for cardiovascular disease. All of our data so far about cardiovascular safety and the COX-2 inhibitors have come as secondary observations from studies of patients treated for arthritis<sup>4</sup> or tumor prevention in persons with bowel cancer diathesis<sup>5</sup> so we really need to have the safety studies with use in patients with cardiovascular risk factors.

Glucosamine and chondroitin sulfate have been proposed as a way to forestall arthritis or arthritis pain because they are precursors of the proteoglycans in cartilage that tend to erode in osteoarthritis. While there is a lot of anecdotal evidence and popular interest in these substances, the latest clinical trial of their use for this purpose has been disappointing. The Glucosamine/chondroitin Arthritis Intervention Trial (GAIT), a randomized, placebo- and celecoxib-controlled trial of glucosamine, chondroitin sulfate, or the two in combination showed no objective evidence of benefit on osteoarthritic knee pain.<sup>6</sup>

Folic acid is probably important in keeping levels of homocysteine down. Elevated homocysteine is an independent risk factor for atherothrombosis. Those individuals who have hyperhomocysteinemia on a genetic basis tend to have thrombotic disease at a young age. However, in the general population, the hazards of homocysteine may be considered fairly minor. For example, higher values of C-reactive protein confer about a two-fold increase in risk when corrected for everything else. It appears that in a large population, however, homocysteine gives a relative risk of only approximately 1.1 to 1.2.<sup>7</sup> Folic acid, which does decrease homocysteine levels, has not been shown in intervention trials like the HOPE-2 trial to provoke a cardiovascular outcomes benefit.<sup>8</sup> In addition, in the US there is a secular trend towards a decrease in homocysteine levels because, as a public health policy measure, grains and cereal in the marketplace are being enriched with folate in an effort to reduce the incidence of neural tube defects (which are more likely to occur in fetuses of pregnant women who are deficient in folic acid). A benefit of the global supplementation of the diet with folic acid seems to be a drifting down of the average American homocysteine level. So even the modest hazard of cardiovascular risk due to homocysteine in the population may be declining. If you do have a patient with a nutritional deficiency who has reduced intake of dietary folic acid, then giving folic acid supplementation is reasonable. The theoretical downside of folic acid supplementation would be the potential to mask pernicious anemia.

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