A meta-analysis of randomized trials published in the Journal of the American Medical Association in 2001 raised cautionary flags about the effects of cyclooxygenase-2 (COX-2) inhibitors Vioxx and Celecoxib, which increased the relative risk of cardiovascular events and sudden or unexplained death and significantly increased the annual rates of myocardial infarction for patients receiving these agents. In the interval following this report, over 120 publications appeared concerning these unexpected problems, particularly as nonsteroidal antiinflammatory drugs (NSAIDs) had been prescribed in patient cohorts where atherosclerosis was likely to be prevalent. The results of randomized trials and observational studies led to the withdrawal of Vioxx from the market in September 2004.

This communication revisits effects of high-dose aspirin (13.5 mg/kg) and dipyridamole (15 mg/kg) in two animal models using equivalent doses of these agents prescribed for man for stroke prevention and treatment during the 1980s. Direct observations of arteries showed two unexpected effects: in arterial trauma, inhibition of reendothelization after injury with thicker intimal lesions after healing; and, in subhuman primates with atherosclerosis, progression of more severe plaques with unstable cores and thrombosis of arteries not before seen in this model.

In rabbits, after a standard arterial injury that caused aortic endothelialization, described by Bomberger and colleagues, endothelial regrowth was inhibited by 66% at 4 days, 22% at 7 days, and 28% at 14 days in animals receiving this drug combination. Sample results are illustrated in Figure 1, and later studies showed that the retarded healing caused by the aspirin-dipyridamole combination caused thicker intimal lesions. We recommended at that time that antiplatelet drugs should be used cautiously in our atherosclerotic patients.

In a study using 10 atherosclerotic rhesus monkeys in whom disease had developed after 58 months, we measured disease severity by angiography and arterial biopsies and then treated seven individuals with aspirin-dipyridamole for 12 months in equivalent daily doses suggested for humans at that time (four regular aspirin and eight dipyridamole tablets). The results proved dramatic and unexpected. Despite comparable serum cholesterol levels during the treatment period, ranging 309 to 668 mg/dL (average 501 experimental; 525 control), atherosclerotic plaques progressed much more rapidly in the ensuing 12 months in animals receiving the antiplatelet combination as measured by angiographic and morphometric grading. One animal on drug treatment developed thrombosis on a plaque of the left subclavian artery, its origin. Most significantly, plaques in the treated animals all exhibited deeply staining potentially unstable cores shown in representative carotid atheromas in Figure 2. Similar deeply stained cores and more severe lesions as compared with controls appeared in plaques sampled from the femoral, inferior mesenteric, and spermatic arteries and the infrarenal aorta.

Clearly, dipyridamole differs in its action from the current COX-2 inhibitors and other NSAIDs by its action as a coronary vasodilator. It acts on platelets as a phosphodiesterase inhibitor and antiaggregant. Was it this action that related to the development of accelerated atherosclerosis in our model? Would different doses of either aspirin or dipyridamole have made a difference?

This single study, though labor intensive, did not answer these questions. I was surprised at the time, however, that these observations did not attract more attention and interest, but let the matter drop. I now believe that the issue needs to be revisited for these classes of drug combinations. In cynomolgus monkeys, Hollander, long past, noted that the addition of aspirin-dipyridamole to a regression diet did not improve the course of disease in their model, but they did not impute specific harm.

At a time when some believe that all clinical scientific truth can be derived solely from randomized clinical trials, and given the expense, risks, and equivocations of some current trials, I suggest that COX-2 inhibitors for pain and other antiinflammatory/antiplatelet agents should be tested by preliminary observations on established atherosclerotic disease using animal models. Subhuman primates exhibit similar atherogenic responses to human disease: results will become evident by 12 months. Studies in affected subhuman primates could provide dose-related data and suggest guidelines before antiplatelet and antiinflammatory drugs are widely and publicly marketed to human beings with preexisting atherosclerosis.

References