More Data Fail to Resolve Issue of COX-2 Effect

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Contributing Writer

Despite widely reported results on the safety of Vioxx and now Celebrex and Bextra, there is still a paucity of information on the true long-term effects these drugs as a class, and all of it will take months —if not years— to sort out.

The future of celecoxib (Celebrex) was uncertain at press time. Pfizer Inc., its maker, has announced that an increased risk of heart problems was found in one of two trials examining celecoxib for the prevention of colon cancer. The National Cancer Institute, which was conducting the study for Pfizer, suspended use of the drug after finding a 3.4 times greater risk of cardiovascular events in those taking 400 mg of celecoxib twice daily and a 2.5 times greater risk in those taking 200 mg of the drug twice daily, compared with placebo patients. The average duration of treatment in the trial was 33 months.

There was no link between COX-2 use and nonfatal MI in one study, but rofecoxib was associated with 'significantly higher odds of MI' than celecoxib.

Soon thereafter, research investigators suspended the Alzheimer's Disease Anti-Inflammatory Prevention Trial after preliminary data indicated a 50% increased risk for cardiovascular events in participants assigned to take 220 mg twice daily of the nonselective NSAID naproxen (Aleve, Naprosyn). Yet no significant increase in cardiovascular risk was seen in participants taking 200 mg twice daily of celecoxib.

In separate press releases, the Food and Drug Administration and the National Institutes of Health announced that only preliminary data had been reviewed. The agencies are in the process of obtaining and reviewing all of the available data.

John M. Flack, M.D., director of the cardiovascular epidemiology and clinical applications program at Wayne State University, Detroit, said, "I don't think there's enough evidence at all to say this is a class effect, but I also don't think you can quite shut the door on it yet."

Leading up to the results of the adenoma prevention trial, the preponderance of evidence supported the notion that celecoxib (Celebrex) does not increase the risk of MI, but that rofecoxib (Vioxx), now removed from the market, does.

That view is supported by a study from Stephen E. Kimmel, M.D, and his associates at the University of Pennsylvania, Philadelphia. They reviewed records on 1,718 patients with a first, nonfatal MI who were admitted to 36 hospitals, and compared them with records on 6,800 randomly selected controls from the same five-county area in Pennsylvania (Ann. Intern. Med. 2005;142:157-64).

Patients were asked about their medication use through phone interviews (although only half responded), and were divided into nonusers of NSAIDs, rofecoxib users, celecoxib users, and nonselective NSAID users.

The investigators found that there was no link between COX-2 use and nonfatal MI, but the use of rofecoxib was associated with "significantly higher odds of MI," when compared with celecoxib (adjusted odds ratio 2.72).

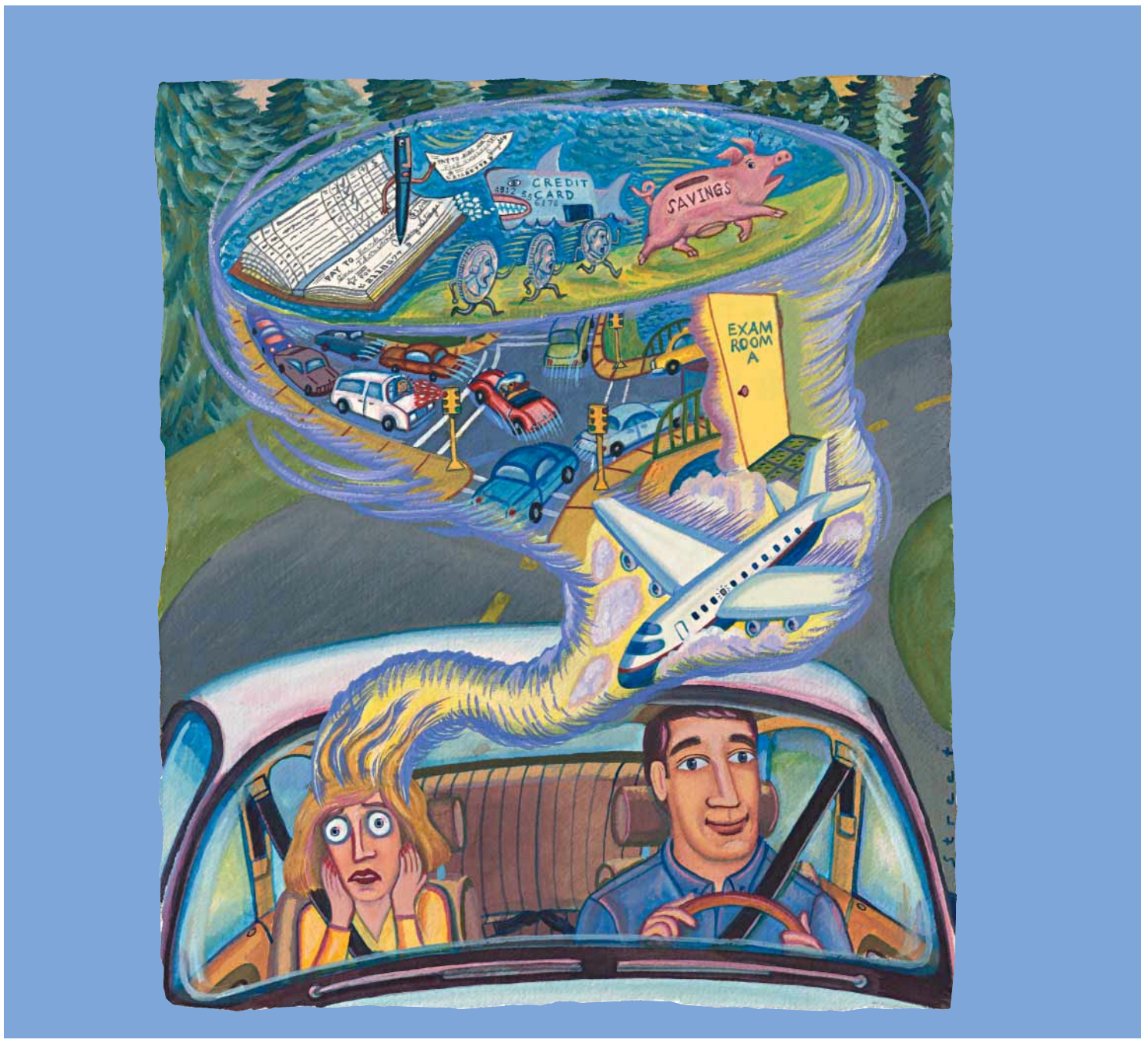
"The study supports the hypothesis that different COX-2 inhibitors differ in their cardiovascular effects," the authors wrote. Though the reason for the differences—and the potential clinical effect—still isn't clear, rofecoxib has been shown to cause greater increases in blood pressure and more peripheral edema, they noted. The study was supported by the National Institutes of Health, Searle Pharmaceuticals (now Pfizer), and Merck & Co.

In an accompanying editorial, Axel

NEXT ISSUE

'Acquainted With The Night'

The subject of Dr. Rodrigo Munoz's book review takes a negative view of the mental health profession.



Finckh, M.D., of Brigham and Women's Hospital, Boston, and Mark D. Aronson, M.D., of Beth Israel Deaconess Medical Center, Boston, said, "Overall, these studies suggest that not all COX-2 inhibitors share the same cardiovascular risk as rofecoxib, but the evidence is currently too limited to exclude the possibility of a COX-2 inhibitor class effect" (Ann. Intern. Med. 2005;142:212-4).

Noting that the drugs work by slightly different mechanisms and that there's still much that is not known, Dr. Flack said, "I think there are some bad actors in this class," and some that haven't been studied enough.

Even so, prior to the adenoma prevention trial, Dr. Flack said that he felt comfortable prescribing celecoxib, especially because those who took the drug in Dr. Kimmel's study were more likely to have cardiovascular risk factors, and yet still had a lower rate of MI.

See related story on page 87.

"In the face of conflicting evidence, when Celebrex is used it can be used most safely at dosages of under 400 mg/day. This new data will undoubtedly turn up the scrutiny of this class of drugs for cardiovascular safety," Dr. Flack noted.

At the same time, scrutiny of valdecoxib (Bextra) led the Food and Drug Administration to require a label revision warning against the drug's use in patients with coronary artery bypass grafts (CABG).

In early December, Pfizer added the warning on the basis of results of a Pfizer study of 1,500 patients who were treated after CABG. These results showed an increased risk of cardiovascular events, including heart attack, stroke, deep vein thrombosis, and pulmonary embolism.

At the same time, a black box warning was added to valdecoxib's label noting that the drug can cause potentially fatal skin reactions, most likely in the first 2 weeks of therapy. Because the drug contains a sulfa moiety, patients who are allergic to sulfonamides are more likely to have the skin reactions, according to the FDA.

The CABG warning came on the heels of a report by Garret A. FitzGerald, M.D., director of the center for experimental therapeutics at the University of Pennsylvania, of a metaanalysis of surgical patients in two studies in which patients taking valdecoxib had more than twice the risk of stroke and MI, compared with placebo patients. ■