HEART OF THE MATTER

AIM-HIGH and HDL

When the National Heart, Lung, and Blood Institute announced that the Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health (AIM-HIGH) trial was being terminated because of the futility of showing benefit, the study's failure made front page news.

The medical community, patient population, and interested public ask "why?" at this unexpected result of the study that compared extended-release niacin (Niaspan) plus simvastatin with placebo plus simvastatin.

ANTONIO M. GOTTO JR., M.D.

Cardiologists and lipidologists may be better able to answer this question when the full results are published. More information will certainly be required concerning the reported increase in stroke in the niacin arm (28 vs 12). At this stage, a hypothesis regarding the lack of benefit must be considered tentative at best.

However, the first thing that comes to mind is whether the study was sufficiently powered. A clinical trial currently underway at Oxford (England) University, HPS2-THRIVE, is comparing extended-release niacin and laropiprant (a prostaglandin receptor antagonist to decrease flushing approved in Europe but not the United States) against a background of simvastatin. HPS2-THRIVE aims to enroll 25,000 subjects, so this difference in size compared with AIM-HIGH must indicate large differences in expected event rate.

One should also bear in mind that the decrease in events reported with niacin in the Coronary Drug Project (J. Am. Coll. Cardiol. 1986;8:1245-55) was against a background of placebo. Statins have set a very high bar for efficacy, and it can be difficult to demonstrate incremental benefit with an add-on to statin therapy, as was the case in the ENHANCE trial with ezetimibe. In fact, there was substantial use of ezetimibe in the placebo group of AIM-HIGH, which therefore was not a true placebo group, in order to reach a target LDL cholesterol level of less than 80 mg/dL. This is somewhat ironic since niacin plus statin was reported to be more effective than ezetimibe plus statin in reducing carotid intima-media thickness in the ARBITER 6-HALTS study (N. Engl. J. Med. 2009;361:2113-22).

The National Lipid Association has recommended that physicians should wait until the full results of AIM-HIGH are reported before integrating the findings into their clinical practice, and that patients should not stop taking niacin without the advice of their physician.

I agree with this recommendation. It remains to be seen whether we will ever know the full explanation for the futility results of AIM-HIGH. We certainly will know much more when the results are analyzed and when HPS2-THRIVE is reported.

In the meantime, there are alternative ways of raising HDL currently being tested, including with the cholesteryl ester transfer protein (CETP) inhibitors anacetrapib and dalcetrapib, so the final results are far from complete concerning the benefit of raising HDL cholesterol, particularly in patients with low HDL cholesterol. AIM-HIGH does not disprove the theory that raising HDL will be beneficial, and there are abundant data showing that low HDL increases cardiovascular risk.

Hence, AIM-HIGH does not provide support for the "HDL hypothesis," but neither does it drive the final nail in the coffin. ■

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FDA Warns of Bladder Ca Risk With Type 2 Diabetes Drug Pioglitazone

Taking the type 2 diabetes drug pioglitazone for more than 1 year may increase the risk of bladder cancer, the Food and Drug Administration announced.

A review of the 5-year data from an ongoing 10-year epidemiologic study of almost 200,000 patients with type 2 diabetes found that overall, there was no increased risk of bladder cancer pioglitazone users compared with never-users, after adjustment for age, sex, smoking, use of other diabetes medications, and other risk factors. However, the risk did increase with higher doses and increasing duration of treatment: Treatment with pioglitazone for more than 12 months was linked with a 40% increase in the risk of bladder cancer.

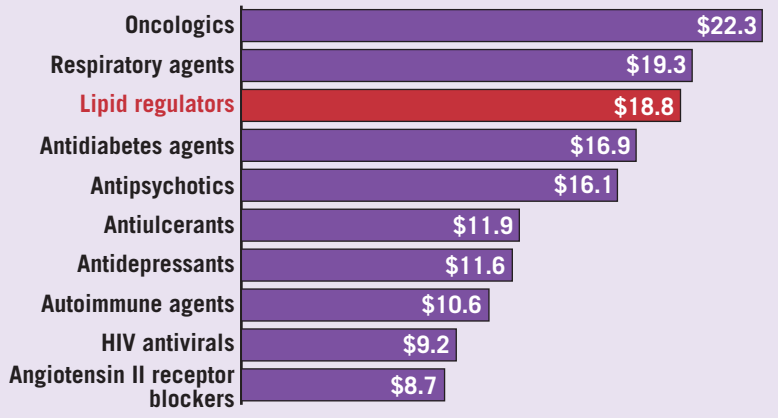
Pioglitazone, marketed as Actos (Takeda), is also available in combination with metformin (Actoplus Met, Actoplus Met XR) and with glimepiride (Duetact). The FDA is recommending that pioglitazone not be used in patients with active bladder cancer, and that it be used cautiously in patients with a history of bladder cancer.

The FDA also plans to review the results of a French study that prompted French authorities in June to suspend the use of the drug in France and German authorities to proscribe starting pioglitazone treatment in new patients.

–Elizabeth Mechcatie

VITAL SIGNS

Lipid Regulators Were the Third–Best-Selling Drug Class in 2010



Note: Figures represent U.S. wholesale revenue in billions.
Source: IMS Institute for Healthcare Informatics

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