Results of a controversial study as- say ability to slow atherosclerotic progression, when used in conjunction with a high dose statin regimen, have cardiologists split on whether the findings signal a flawed study or a flamed drug.

The results were “disappointing,” but not surprising because I had a lot of concern that this was not the right patient population and not the right methodol- ogy,” said Dr. Michael Davidson, professor of medicine and director of preventive cardiology at the University of Chicago.

But other experts cited the study’s nega- tive result to limitations of ezetimibe itself. “It appears that this method for lowering LDL cholesterol is not beneficial,” said Dr. Steven Nissen, chairman of the department of cardiovascular medicine at the Cleveland Clinic. “Statins do many other things that ezetimibe does not do: Statins raise HDL cholesterol, lower triglycerides, and reduce inflammation.”

One explanation why ezetimibe plus sim- vastatin failed to slow atherosclerotic pro- gression better than simvastatin alone “is that there are differences in the drug effects that go beyond their reduction of LDL,” commented Dr. Christie M. Ballantyne, professor of medicine at Baylor College of Medicine, Houston, and chair of the section of atherosclerosis and vascular medicine.

Amid a congressional investigation, re- sults from the Effect of Combination Ezet- imibe and High-Dose Simvastatin vs. Sim- vastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia (ENHANCE) trial were released months before a formal meeting report, in a statement issued by Merck/Schering-Plough Pharmaceuticals.

The company, which markets ezetimibe as a solo agent (Zetia) and in combination with simvastatin (Vytorin), had been under pressure to release results from the tri- al, which ended in April 2006. A full report is expected at the annual meeting of the American College of Cardiology in March. Merck also markets a formulation of simvastatin (Zocor).

ENHANCE was designed to test whether adding a 10 mg/day dosage of ezetimibe to an 80 mg/day dosage of simvastatin led to slower progression of atherosclerosis than use of the statin alone in patients with hetero- zygous familial hypercholesterolemia. The study randomized about 360 patients into two treatment arms; after washout, the mean baseline LDL cholesterol was about 319 mg/dL. Atherosclerotic burden was measured as intima-media thickness (IMT) using carotid ultrasound. The average base- line IMT in both groups was 0.69 mm.

Treatment with simvastatin alone over 2 years led to an average drop in LDL choles- terol of about 41% (a drop of about 130 mg/dL); the addition of ezetimibe led to a mean LDL decline of 58%, an additional 17% absolute drop that translated into an extra LDL fall of about 90 mg/dL.

Despite this LDL reduction, the average change in IMT was an increase of 0.0058 mm in the simvastatin-alone group, and an increase of 0.011 mm in those also treat- ed with ezetimibe. This difference in the primary end point was not statistically sig- nificant, and thus the findings failed to show a benefit from adding ezetimibe.

There was a small increase in atheroscle- rotic progression with ezetimibe—the rate was almost twice as great as among patients on simvastatin only—but the difference was not statistically significant. The study was not designed to assess clinical events such as cardiovascular deaths or myocardial infarctions. Clinical and adverse events were similar in both treatment arms.

The undeniable fact, however, was that treatment with ezetimibe in this study failed to slow further atherosclerotic pro- gression better than just cut LDL cholesterol to very low levels by a whopping additional 50 mg/dL. “It’s a paradox,” Dr. Nissen said. He cit- ed a similarly designed 2001 study with 330 patients with heterozygous familial hyper- cholesterolemia who had already been on statin treatment, and its reliance on IMT measurements at three different sites in the carotid arteries, some of which are hard to measure reliably, Dr. Davidson said. He cited an effort by Merck/Schering-Plough to refine the analysis by limiting the IMT measures used to only those from the common carotid as the main reason why release of the results had been delayed. Dr. Davidson is a consultant to and has re- ceived research support from Merck and Merck-Schering-Plough.

But relatively small, IMT studies have been fine in the past, contended Dr. Nis- sen, who disclosed that he has no conflicts of interest.

One thing experts agreed on was that ezetimibe’s role remains unchanged: it’s a second-line agent for patients who are already on a maximum statin dose but are still not at their LDL goal, and an alter- native for those who can’t tolerate statins.

But sales data suggest that not all pharma- ceuticals have been using it this way. According to two analyst reports, combined U.S. sales of Zetia and Vytorin were more than $3 billion in 2006, and during the first half of 2007 alone combined sales topped $2 billion.

Using ezetimibe first “was never an evi- dence-based position,” said Dr. Ballantyne, who is a consultant to and receives re- search support from Merck, Merck/Schering-Plough, and other companies.

Calcium Supplementation Increases MI Risk in Older Women

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Calcium supplementation significantly increased the risk of a myocardial infarction among healthy, post- menopausal women, compared with those taking plase- bo, in a secondary analysis of an osteoporosis study.

Physicians should consider this increased cardiovascu- lar risk against other clinical benefits of calci- um supplementation in older women until confirmatory studies can be completed, the authors suggested. “It is an important finding because so many women are prescribed calcium supplements,” Dr. Barbara Redberg said in an interview. “I would not recommend calcium supple- mentation based on this finding.” This raises enough evidence of benefit without risk,” said Dr. Redberg, who was not involved in the study.

The HDL/LDL cholesterol ratios improved among the 732 women who took daily calcium supplementation, compared with the 739 participants who took placebo. This suggests that a different calcium form spurred the in- crease in myocardial infarction.

“Is this an interesting point. It shows that just im- proving cholesterol does not reduce the risk of a heart attack,” Dr. Redberg, chair of the department of cardiovas- cular services and professor of medicine at the Uni- versity of California, San Francisco. “It was the same find- ing with estrogen: It lowered LDL, increased HDL, but did not reduce the number of heart attacks in studies.”

The current findings contrast with previous suggestions of cardiovascular benefit from calcium supplemen- tation. One study found that calcium increases the HDL/LDL cholesterol ratio by almost 20% (Am. J. Med. 2002;112:343-7). In another, a one-third decrease in deaths from cardiovascular events was observed among women who had the greatest intake of calcium from ei- ther diet or supplements in the Iowa Women’s Health Study (Am. J. Epidemiol. 1999;149:151-61).

Following completion of a 5-year osteoporosis study (Am. J. Med. 2006;111:777-85), Dr. Mark J. Bolland and his associates at the University of Auckland (New Zealand) reaccessed their data to compare cardiovascular events. Women were randomized to 1 g/day of elemental calcium (Citracal) or placebo. All of the 1,471 participants were postmenopausal for at least 5 years and older than age 55 years at baseline, and 10% of those were older than age 80 at baseline.

Death, sudden death, myocardial infarction, angina, other chest pain, stroke, and transient ischemic attacks were all events. A total of 136 women in the calcium group stopped taking the placebo before the study end. A total of 21 of the 732 women in the calcium group experienced cardiovascular events, compared to 12 events in the placebo group who had 10 such events. A composite end point of sudden death, myocardial infarction, angina, or chest pain was also higher in the calcium group (155 events among 87 women) compared with the placebo group (137 events among 93 women). No significant differences were found in angina, chest pain, transient ischemic attack, stroke, or sudden death events between groups. There were 34 deaths in the calcium group and 29 in the placebo, a nonsignificant difference.

Dr. Redberg was not surprised by the elevated MI risk. She said research by Linda Demer, vice chair of med- icine at the University of California, Los Angeles, has in- dicated increased cardiovascular risk associated with calcium. “It’s called the calcium paradox. Women lose calcium from their bones as they get older and it ends up in their arteries and the lining of their vessel walls, lead- ing to accelerated atherosclerosis. This study is a confirma- tion of that hypothesis.”

The mean age was 74 years and all participants were white, a possible limitation for generalizing results to oth- er ages or racial groups, the authors said. However, Dr. Redberg said that the inclusion of older women in the study is a strength because they are the most likely to be prescribed calcium supplements. It is very unusual for studies to include people older than age 80, she added.

“What is effective for women for preventing osteo- porosis?” Dr. Redberg said. “First we had estrogen, then calcium, and now we have seen that all have been shown to have significant side effects or risk. It may be safer to prescribe diet and weight-bearing ex- ercises to prevent osteoporosis.”