Ezetimibe Gets LDL to Goal in High-Risk Patients

BY BRUCE JANCIN
Denver Bureau

BARCELONA — The addition of 10 mg/day of ezetimibe to maximum-dose rosuvastatin in a high-risk population enabled 94% of the patients to achieve an LDL-cholesterol level below the goal of 100 mg/dL and 80% to get below 70 mg/dL, Dr. Christie M. Ballantyne reported at the joint meeting of the European Society of Cardiology and the World Heart Federation.

The combination also tripled the success rate in achieving both an LDL-cholesterol level below 70 mg/dL and a high-sensitivity C-reactive protein level (CRP) under 2.0 mg/L, compared with the results with 40 mg/day of rosuvastatin alone, added Dr. Ballantyne, professor of medicine at Baylor College of Medicine, Houston.

The National Cholesterol Education Program recommends the 70-mg/dL LDL-cholesterol target as an optional, more aggressive goal in very-high-risk patients.

Getting the CRP below 2.0 mg/L isn't currently recommended in any major guidelines; however, a recent secondary analysis of the PROVE-IT trial (J. Am. Coll. Cardiol. 2005;45:1644-8) concluded that rates of recurrent MI or cardiovascular death were lower in patients who achieved their LDL target plus a CRP below 2.0 mg/dL than in those who met their LDL goal but had an elevated CRP, he said.

Dr. Ballantyne reported on 469 high-risk patients in the United States, German-speaking Europe, and South Africa who participated in the Examination of Potential Lipid-Lowering Effects of Rosuvastatin in Combination With Ezetimibe Versus Rosuvastatin Alone (EXPLORER) trial.

The participants were randomized to 6 weeks of open-label daily rosuvastatin (Crestor) at 40 mg or to ezetimibe (Zetia) 10 mg plus rosuvastatin 40 mg. The mean baseline LDL cholesterol was 190 mg/dL, and more than one-third of EXPLORER participants had diabetes, a coronary heart disease (CHD) equivalent.

Study participants who received the combination therapy showed greater improvement in levels of LDL cholesterol, CRP, and triglycerides, as well as the ratio of LDL to HDL cholesterol than did those with rosuvastatin alone (See box above.)

This was a high-risk population similar to the patients who were enrolled in the Scandinavian Simvastatin Survival Study (4S) in the 1990s, Dr. Ballantyne noted in an interview.

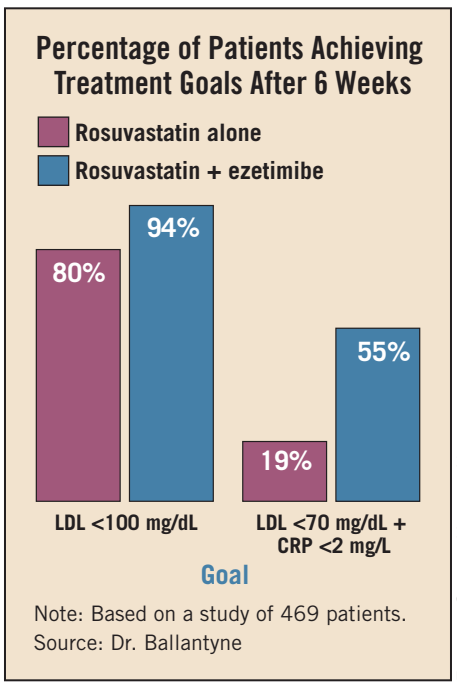
"The 4S study was really a landmark trial. They were able to reduce LDLs of 190 mg/dL by 35%, and it reduced events by 35% with a 42% decrease in CHD mortality. So it's amazing that here we are 12 years later and we're doing a study in which we took LDLs of 190 and reduced them by 70%, down to a mean of 57 mg/dL, and with an LDL-to-HDL ratio of just about 1," Dr. Ballantyne continued.

Both treatments were well tolerated. The price paid in terms of side effects for the combination therapy's greater efficacy was limited to an increased incidence of abnormal liver function tests, rising from 0.4% with rosuvastatin alone to 2.5%.

The laboratory abnormalities were readily reversed upon discontinuation of the ezetimibe.

A large-scale, long-term randomized trial of the rosuvastatin/ezetimibe combination with clinical end points is not in the cards, since the drugs are marketed by different companies, he said. However, such a study is already underway comparing ezetimibe plus simvastatin with simvastatin alone. Both are made by AstraZeneca, which sponsored the EXPLORER trial.

Dr. Ballantyne has received research support and consulting fees from AstraZeneca and from Merck Schering Plough, which markets ezetimibe. ■



ELSEVIER GLOBAL MEDICAL NEWS

6-Week Outcomes in EXPLORER

	Rosuvastatin (40 mg) Plus Ezetimibe (10 mg)			Rosuvastatin (40 mg) Alone		
	Baseline	Week 6	Reduction	Baseline	Week 6	Reduction
LDL cholesterol (mg/dL)	189	57	70%	191	82	57%
LDL/HDL ratio	4.1	1.1	72%	4.1	1.6	60%
CRP (mg/L)	2.5	1.2	46%	2.4	1.7	29%
Triglycerides (mg/dL)	186	114	35%	186	138	25%

Note: Based on a study of 469 patients.
Source: Dr. Ballantyne

ELSEVIER GLOBAL MEDICAL NEWS

FDA Warns Ibuprofen May Block Aspirin's Cardioprotection

BY ELIZABETH MECHCATIE
Senior Writer

Concomitant use of low-dose aspirin and ibuprofen may interfere with aspirin's antiplatelet effects, possibly attenuating its cardioprotective benefits, according to a recent statement by the Food and Drug Administration's arm responsible for compiling adverse drug events.

"Platelet function tests suggest there is a pharmacodynamic interaction between 400 mg of ibuprofen and low-dose aspirin when they are dosed concomitantly," the FDA wrote in a statement posted on its MedWatch Web site in September.

Experts stress, however, that virtually all nonsteroidal anti-inflammatory drugs have the potential to interfere with aspirin's cardioprotective effects. Compared with ibuprofen, there may be fewer data on the other NSAIDs, but "if physicians only pay attention to the FDA statement" they're likely to miss the potential effects of these other NSAIDs on aspirin's antiplatelet properties, said rheumatologist Dr. Roy Altman, of the University of California, Los Angeles.

The FDA's statement reinforces the importance of asking patients about over-the-counter drug usage. "Some colleagues may have let that mind-set go by the wayside," said family physician Thomas A. Kintanar of Indiana University School of Medicine's Fort Wayne branch. It also doesn't hurt to focus on ibuprofen, which is one of the most widely used OTC drugs on the market.

Nevertheless, clinical studies have yet to be conducted to evaluate and quantify the inhibitory effect of ibuprofen on aspirin.

Nor are enough data available to address the effect of taking less than 400 mg of ibuprofen on aspirin's cardioprotective effects. And there are "no clear data" on the potential antiplatelet effects associated with the chronic use of ibuprofen at doses above 400 mg.

The FDA advised health care professionals to counsel patients taking immediate-release low-dose (81 mg) aspirin (not enteric coated) and 400 mg of ibuprofen to take the ibuprofen at least 8 hours before or at least 30 minutes after taking the aspirin to minimize the pharmacodynamic interaction. Other analgesics that do not interfere with aspirin's antiplatelet effects "should be considered" for patients at high risk for cardiovascular events. However, other nonselective, over-the-counter NSAIDs should also be considered as having the potential to affect the antiplatelet benefits of aspirin "unless proven otherwise."

The warning reinforces the importance of asking patients about over-the-counter drug usage.

DR. KINTANAR

The recommendation on timing of the ibuprofen dose does not apply to patients taking enteric-coated low-dose aspirin, as such an advisement cannot be made based on the data available. Only one study showed that when 400 mg of ibuprofen is administered 2, 7, and 12 hours after enteric-coated low-dose aspirin, the antiplatelet effects are attenuated.

The mechanism underlying the aspirin-ibuprofen interaction may be due to "competitive inhibition of the acetylation site of cyclooxygenase in the platelet," according to the FDA. Occasional use of ibuprofen, it said, is unlikely to have a negative impact on aspirin's cardioprotective effects because of the long-lasting effects of daily aspirin.

Dr. Raymond Gibbons, president of the American Heart Association (AHA), said in an interview that although the potential interaction between ibuprofen and aspirin has been recognized as a concern in the past, the advisory is a useful reminder to health care professionals about this issue.

These concerns are based on science that dates back to 2001, he said, adding that an AHA scientific advisory in the spring of 2005 on cyclooxygenase-2 inhibitors noted that data showed that ibuprofen interfered with aspirin and could possibly reduce the protective effects of aspirin.

He stressed the importance of the recommendation that analgesics that do not interfere with the antiplatelet effects of aspirin should be considered for high-risk patients. The data on ibuprofen are "far more suggestive of a problem" than, for example, data on acetaminophen or diclofenac, which are not associated with this risk, said Dr. Gibbons, the Albert M. and Gladys Gray professor of medicine at the Mayo Medical School, Rochester, Minn.

As for the recommendation on timing the ibuprofen and aspirin doses to avoid the interaction, Dr. Gibbons said he would be "cautious" about relying on appropriate timing, "because we don't have a tremendous amount of evidence in the presence of all the confounders" in patients. "I'd feel more comfortable if we emphasize the importance of this potential interaction and avoid ibuprofen in high-risk patients."

Dr. Kintanar said he'd be comfortable allowing a compliant patient to follow the FDA's advice. However, it is rare to have that comfort level about a patient's level of compliance, he said.

For more information, go to www.fda.gov/medwatch/safety/2006/safety06.htm#aspirin. ■