High-Dose Statins Standard for Coronary Disease

BY MITCHEL L. ZOLER
Philadelphia Bureau

DALLAS — Aggressive statin therapy is now the standard of care for patients with established coronary heart disease, even though the results from the most recent major study of a high-dose statin regimen failed to show a statistically significant benefit, compared with a lower-dose statin regimen, in almost 9,000 patients.

The 11% relative reduction in major coronary events (death, myocardial infarction, or cardiac arrest and resuscitation) seen in the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study, which compared a 80 mg/day regimen of atorvastatin against a 20 mg or 40 mg/day regimen of simvastatin, was "consistent with the results of other statin trials, such as PROVE-IT and TNT," Dr. Terje R. Pedersen said at the annual scientific sessions of the American Heart Association.

"There is no doubt that lower levels of low-density lipoprotein cholesterol are better," said Dr. Pedersen, a professor of medicine and director of the Center for Preventive Medicine at Ullevål University Hospital, Oslo. He was the lead investigator for the IDEAL study, which was published concurrently with his report at the meeting (JAMA 2005;294:2437-45).

The results of both IDEAL and TNT (Treating to New Targets) "strengthened the case for incremental benefits from lowering LDL cholesterol well below 100 mg/dL," commented Dr. Scott Grundy, director of the Center for Human Nutrition at the University of Texas Southwestern Medical Center in Dallas. Regimens that produce very low levels of LDL cholesterol "will be increasingly accepted as the standard treatment for secondary prevention."

'Results from a single trial are sometimes hard to interpret ... but if you put them all together, people are moving toward more intensive statin treatment.'

"Results from a single trial are sometimes hard to interpret. The results from IDEAL, TNT, PROVE-IT [Pravastatin or Atorvastatin Evaluation and Infection Therapy], REVERSAL [Reversal of Atherosclerosis With Aggressive Lipid Lowering], and other trials may not always reach statistical significance, but if you put them all together, people are moving toward more intensive statin treatment," commented Dr. Steven E. Nissen, medical director of the Cardiovascular Coordinating Center at the Cleveland Clinic. "You should try to get the LDL cholesterol as low as you can, safely. In both IDEAL and TNT, most patients did not get to 70 mg/dL or less, but even if only 25%-35% of patients get there, that's good."

IDEAL enrolled 8,888 patients aged 80 or younger who had a history of a definite myocardial infarction and who qualified for statin therapy based on national treatment guidelines at the time of enrollment. Patients were entered at 190 ambulatory cardiology and private specialist centers in Denmark, Finland, Iceland, the Netherlands, Norway, and Sweden from March 1999 to March 2001. Patients were randomized to treatment with either 20 mg/day simvastatin or 80 mg/day atorvastatin and followed for an average of 4.8 years.

After the first 24 weeks of treatment, 21% of patients in the simvastatin group had their dosage raised to 40 mg/day; by the end of the study, 23% of patients in the simvastatin group were receiving 40 mg/day, with the rest on 20 mg/day. By the end of the study, 13% of patients in the atorvastatin group were receiving 40 mg/day, with the remainder on 80 mg/day.

The incidence of major coronary events was 10.4% in the simvastatin group and 9.3% in the atorvastatin group, an 11% relative risk reduction that fell slightly short of statistical significance. But Dr. Pedersen said that other secondary end points showed statistically significant differences in favor of the high-dose group, including a 13% relative reduction in major cardiovascular disease events and a 16% cut in any coronary heart disease event.

With safety data from almost 4,000 patients treated with 80 mg/day of atorvastatin for almost 5 years, the results also bolstered the apparent safety of aggressive lipid lowering. The results showed no difference between the two groups in all-cause mortality, and no difference between the two study groups in the incidence of serious adverse events. A small proportion of patients, less than 1.5%, had major liver enzyme elevations on the 80-mg/day regimen. Myopathy was diagnosed in 0.14% of patients on this regimen, and 0.05% had rhabdomyolysis.

The IDEAL study was sponsored by Pfizer Inc. Dr. Pedersen has been a consultant to and a speaker for Pfizer. ■

Statins Don't Affect Risk of Cancer, Metaanalysis Finds

BY MARY ANN MOON
Contributing Writer

Statins neither raise nor lower the risk of cancer or cancer mortality, according to a metaanalysis of 26 randomized clinical trials.

Several retrospective studies have suggested that statins reduce the risk of developing cancer by as much as 50%. Some researchers have proposed that the drugs may inhibit carcinogenesis by decreasing systemic inflammation, interfering with neovascular formation, and inhibiting cell proliferation.

However, three metaanalyses have failed to confirm that statins exert a protective effect against cancer, and some investigators have noted that statins have properties that could actually enhance cancer risk, such as inhibiting selenoprotein synthesis and impairing the function of natural killer cells.

To shed light on the issue, Krista M. Dale, Pharm.D., of the University of Connecticut School of Pharmacy, Hartford, and her associates conducted a much larger metaanalysis of 26 randomized clinical trials involving 86,936 subjects. The participants were followed up for 2-10 years for the development of cancer.

The trials included only placebo-controlled or standard-treatment-controlled studies enrolling a minimum of 100 subjects each. Most of these trials assessed the ability of statins to prevent coronary artery disease, but all examined cancer diagnosis or cancer death as a primary or secondary end point.

Statins did not reduce the risk of cancer or of cancer death, Dr. Dale and her associates said (JAMA 2006;295:74-80).

When six major subtypes of cancer—breast, colon, gastrointestinal, prostate, respiratory tract, and skin cancers—were considered individually, statins did not reduce the risk of any of these types.

Similarly, when pravastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, and lovastatin were considered individually, none of the agents reduced the risk of cancer or cancer death.

And when the metaanalysis was narrowed to assess natural versus synthetic statins and low-lipophilic versus high-lipophilic statins, the results did not change.

"We thought that hydrophilic statins, with their impaired ability to penetrate biological membranes, might provide different effects than lipophilic statins, which readily enter cells, but this was not evident in our study. Similarly, naturally derived statins have a markedly different structure than synthetic statins, but neither type affected the results," the investigators noted.

"Our results are in agreement with three previous case-control studies that found that statins did not reduce the incidence of cancer," Dr. Dale and her associates said. ■

Fiber Intake May Influence C-Reactive Protein Level in Higher-Risk Patients

BY PATRICE WENDLING
Chicago Bureau

QUEBEC CITY — Increasing dietary fiber intake might be warranted in patients with diabetes, hypertension, and obesity, Dr. Dana King said at the North American Primary Care Research Group annual meeting.

Dr. King presented a study in which adults with low fiber intake and at least two of the three conditions were twice as likely to have elevated C-reactive protein (CRP) levels, compared with adults with no risk conditions, even after controlling for confounding factors. In addition, the influence of fiber on CRP values was greater as the number of conditions increased, said Dr. King, professor at the Medical University of South Carolina, Charleston.

There is some evidence to suggest that dietary fiber reduces cholesterol and influences inflammation. But CRP increases the risk of cardiovascular disease independently from cholesterol, he said.

Both the American Diabetes Association and the American Heart Association suggest adults consume 25-30 g of fiber per day. However, neither group has specific recommendations for higher intake among high-risk patients, Dr. King said.

The cross-sectional study included 7,891 participants in the 1999-2002 National Health and Nutrition Examination Survey at least 20 years of age who had valid high-sensitivity CRP measurements and dietary information. The participants were asked to recall fiber consumption in the previous 24 hours. Fiber supplements were not counted toward total intake.

Individuals with two or more conditions—diabetes, hypertension, or obesity—who consumed 20 g per day or more of fiber had significantly lower median CRP (3.1 mg/L) than people who consumed 8.8 g/day or less (4.5 mg/L).

CRP was four times higher in people with these conditions who consumed less than 8.8 g/day of fiber than people without these conditions (1.4 mg/L).

Even after controlling for age, race, gender, and tobacco use, adults with two or more conditions had double the risk of having elevated CRP (odds ratio 2.3), compared with adults with no risk conditions (OR 1.5). Only 2%-3% of patients in the study had rheumatoid arthritis, which can raise CRP levels.

Only dietary fiber showed a consistent association with CRP. There was no consistent association between CRP and other dietary components such as fat, polyunsaturated fat, protein, carbohydrates, or fish-oil consumption, he said.

It's unclear what biological mechanisms might be at work, but fiber itself might not be the source of the observed benefits.

"We could very well be looking at a surrogate," Dr. King said. "Fiber may not be changing CRP. There have been a couple of studies, including our own, that have looked at other things that travel along with fiber, other nutrients, such as magnesium.

"There is a high correlation between magnesium intake and fiber intake, and there is a high predictive value of high magnesium intake and lower blood pressure and lower cardiovascular disease. So they may be traveling together. We are still in the process of sorting these things out." ■