Rosuvastatin Linked to Excess Adverse Events

Use is associated with reports of rhabdomyolysis, proteinuria, nephropathy, and renal failure.

BY MITCHEL L. ZOLER
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Newly published analysis of the adverse event reports filed during the first year rosuvastatin was on the U.S. market showed that its use was linked to significantly more adverse events than other statins.

From October 2003 to September 2004, more than 5 million prescriptions for rosuvastatin (Crestor) were filled in the United States. Rosuvastatin use was associated with about 28 adverse events reports of rhabdomyolysis, proteinuria, nephropathy, or renal failure for every 1 million prescriptions filled, a rate two to eight times higher than that for atorvastatin (Lipitor), pravastatin (Pravachol), or simvastatin (Zocor), according to a report published online (Circulation [Epub ahead of print], May 23, 2005. Article DOI number: 10.1161/circulationaha.105.555482. Available at www.circ.ahajournals.org).

But experts differed on the clinical message of these findings.

"This additional safety information is important for both patients and physicians to consider, among other factors, when balancing the risks and benefits in choosing a statin," said Richard H. Karas, M.D., director of the Preventive Cardiology Center and the Women's Heart Center at Tufts–New England Medical Center in Boston, and senior author of the new report. He and his associates concluded that "it would seem prudent at the current time for health care providers to consider other statins as first-line therapy."

A more skeptical reading of the findings was given by Scott M. Grundy, M.D., who wrote an editorial that accompanied the report (Circulation [Epub ahead of print], May 23, 2005. Article DOI number: 10.1161/circulationaha.105.557652. Available at www.circ.ahajournals.org).

"I don't see any clear-cut evidence to choose one statin over another," he said during a press briefing. "On the basis of this study, I don't know that rosuvastatin is more dangerous" than other statins, said Dr. Grundy, director of the Center for Human Nutrition at the University of Texas Southwestern Medical Center in Dallas.

Dr. Grundy cited the limitations of adverse event reports as a way to gauge the safety of a drug and to compare safety among drugs. He also noted that in March 2005, the Food and Drug Administration denied a request to remove rosuvastatin from the U.S. market that had been filed last year by Sidney M. Wolfe, M.D., director of the Health Research Group of Public Citizen.

"The FDA had the same database [that Dr. Karas used] and they did not determine that rosuvastatin was more dangerous [than other statins]," Dr. Grundy said at the press briefing. "The disagreement is about whether the evidence is strong enough evidence to say that there is a difference [among statins]. The new paper says there might be, but the FDA did not reach that conclusion."

The new study analyzed reports for a variety of individual adverse events, such as myopathy and liver effects, as well as for several combinations of events including the primary analysis, which totaled the reports of rhabdomyolysis, proteinuria, nephropathy, or renal failure.

The analysis looked at reports for all statins during the first 12 months when rosuvastatin was available in the United States, as well as reports that were made during the year when each statin was first available. This additional analysis was included because adverse event reports are often more common when a drug is first sold, Dr. Karas said.

The consistent pattern in virtually all of these comparisons was that the number of adverse event reports for rosuvastatin was significantly higher than for atorvastatin, pravastatin, or simvastatin.

Dr. Karas noted that the adverse events associated with rosuvastatin did not seem to be linked with overdosing, because the average dosage in these reports was 17 mg/day, and more than 60% of patients in the reports received 10 mg/day or less. The approved dosage for rosuvastatin is 5-40 mg/day.

Despite the significantly higher relative risk linked to rosuvastatin use, Dr. Karas as well as the other speakers at the press briefing stressed that the absolute incidence of adverse events was low with rosuvastatin as well as with all other approved statins.

"This paper heightens our sensitivity to the possibility of a signal of increased adverse events with rosuvastatin, but it has limitations," commented Elliott Antman, M.D., director of the coronary care unit at Brigham and Women's Hospital in Boston and senior associate editor of Circulation.

"The overarching issue is to get patients [who need treatment] on statins to help achieve their lipid goals. If rosuvastatin is the statin that is most available to a patient based on insurance reimbursement, then that's perfectly acceptable," Dr. Antman said. ■

Adverse Event Reports for Statins

	Rosuvastatin	Atorvastatin	Pravastatin	Simvastatin
Number of AERs*	145	315	52	381
Number of prescriptions	5,200,000	72,900,000	15,000,000	29,800,000
AERs per 1 million prescriptions	27.9	4.3	3.5	12.8

*AERs = composite total of adverse event reports, including reports of rhabdomyolysis, proteinuria, nephropathy, and renal failure.

Note: Based on data from October 2003 to September 2004, the first year of marketing for rosuvastatin.

Source: http://circ.ahajournals.org/cgi/reprint/circulationaha.105.555482v1

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Natural Supplements: An Option for Lowering Blood Lipids

BY DOUG BRUNK
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LA JOLLA, CALIF. — Several natural supplements are useful for lowering blood lipids, Erminia M. Guarneri, M.D., said at a meeting on natural supplements in evidence-based practice sponsored by the Scripps Clinic. They include:

► **Soluble fiber.** Ingesting 2-10 g/day of soluble fiber has been found to lower total cholesterol levels by 15%-18% (Am. J. Clin. Nutr. 1999;69:30-42). Common sources include oats, psyllium, pectin, and guar gum. GI complaints from ingesting soluble fiber are frequent.

► **Phytosterols.** Produced by plants, these substances impair intestinal absorption of cholesterol. Studies have found that 2-3 g/day of phytosterols can reduce LDL-cholesterol levels by 10%-15%. In one study of 167 patients on stable statin therapy, the 83 patients who received three servings per day of a plant stanol-ester spread showed reduction in LDL cholesterol of more than 16% at 8 weeks, compared with a nearly 7% reduction in the 84 placebo patients. The stanol spread provided the equivalent of 2-3 g/day of phytosterols (Am. J. Cardiol. 2000;86:46-52).

In an unpublished study of 14 Scripps patients who were "maxed out on nutrition and cholesterol-lowering medicines," adding 2 g/day of phytosterols led to a 14% reduction in total cholesterol, a 16% reduction in LDL cholesterol, an 11% reduction in triglycerides, and a 2% increase in HDL cholesterol.

Although some margarines contain phytosterols, those foods should be avoided, especially if they contain partially hydrogenated oils, said Dr. Guarneri, a cardiologist who is founder and medical director of the Scripps Center for Integrative Medicine in La Jolla, Calif. She recommends getting phytosterols from two products: CholestePure (Emerson Ecologics) and UltraMeal Plus (Metagenics).

► **B vitamins.** Deficiencies of vitamin B_6, vitamin B_{12}, and folic acid have been linked to elevated plasma homocysteine levels, which are a strong predictor of mortality in coronary artery disease patients.

In fact, one study of 587 coronary artery disease patients found that the risk of mortality was 3.8% for those with a plasma homocysteine level of less than 9.0 μmol/L and 24.7% for 15 μmol/L or greater.

Dr. Guarneri recommends Cardio B (Ortho Molecular Products), a mix of folic acid and vitamins B_6 and B_{12}, "in one pill, instead of popping a bunch of pills," she said at the meeting, which was cosponsored by the University of California, San Diego.

► **Niacin.** Regular use of this supplement has been found to lower LDL cholesterol by 5%-25%, lower triglycerides by 20%-50%, and raise HDL cholesterol by 15%-35%.

"The first treatment [for low HDL] is to get the weight off the midline," Dr. Guarneri said. "But if I have to reach for a supplement to fix this, I fix it with niacin," he added. "People often see me and say, 'I'm drinking all this wine to raise my HDL.' A lot of times all that wine gives you more weight on the midline, so that's not necessarily the solution. The niacin is."

Side effects may include flushing, hyperglycemia, hyperuricemia, upper GI distress, and hepatotoxicity.

Niacin is contraindicated in patients with liver disease and severe gout, and in those with peptic ulcer.

"I like short-acting niacin so people can take it with each meal if they need to, as opposed to the long-acting prescription niacin, which you're really only supposed to take once a day," she added. "When I use short-acting niacins, I can also use them at higher doses. Start low and go up slowly, [but] you do have to monitor liver function."

For patients with arrhythmia, Dr. Guarneri called magnesium one of her favorite supplements to use. Magnesium is a front-line treatment for torsades de pointes, and some studies have found it beneficial for mitral valve prolapse patients who have low magnesium levels.

"At least one study demonstrated a decrease in blood pressure with a 1,000-mg dose [of magnesium]," she said. "If someone has normal renal function, and they have arrhythmia or skipped heartbeats, and I get them off caffeine and sugar, I will use chelated magnesium and titrate it and warn them about the potential for soft stool."

The cardiac benefits of the following supplements are less clear, she noted, and called for more research on them: L-arginine, coenzyme Q_{10}, hawthorn, ginkgo biloba, red yeast rice, policosanol, and horse chestnut.

Dr. Guarneri said that she has no financial interest in any of the products she recommended. ■