Vytorin Cut Cardiac Risk in Kidney Disease

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DENVER – A once-daily combination of ezetimibe 10 mg and simvastatin 20 mg reduced the risk of major atherosclerotic events in patients with chronic kidney disease by 16.5%, according to a randomized, placebo-controlled trial funded by the drug's maker, Merck.

However, the combination (trade name Vytorin) did not slow progression to end-stage renal disease in the trial or significantly impact mortality.

The "trial results provide clear evidence that lowering cholesterol with [Vytorin] reduces the risk of major atherosclerotic events," in patients with chronic kidney disease, said Dr. Colin Baigent, Oxford University professor of epidemiology, and the lead investigator of the Study of Heart and Renal Protection (SHARP) trial. He presented the study results at the meeting.

Merck will seek Food and Drug Administration approval for Vytorin use in chronic kidney disease (CKD) patients based on the SHARP trial results, the company said.

In SHARP, 4,650 patients with CKD were randomized to Vytorin, and 4,620 to placebo. The median duration of therapy was 4.9 years. The mean age at baseline was 62 years, and patients had no revascularization or MI histories; 23% had diabetes, and 15% had vascular disease.

About a third of the patients started the trial on dialysis; the remainder had a baseline average estimated glomerular filtration rate of 26.5 mL/minute per 1.73 m^2.

The average LDL cholesterol at enrollment was 108 mg/dL. Midway through the trial, Vytorin lowered LDL cholesterol by an average of 32 mg/dL.

Major atherosclerotic events – coronary death, MI, nonhemorrhagic stroke, or revascularization – occurred in 11.3% (526) of patients in the Vytorin group, and in 13.4% (619) of patients in the placebo group. That translated to a significant 16.5% risk reduction among Vytorin users, results similar to previous statin studies in other populations, Dr. Baigent noted.

The rate of treatment compliance was about two-thirds among patients in both the placebo and Vytorin arms of the trial. "With full compliance, we would be likely to reduce the risk of vascular events by about a quarter," he predicted.

However, lowering patients' LDL did not affect progression to end-stage renal disease, which developed in about a third of patients in each arm: 33.9% of the treatment group, and 34.6% of the controls.

Cancer was also on the minds of investigators during the trial, due to reports about possible carcinogenicity associated with use of ezetimibe (trade name Zetia). The FDA concluded in December 2009 that "it is unlikely that Vytorin or Zetia increases the risk of cancer or cancer-related death," and the SHARP results supported the assertion.

There were 438 cancers diagnosed and 150 cancer deaths in the Vytorin group, compared with 439 cancers diagnosed and 128 cancer deaths in the placebo group. The differences were nonsignificant.

Overall, cardiac, renal, and vascular-related deaths were less frequent in Vytorin users, but nonvascular deaths were more frequent. As with cancer deaths, however, the differences between the groups were small and not significant.

Similarly, there were no significant differences in myopathy, rhabdomyolysis, liver dysfunction, pancreatitis, or gallstone complications between groups.

The study largely "confirms what we already know" – that statins benefit kidney patients, said nephrologist Pablo Pergola, clinical associate professor of medicine at the University of Texas Health Science Center, San Antonio.

Dr. Pergola was curious, however, about what role, if any, ezetimibe may have played in the outcomes.

"My guess is it's not something special ezetimibe is doing," Dr. Baigent said. "It's lowering LDL cholesterol in the same way statins do."

Dr. Baigent and Dr. Pergola said they have no conflicts of interest. Dr. Baigent added that the trial was run independently of Merck, and that he and his colleagues do not accept payments from the pharmaceutical industry, other than the costs of attending scientific meetings. ■