Major CV Events Not Decreased With Vytorin

BY JANE SALODOF MACNEIL
Senior Editor

Combined simvastatin plus ezetimibe treatment not only failed to reduce major cardiovascular events, but also was linked to an increase in cancer deaths among asymptomatic patients with aortic stenosis, according to the first report of a randomized, placebo-controlled, phase III trial.

The only positive outcome of the 1,873-patient SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study was in the secondary end point of reduced ischemic events. Relative risk fell 22% in patients treated with the drug combination, which is marketed as Vytorin in the United States.

Concern over the unexpected increase in cancer deaths prompted an immediate independent analysis of cancer incidence and mortality among 20,000 patients treated so far in two other ongoing Vytorin trials: SHARP (the Study of Heart and Renal Protection) and IMPROVE-IT (the Improved Reduction of Outcomes: Vytorin Efficacy International Trial).

Dr. Richard Peto of the clinical trial service unit at the University of Oxford (England) and his colleagues found no increased cancer risk in those studies, and concluded that "the SEAS, SHARP, and IMPROVE-IT trials do not provide credible evidence of any adverse effect on cancer."

"Even if you add them together, the total evidence of adverse effect is no more surprising than getting heads if you toss a coin," Dr. Peto, a professor of medical statistics and epidemiology at the university, said in a Webcast presentation of SEAS results and the analysis.

Dr. Terje R. Pedersen, chairman of the SEAS trial, said the investigators would have preferred to report the data at a scientific meeting, but intense interest made secrecy difficult. "There were a lot of rumors out there," said Dr. Pedersen, professor of medicine and head of the center for preventive medicine at Ullevål University Hospital, Oslo.

Merck Sharp & Dohme and Schering-Plough Corp. (companies that market the two drugs as Vytorin) funded the SEAS study. Starting in 2001, investigators enrolled 1,873 patients with mild to moderate symptoms of aortic stenosis at 173 centers in seven countries in Northern Europe.

The population was randomized to 40 mg of simvastatin (Zocor) plus 10 mg of ezetimibe (Zetia) daily, or to placebo. Data collection ended June 30, 2008, after the last patient had been followed for 4 years. As expected, Vytorin reduced LDL cholesterol significantly, from 140 mg/dL at baseline to 52 mg/dL at 8 weeks; little change was seen in the placebo group.

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The combination failed to meet the primary end point of significantly fewer major cardiovascular events. These occurred in 355 patients on placebo and 333 in the Vytorin group. A secondary end point of fewer aortic valve events also did not show a significant difference (326 events with placebo vs. 308 with Vytorin).

Ischemic cardiovascular events were significantly reduced, occurring in 187 patients on placebo and 148 in the Vytorin group. Dr. Pedersen attributed this to fewer coronary artery bypass grafting procedures when aortic stenosis patients underwent cardiac surgery.

In the safety analysis, significantly more placebo patients developed cancer during the study: 93 (9.85%) vs. 65 (7.0 %) in the treatment group. More cancer deaths occurred, however, in the Vytorin cohort vs. the placebo group: 39 (4.13%) vs. 23 (2.48%), a nonsignificant difference.

Dr. Peto used different figures, reporting the total number of patients with cancer as 102 in the treatment group and 67 in the control group. He reported that "no overall increase" in incidence was found in the combined SHARP and IMPROVE-IT data, in which 313 treated patients and 326 controls had cancer.

Other factors arguing against increased risk, he said, were that the cancers did not concentrate in any one anatomical site and that relative risk did not increase significantly over time in all three studies. Based on cancer incidence, the relative risk with treatment went from 0.95 in the first year to 1.15 in the second year, to 1.17 in the third year, and to 1.01 in the fourth year.

"Likewise, nor does the relative risk for cancer mortality increase with time," he said.

Summarizing the SEAS findings, Dr. Pedersen called the combined treatment "safe and well tolerated."

In a subsequent interview, Dr. Richard Steingart, chief of cardiology at Memorial Sloan-Kettering Cancer Center, New York, challenged the SEAS hypothesis that Vytorin could slow aortic stenosis. "I think that was a bit of a reach anyway, and it turned out it didn't," he said.

Moreover, SEAS did not answer questions raised by the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial, according to Dr. Steingart and Dr. Harlan M. Krumholz, a professor of internal medicine, epidemiology, and public health at Yale University in New Haven, Conn. As designed, it could not tease out whether ezetimibe adds any benefit when combined with a statin.

"The SEAS study provides no evidence to support the use of Vytorin, and raises a concern that is hard to dismiss," Dr. Krumholz said in a separate interview. "For me," he added, "the bottom line is this: If you can take a statin and be treated adequately, you should not be on this drug."

Although Dr. Krumholz said he awaits the two larger trials to settle questions of benefit and safety, an added concern for Dr. Steingart is that these trials may not resolve the issue. The approval and ensuing widespread use of ezetimibe based on surrogate end points may make it impossible to determine clinical end points, he warned.

Moreover, the cancer data in SEAS could discourage patients from enrolling in IMPROVE-IT. "If I were recruiting for this trial, I would think these issues would make it very difficult," he said.

The unusual reporting of results by Webcast instead of peer review also is an issue. "I don't think this is a great precedent," Dr. Steingart said, adding that although he found the cancer analysis reassuring, it would not deter inquiry into a possible cancer link.

"How could they be so confident?" Dr. Krumholz asked, agreeing that Vytorin's causing cancer is unlikely but not ruled out by the hasty analysis. "I just don't know why they rushed as opposed to deliberating."

Lee A. Davies, director of global product communications and advocacy relations for Schering-Plough, said that fuller results may be presented as soon as the European Society for Cardiology convenes this month. "Nonetheless, given the confluence of our earnings release, the findings in the study, and the importance of restoring confidence in the transparency of the pharmaceutical industry, we felt strongly that it was important to disseminate the results now and to provide our view of them," he said.

The company has posted a letter to physicians at www.mspppharma.com. ■

Repeated Measurements Can Unveil Masked Hypertension

BY CAROLINE HELWICK
Contributing Writer

NEW ORLEANS — "Masked hypertension," thought to affect about one in eight individuals, can be identified through repeated office blood pressure measurements in persons who show discrepancy between office and home blood pressure levels, according to Italian investigators.

"We were able to diagnose masked hypertension by using repeated office measurements. It matches what our patients found in home monitoring," said principal investigator Dr. Giuseppe Crippa of Guglielmo da Saliceto Hospital, Piacenza, Italy.

Masked hypertension is defined as normal office blood pressure but high ambulatory blood pressure or home blood pressure. It is estimated that the condition is as prevalent as white-coat hypertension and is often missed in clinical practice, Dr. Crippa explained at the annual meeting of the American Society of Hypertension.

His study compared the level of agreement between office blood pressure (OBP), repeated office blood pressure (ROBP), and daytime ambulatory blood pressure (ABP) in 48 pharmacologically untreated patients with normal office blood pressure (less than 140/90 mm Hg) but elevated daytime ABP (at least 135/85 mm Hg).

Since ABP averages multiple measurements, it is the accepted standard for diagnosing masked hypertension. For follow-up, home blood pressure measurement is regarded as a simpler, reliable, and cost-effective alternative, he said.

OBP values were derived from the average of at least three sphygmomanometric measurements obtained during at least three separate visits over a 3-week period. ABP values were calculated as the average of daytime readings taken every 15 minutes and nighttime readings obtained every 30 minutes. ROBP was performed after 20 minutes of rest with the patient seated comfortably alone; 10 consecutive measurements were taken every 2.5 minutes, with the average of the final six readings considered the final value.

This is important, Dr. Crippa noted, since the average blood pressure varies highly over 20 consecutive measurements. For example, in one patient, the initial reading taken at 8:02 a.m. was 210/121 mm Hg and pulse rate was 96 beats per minute (bpm); midway through the ROBP it dropped to 140/79 mm Hg and 80 bpm; and concluded at 137/77 mm Hg and 72 bpm. Over the 20 readings, the average of the first 4 was 185/106 mm Hg, while the average of the final 6 readings was 138/77 mm Hg.

In the study, the OBP readings (both systolic and diastolic) were slightly but significantly lower than those achieved with ABP or ROBP. The differences between OBP and both ABP and ROBP were statistically significant. The ABP and ROBP readings were not significantly different and, in fact, were highly correlated with each other, Dr. Crippa reported.

With ABP as a reference for the diagnosis of masked hypertension, ROBP failed to identify this condition in just 2 out of the 48 patients.

"According to our results, ROBP seems to provide reliable information on blood pressure status that compares favorably with the most precise and exhaustive technique for the diagnosis of masked hypertension, i.e. [ambulatory blood pressure monitoring]," he said. "In a population of untreated subjects, ROBP and ABP monitoring provided a very similar proportion of individuals with masked hypertension, and the level of agreement, for the same subject, was more than acceptable. The precision and power of detection by ROBP seems very high, with an attractive cost/efficacy ratio."

The majority of subjects (94% according to ABP monitoring values) had OBP values in the prehypertensive range, he added, suggesting that masked hypertension might be regarded as a high-risk subset of prehypertension. ■