Vytorin Fails CV Benefits Test As Hint of Cancer Risk Arises

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 in 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 so far treated 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 closed 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.

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 compared with 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."

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 later 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."

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

Both Good and Bad ICD Shocks May Trigger Risks

BY SHERRY BOSCHERT
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SAN FRANCISCO — Inappropriate shocks from implantable cardioverter defibrillators are common and may cause harm, a review of the medical literature suggests.

"There are not a great deal of data that enable us to separate out the adverse effects of inappropriate versus appropriate shocks," but both seem to be associated with an increased risk for death and other adverse outcomes, Dr. Alfred E. Buxton said at the annual meeting of the Heart Rhythm Society.

The literature suggests that 30%-60% of patients with implantable cardioverter defibrillators (ICDs) get appropriate shocks delivered to terminate a life-threatening arrhythmia, and as many as 20%-30% of patients get inappropriate shocks at other times.

'ICD shocks, while potentially life saving, [also] have potential adverse effects.'

DR. BUXTON

"ICD shocks, while potentially life saving, have potential adverse effects," said Dr. Buxton, professor of medicine at Brown University, Providence, R.I. Shocks have been associated with increased noncardiac mortality, reduced quality of life, and device-induced proarrhythmias.

Compared with patients who had never been shocked by their ICDs, patients who'd had any ICD shock had a quadrupled risk for death from any cause in an analysis of data from the 719-patient Multicenter Automatic Defibrillator Implantation Trial II (MADIT II). Inappropriate shocks were associated with a doubling in all-cause mortality, and appropriate shocks were associated with a tripling in all-cause mortality, compared with no shocks (J. Am. Coll. Cardiol. 2008;51:357-65).

Inappropriate shocks occurred in 12% of patients and comprised 31% of all shocks in the MADIT II trial.

Clearly, needing an ICD shock to terminate a life-threatening arrhythmia puts a person at risk for death, "but there is probably also some additive effect of inappropriate shocks," Dr. Buxton said. He has been a consultant or speaker or received funding from companies that make cardiac devices including Boston Scientific, GEHealthcare, Medtronic, and St. Jude Medical.

Previous analyses also identified adverse effects associated with ICD shocks. Approximately half of 60 patients were shocked by their ICDs within 2 years of implantation in a 1998 study. Anxiety and sadness increased and initiation of new activities decreased in patients who'd had a shock compared with no shocks, and the same was seen in patients with five or more shocks, compared with just one or no shocks, he said.

A 1999 analysis of the Coronary Artery Bypass Graft Patch trial found no difference in quality of life after 6 months between 228 control patients without ICDs and 101 patients with ICDs who hadn't been shocked, but lower quality of life in 101 other patients with ICDs who had been shocked, compared with controls.

About a third of 373 patients with ICDs in the Antiarrhythmics vs. Implantable Defibrillators (AVID) trial received at least one shock within 1 year, and receiving more than one shock was associated with a significant reduction in mental well-being and physical function, a 2002 analysis concluded.

Data from several studies suggest that there is a complex interaction between depression and ICD shocks.

Depression may increase the likelihood of developing arrhythmias and having shocks, and has been associated with decreased heart rate variability, he said. But a 1993 study of 241 patients followed for a mean of 26 months found no significant difference in overall survival rates for patients who had or had not been shocked. At least one shock occurred in 76% of patients, and 63% of the cohort had inappropriate shocks. Mortality rates were similar for patients with appropriate shocks (38% died) and inappropriate shocks (35%).

And an unpublished secondary analysis of the 2004 Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) found a significantly higher death rate in patients who had received ICD shocks, compared with non-ICD patients and those with ICDs but no shocks, Dr. Buxton said. ■