Zetia Fails to Show Benefit Over Niacin for Heart Patients

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Results reported here Sunday may not put the nail in the coffin for a once wildly popular cholesterol-lowering drug, but they do put Zetia at the bottom of the list of medications that doctors will be using.

So said Dr. Anthony DeMaria, a leading cardiologist who is also the editor in chief of the Journal of the American College of Cardiology.

He was referring to the results of a study that compared niacin -- a form of vitamin B -- to Zetia in high-risk patients who need more than a drug like Lipitor or Crestor to control their cholesterol.

The niacin used in the study is not variety available in health food stores and drug stores. It is a prescription product that has a special timed-release formulation, which may cut down on the hot flashes that are associated with niacin use.

Zetia, known generically as ezetimibe, is highly effective at reducing LDL, the so-called bad cholesterol. But niacin boosts HDL, or good cholesterol.

In the study reported at the American Heart Association meeting here -- and published online by the New England Journal of Medicine -- good trumped bad.

Niacin had a beneficial effect on the plaque buildup in the walls of the arteries that supply blood to the brain, but despite the fact that Zetia reduced LDL by almost 20 percent in patients who already had LDL cholesterol levels of less than 100 mg/dL, patients taking the drug had a slight worsening of the plaque build-up.

"This trial doesn't quite put the nail in the coffin for ezetimibe, but it pushes it way down on the list of medications for cholesterol-lowering therapy," DeMaria said.

Moreover, nine patients in the Zetia arm had heart attacks, stroke, or died from heart disease, versus just two patients taking niacin.

"Niacin had a superior effect on the artery wall," said Dr. Allan Taylor, a cardiologist at Walter Reed Army Medical Center who headed the study. "The take-home message is clear: niacin should be the choice when considering an add-on therapy."

Taylor pulled no punches at a press conference to discuss the results, pressing the point that at time when the nation is watching the bottom line on healthcare costs, it's time to switch to niacin -- which even in the branded formulation called Niaspan, which was used in the trial, is cheaper than Zetia. Noting that in 2008, 9 million Americans were taking Zetia versus just 2.5 who were taking niacin, Taylor said that switching would reap big potential savings as well as better outcomes.

Yet, Taylor's position was questioned by reporters who noted that he disclosed receiving more than $10,000 in lecture fees from Abbott, which makes Niaspan.

Dr. Jim Stein of the University of Wisconsin put it this way:

"Doctors need to stop using so much ezetimibe," Stein said. "Using this drug is not practicing evidence-based medicine. It is taking a path of least resistance -- the easy way out of getting numbers to targets. But we don't treat numbers, we treat patients, and are obligated to use drugs that are proven in clinical trials to reduce things they care about -- heart attacks, strokes, and death -- and to do so safely."

The trial itself was small; just 208 patients had completed the 14-month study when it was terminated because "the clinical question was answered and having answered it, the trial lost clinical equipoise," Taylor said.

That early termination caused some critics to question the impact of the results.

Dr. Roger S. Blumenthal of Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, said that since the trial was originally designed as a 360-patient study, continuing the study until all patients had completed the trial would have provided more compelling evidence.

"The absolute difference might have gotten smaller, or it might have gotten bigger," Blumenthal told MedPage Today.

He made that same point in an editorial that was published along with the study.

The premature termination, as he and his Hopkins colleague Dr. Erin D. Michos, wrote, "was unfortunate and may exaggerate the potential benefit of niacin therapy."

But Blumenthal agreed that Taylor made a valid point about the lack of clinical equipoise and said the investigators clearly had a right to terminate the study.

Dr. John J. P. Kastelein of the Academic Medical Center in Meibergdreef, the Netherlands, also faulted the early termination of the trial. Kastelein, who served as discussant for the trial, also co-authored a second editorial NEJM editorial that was published along with the trial results.

At a press conference, Kastelein said early termination opened the door to "random results."

Because of his leading role in trials that have investigated ezetimibe, Kastelein's NEJM editorial offered what where arguably the most interesting comments about ARBITER 6-HALTS

He was lead author and prinicipal investigator of the ENHANCE trial, another study that sought to prove a benefit for ezetimibe in slowing plaque progression. ENHANCE, like ARBITER, relied on measurement of the artery wall to compare the efficacy of a statin (simvastatin) alone to the combination of ezetimibe and simvastatin marketed as Vytorin.

That trial was also negative. and when it was reported at the American College of Cardiology and simultaneously published in NEJM, Taylor wrote an editorial suggesting that ezetimibe was being overused.

In his turn as editorialist, Kastelein agreed with the ARBITER 6-HALTS investigators, writing that the results "available to date provide support for the concept that the use of statins to reduce LDL cholesterol to target levels with the subsequent addition of a drug to raise HDL cholesterol levels (niacin), rather than a drug to lower LDL cholesterol levels (ezetimibe), is a more effective treatment for patient at high cardiovascular risk."

Ezetimibe and the ezetimibe/simvastatin combo pill were developed by Merck/Schering-Plough, a joint development agreement that has now evolved into a merger between the two pharmaceutical giants.

Early Saturday morning, Merck issued a press release confirming completion of the merger, stating, "Merck today confirms and underscores its commitment to marketing and developing cardiovascular medicines for a range of cardiovascular disorders."

In response to ARBITER 6-HALTS, Merck issued a seven-page statement confirming its continued support of its ezetimibe products.

"The results of the small ARBITER 6 study do not, in any way, change our view of Zetia and Vytorin as effective medicines for fighting LDL cholesterol," said Peter S. Kim, president of Merck Research Laboratories.

Dr. Douglas Weaver, immediate past president of the American College of Cardiology, called niacin "an effective, but underutilized drug."

"This study shows that until the ongoing large study of [ezetimibe] is completed, the clinical effectiveness of [ezetimibe] is unknown and the drug should be reserved for those patients who cannot achieve suitable cholesterol levels with statins alone or with a combination of statins and niacin," he added.

"For patients who cannot reach their cholesterol goals with statin therapy alone, this study, though small, shows that niacin is a much better choice than ezetimibe as an add-on medication. Until there is an outcomes trial, ezetimibe and Vytorin should be drugs of last resort. This study

further reinforces our recommendations that statins should always be the first-line treatment," Weaver said.

Taylor carefully avoided making claims about the efficacy of ezetimibe, although he acknowledged that a number of studies have questioned the efficacy of the drug, and he has authored editorials that questioned the compound's efficacy.

Ray Gibbons, professor of medicine at the Mayo Clinic in Rochester, pointed out that the patients in the study were already quite well-managed, as most had LDLs of less 100 mg/dL, so they can hardly be considered typical.

"In my practice, I follow previous outcomes studies (and AHA position), i.e., niacin is the preferred second agent if statins at maximum tolerated dose do not get patients to target," Gibbons said.