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In Blowout, Amarin's Fish-Oil-Derived Drug Dramatically Cuts Heart Risk In Study

A drug derived from fish oil cut the rate of cardiovascular problems, including heart attacks and strokes, by 25%, a result that will likely transform the fortunes of its maker, Amarin Pharmaceuticals, and upend decades of thinking about cardiovascular disease.

"What??!!! Fantastic! Wow!" said Sekar Kathiresan, a cardiologist who is director of the Cardiovascular Disease Initiative at the Broad Institute and the Center for Genomic Medicine at Massachusetts General Hospital. "That's awesome! Such great news for patients!"

John F. Thero, Amarin's president and chief executive, said in a prepared statement that the company is "delighted" with the results, which he said "could lead to a new paradigm in treatment to further reduce the significant cardiovascular risk that remains in millions of patients" whose cholesterol is controlled, but whose levels of another risk marker, triglycerides, are high.

Amarin's drug, Vascepa, is already approved by the Food and Drug Administration to cut triglycerides in patients in whom levels have risen above 500 milligrams per deciliter, triple normal. But there had been skepticism regarding whether it would provide a benefit in heart disease, because other fish oil pills had used much lower doses and because it has proved difficult for any drug significantly to reduce the risk of heart attacks and strokes when given on top of cholesterol-lowering medicines, which are already very effective.

But the results from the 8,179-patient study, reported in a press release with few details, seem to leave little doubt that the effect of the drug was substantial in people who had high triglycerides (median triglyceride levels in the study were 219 mg/dL, 50% more than normal) and had either had previous cardiovascular problems, such as a heart attack or stroke, or had diabetes and another risk factor for heart disease.

Patients who received four grams of Vascepa had a 25% lower risk of a cardiovascular problem, defined as a heart attack, a stroke, a heart procedure to open a clogged artery, or chest pain requiring a hospitalization, compared to those who received a placebo. (Half the patients received Vascepa, and half a placebo made of mineral oil.) The result was highly statistically significant, with a p value of less than 0.001. (A result is considered significant if this statistic is less than 0.05).

Doctors will need to see full results, which are being presented at the annual meeting of the American Heart Association in November, to make final judgements about the data. But the magnitude of the results, along with their high level of statistical significance, are likely to

quell criticism. For instance, one concern was that the mineral oil placebo might interfere with the effectiveness of cholesterol-lowering medicines in the placebo group. But even if it exists, that effect is "not likely to be large enough to negate the results of the study," says Steven Nissen of the Cleveland Clinic, who is running a study of a rival fish-oil-derived drug for AstraZeneca.

There are several reasons that Vascepa might have outperformed studies of traditional fish oil, which have had mostly negative results in large clinical trials. Vascepa used a much larger dose. Even studies that have used a prescription product, GlaxoSmithKline's Lovaza, have mostly used a one-gram dose. But Vascepa is also different from Lovaza and over-the-counter fish oil pills because it is made of a purified component of fish oil called eicosapentaenoic acid, or EPA. In previous clinical trials, EPA cuts triglycerides by a third compared to placebo, without increasing levels of LDL, the so-called "bad cholesterol," which other fish oil products can do. The most important reason, though, may be that Amarin chose to test its product only in people who had high triglycerides.

"We may have had it backwards for the past 30 years," says Kathiresan. For years, researchers were infatuated with another blood test, for "good cholesterol" or high-density lipoprotein, called HDL. The idea was that HDL somehow protected people against heart attacks. "In medical school, we were taught to pay attention to HDL and ignore triglycerides," says Ethan Weiss, a cardiologist at UC-San Francisco.

Drug companies including Pfizer, Roche, and Merck spent literally billions of dollars testing medicines that were supposed to boost HDL. None of them worked. Meanwhile, there were hints of effectiveness from triglyceride-lowering drugs, but they were not considered conclusive. But studies of human genetics started recently started to show a very different picture. Scientists started to look at mutations that lowered HDL, and also those that raised triglycerides. The approach showed little direct connection between HDL levels and heart disease. But they did show a link with triglycerides. A recent study, presented by Brian Ference of the University of Cambridge at the annual meeting of the European Society of Cardiology, used genetics to put the blame on another protein, ApoB, which can be involved in both high triglycerides and high LDL.

If the Amarin results hold up, and if they are repeated with AstraZeneca's study of its own fish-oil derived drug, they are likely to bolster the strategy of using genetics to decide what new medicines to invent and develop. The strategy is already in favor at companies including Regeneron, GlaxoSmithKline, and Amgen. But it could become more and more important now.

In the meantime, Amarin shareholders are likely to be pleased by a blowout result. The full presentation of the results is scheduled for 2:16 p.m. on November in Chicago at the AHA meeting.
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