Wendy Todd has high cholesterol, but has often experienced muscle pain while taking statins to treat it. Experts hoped that a new drug would be a viable alternative to statins. It is a drug that reduces levels of LDL cholesterol, the dangerous kind, as much as statins do. And it more than doubles levels of HDL cholesterol, the good kind, which is linked to protection from heart disease. As a result, heart experts had high hopes for it as an alternative for the many patients who cannot or will not take statins.

But these specialists were stunned by the results of a study of 12,000 patients, announced on Sunday at the American College of Cardiology’s annual meeting: There was no benefit from taking the drug, evacetrapib. The drug’s maker, Eli Lilly, stopped the study in October, citing futility, but it was not until Sunday’s meeting that cardiologists first saw the data behind that decision.

Participants taking the drug saw their LDL levels fall to an average of 55 milligrams per deciliter from 84. Their HDL levels rose to an average of 104 milligram per deciliter from 46. Yet 256 participants had heart attacks, compared with 255 patients in the group who were taking a placebo. Ninety-two patients taking the drug had a stroke, compared with 95 in the placebo group. And 434 people taking the drug died from cardiovascular disease, such as a heart attack or a stroke, compared with 444 participants who were taking a placebo.

“We had an agent that seemed to do all the right things,” said Dr. Stephen J. Nicholls, the study’s principal investigator and the deputy director of the South Australian Health and Medical Research Institute in Adelaide. “It’s the most mind-boggling question. How can a drug that lowers something that is associated with benefit not show any benefit?” he said, referring to the 37 percent drop in LDL levels with the drug.

Two other drugs in the same class as evacetrapib, known as CETP inhibitors, have also failed: One, which lowered LDL levels by only 20 percent, had toxic side effects. The other raised HDL levels but did not lower LDL levels at all. Cardiologists thought evacetrapib, a safe and potent drug, would be different.

“All of us would have put money on it,” said Dr. Peter Libby, a Harvard cardiologist. The drug, he said, “was the great hope.”

Evacetrapib acts by siphoning cholesterol out of HDL, a cholesterol-carrying scavenger protein, so the cholesterol can be discarded in bile. Statins, in contrast, pull cholesterol from the other major cholesterol-carrying protein, LDL, into the liver, after which it can be discarded. It seemed logical that evacetrapib, by ridding the body of cholesterol in HDL and lowering the amount of LDL proteins, would work to protect against heart disease.
Researchers have hypotheses, but no one is certain what went wrong. “It may be that the LDL level is less important than how it gets changed,” said Dr. Paul Thompson, a cardiologist at Hartford Hospital. “But we don’t know that.”

Dr. Steven Nissen of the Cleveland Clinic added, “These kinds of studies are wake-up calls.”

Cardiologists still have high hopes for a new class of cholesterol drugs, known as PCSK-9 inhibitors, which cause LDL to plummet to levels never seen in drug treatments. One reason for their optimism is that these drugs have the same end effect as statins: They cause liver cells to draw out cholesterol.

These drugs are being tested in large clinical trials to see if their effects on LDL levels translate into reduced incidences of heart attacks, strokes and death. The Food and Drug Administration has approved the drugs based on their LDL-lowering effects for a number of patient groups, including those at high risk for heart disease who report painful muscle aches or weakness when they take statins.

The PCSK-9 inhibitors can cost more than $14,000 a year, while statins can cost just pennies a day, so determining what portion of patients are truly statin intolerant has become an important question.

A second study presented at the cardiology meeting on Sunday and published online in the Journal of the American Medical Association revealed just how vexing the issue is.

The study, directed by Dr. Nissen and paid for by Amgen, a pharmaceutical company, included more than 500 people with extremely high levels of LDL cholesterol who had tried two or more statins and had reported aching or weak muscles so severe that they said they absolutely could not continue taking the drugs.

The participants were randomly assigned to take either a statin, atorvastatin or a placebo for 10 weeks. Then those taking a statin were switched to a placebo for 10 additional weeks, and those taking a placebo were switched to a statin. The result: Less than half of the patients seemed to be truly unable to tolerate statins, and complained of muscle pain only when they were taking the drug. A quarter of the patients reported muscle problems with a placebo. And nearly one in 10 had muscle issues with both the statin and the placebo.

That indicated that 57 percent of patients actually could tolerate statins. Researchers then randomly assigned the remaining 43 percent to take either Amgen’s PCSK-9 inhibitor, evolocumab, or another cholesterol-lowering drug, ezetimibe, which is often taken by statin intolerant patients but has never been shown to reduce heart disease risk when taken without an accompanying statin. The patients tolerated both drugs.

The statin tolerance results were not a total surprise. Smaller studies had indicated that most patients who said statins caused muscle aches actually could tolerate the drugs. But this was the largest such study and raised a real question about how to treat patients who are at high risk of heart disease and say they cannot or will not take a statin because of intolerable side effects.
“We don’t know how to assess these patients,” said Dr. Robert Eckel of the University of Colorado. No lab test can pick out the truly statin intolerant from those who feel muscle pain that may be caused by something else.

“That is a major, major problem,” said Dr. Thompson, the cardiologist at Harford Hospital, who led a smaller study that came to a similar conclusion about statin intolerance.

Dr. Daniel Rader, a cardiologist at the University of Pennsylvania, would like to give patients who say they cannot tolerate statins a clinical trial in which the patient is the only participant. He would give the patient either a placebo or a statin for a few weeks and then switch the pills. That way the doctor and the patient could get an idea of whether the patient’s muscle pain was really caused by statins.

Wendy Todd, a patient of Dr. Daniel Soffer, also of the University of Pennsylvania, was surprised after she entered a statin intolerance study. She had already tried at least three statins, including atorvastatin, the one being tested, but always developed flulike symptoms and cramps in her legs so painful she could barely walk.

But she had no such effects when she took atorvastatin during the study, without knowing if it was the drug or the placebo. She was astonished, but accepted that she was not actually intolerant to the drug. She began taking it when the study ended. It does not bother her now.

Ms. Todd said she liked Dr. Rader’s idea about an individualized trial for patients like her.

“I would opt for that,” she said.