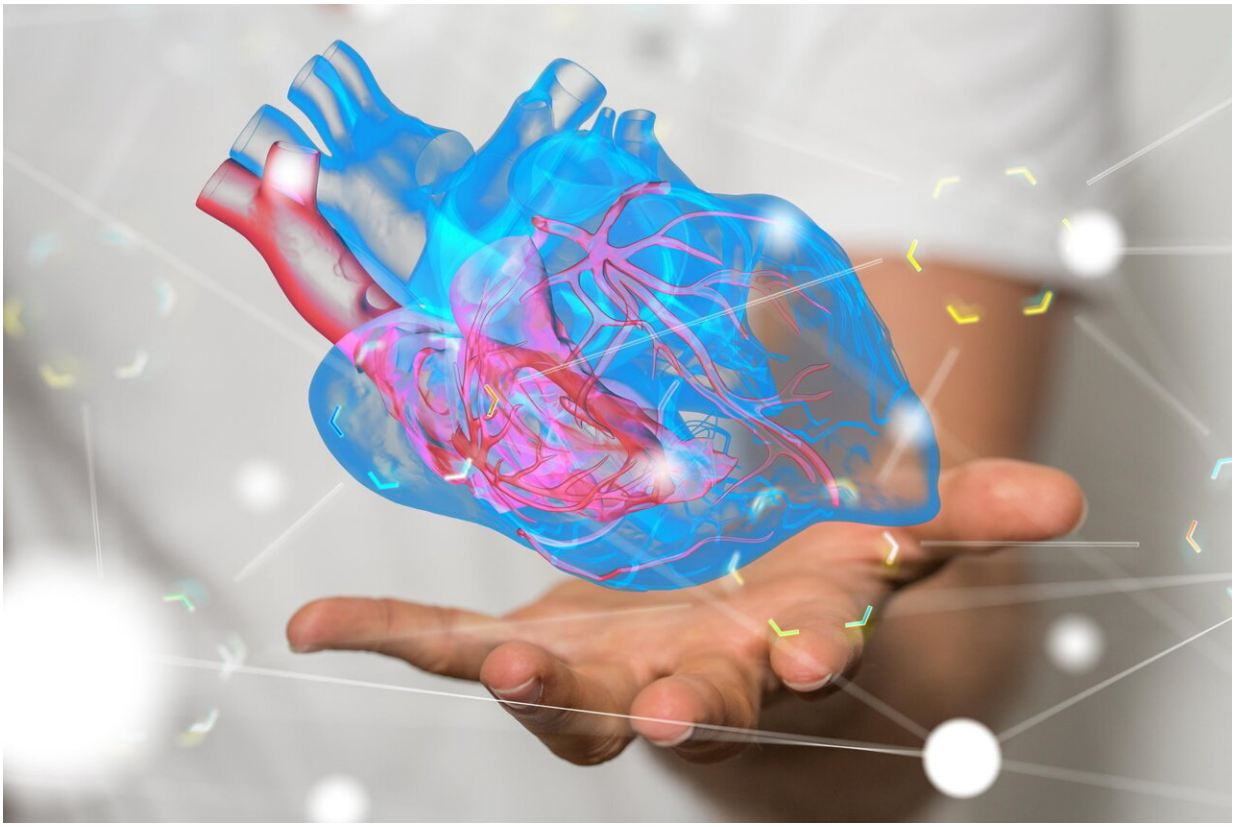
MedicalXpress

Two new studies point to the promise of gene therapy for high cholesterol

November 18 2023, by Robin Foster



Two new gene-editing treatments that target dangerously high levels of cholesterol in people with a genetic predisposition to the condition were found safe and effective in new, groundbreaking research.

While powerful drugs like statins can help manage cholesterol in most people, they can't treat those who have genes that predispose them to heart troubles. But the duo of studies, presented Sunday at the American Heart Association (AHA) annual meeting in Philadelphia, may one day change that.

Both treatments will need years of additional research before the U.S. Food and Drug Administration would even consider approving them, but that didn't dampen the excitement among heart experts.

"There is no way to categorize this other than revolutionary," Dr. Hugh Cassiere, director for critical care services at South Shore University Hospital, Northwell Cardiovascular Institute, in New York, told NBC News. He was not involved with either study.

One of the treatments, from Boston-based Verve Therapeutics, uses a gene-editing approach that targets the PCSK9 gene, making a tiny change to the gene. The effect is akin to a permanent eraser, deleting the gene's ability to fuel a rise in cholesterol levels, Verve co-founder and CEO Dr. Sekar Kathiresan told NBC News.

In theory, the one-time treatment should last a lifetime.

"Instead of daily pills or intermittent injections over decades to lower bad cholesterol, this study reveals the potential for a new treatment option—a single-course therapy that may lead to deep LDL-C lowering for decades," senior study author Dr. Andrew Bellinger, chief scientific officer at Verve, said in an AHA news release.

In Verve's preliminary study, most of the 10 patients received doses that didn't make a measurable difference in their LDL levels, but three were given higher doses. In those patients, LDL cholesterol levels were slashed by more than half.

Verve's research was limited to people with a genetic condition called familial hypercholesterolemia, in which cholesterol levels are high from birth. Many of these patients suffer heart attacks in their 30s or 40s.

Kathiresan, a cardiologist who once worked at Massachusetts General Hospital, told *NBC News* that he has long focused his research on understanding why some people have heart attacks at young ages, and others do not. With a strong history of high cholesterol in his family, his brother died from a heart attack at age 40 in 2012.

That's when Kathiresan decided "to try to develop a therapy that could avert tragedies like what's happened in my family."

Experts welcomed the promise of the new technology.

"While larger and longer-term studies are required to assess both effectiveness, durability and safety, this should be the dawn of an era of therapeutic gene targeting for cardiovascular disease," Dr. Sahil Parikh, director of endovascular services at Columbia University Irving Medical Center in New York City, told NBC News.

Findings on a second novel gene therapy for high cholesterol were also presented at the AHA meeting on Sunday.

The preliminary results offer an early glimpse of what could be the first treatment for a particularly dangerous type of cholesterol called lipoprotein(a).

People with high levels of this particular type of cholesterol are at extremely high risk of having cholesterol clog their arteries. That's because Lp(a) attaches itself to LDL cholesterol, making those LDL particles even stickier and more likely to cause plaque.

The condition is genetic, so diet and exercise make no difference.

"If further trials show that this medication—lepodisiran—is safe and can reduce heart attacks and strokes, it would be good news for patients because it eliminates a risk factor we've been unable to treat," lead study author Dr. Steve Nissen, chief academic officer at the Heart, Vascular & Thoracic Institute at the Cleveland Clinic in Ohio, said in an AHA news release.

Nissen and his colleagues tried a drug called lepodisiran, which targets mRNA. In this case, the mRNA tells the body to produce Lp(a), but the drug shuts down this process.

Nissen's study was small, involving just 48 adults in the United States and Singapore. All had very high levels of Lp(a). Overall, the drug was found to be safe, with no major side effects.

But the drug also exceeded expectations and dramatically lowered their Lp(a) levels. A single shot drove down Lp(a) by more than 94% for nearly one year, the study found.

The findings were published Nov. 12 in the Journal of the American Medical Association.

"This really offers a lot of hope for patients with elevated lipoprotein(a)," Nissen told NBC News. "We're working as fast as we can because there are patients dying every day because of this disorder. We've not been able to treat it, and we need to change that."

As many as 64 million Americans have elevated Lp(a) levels, most commonly those of African and South Asian descent, NBC News reported.

Nissen predicted lepodisiran could someday be used as an "annual vaccine-like treatment for this previously untreatable disorder."

More information: Steven E. Nissen et al, Lepodisiran, an Extended-Duration Short Interfering RNA Targeting Lipoprotein(a), *JAMA* (2023). DOI: 10.1001/jama.2023.21835

Visit the U.S. Centers for Disease Control and Prevention for more on familial hypocholesterolemia.