

# Triglycerides: A new frontier in detecting and treating disease

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When it comes to thinking about lipids and heart health, cholesterol often comes to mind. Along with age, blood pressure, and underlying conditions, cholesterol—a fat that circulates in the bloodstream—is one

of many indicators of cardiovascular health that physicians look at through routine medical check-ins.

It's also used in [10-year risk predictions](#) for atherosclerosis, a narrowing or hardening of the arteries caused by the accumulation of a substance called plaque, which can rupture or block blood flow and increase the odds for having a heart attack or stroke.

If a person has increased [risk factors](#) for developing atherosclerosis, they may be prescribed statins, a class of cholesterol-lowering drugs, which have been shown to lower risks for cardiovascular events by about [one-third](#).

In recent years, researchers have also been studying if measuring components of triglycerides—tiny fat particles that support the structure of cells and metabolism—in [low-density lipoprotein](#) (LDL) cholesterol could improve risk predictions for [cardiovascular disease](#) and lead to new treatments.

"For many years, people ignored triglycerides," said Alan T. Remaley, M.D., Ph.D., a senior investigator in the Lipoprotein Metabolism Laboratory, located within NHLBI's Division of Intramural Research. "The world is changing a little bit from both a diagnostic standpoint as well as new therapies. It's kind of a new era."

As investigators from Remaley's lab have [studied](#) ways to improve both predictions and treatment, they see emerging opportunities. This could potentially benefit one in four American adults who has elevated triglycerides and provide novel therapies for people with inherited metabolic disorders.

Familial hyperchylomicronemia, for example, affects about [one or two in a million people](#), due to a mutation in the LPL gene, which breaks fat

into triglycerides. Due to this mutation, people living with this rare condition could have [triglyceride levels](#) five times higher than normal.

As a first step to exploring therapies to lower dangerously high [triglyceride](#) levels, Anna Wolska, Ph.D., a scientist in the Lipoprotein Metabolism Laboratory, developed a [peptide](#), or tiny molecule, that could lower triglyceride levels in mice by more than 80% within a few hours.

"This peptide is unlike any molecule I've seen before," said Matt Devalaraja, Ph.D., founder of Protean Bio. "If it behaves anything close to what it does in mice, we have a drug in here."

Devalaraja has now launched studies to investigate how the peptide could treat [acute pancreatitis](#), an inflammation of the pancreas that can result from high triglyceride levels.

In about four years, Devalaraja envisions the therapy will be ready to test in a small phase 2 study with patients. In the meantime, the team will continue to study the peptide in the lab and through a preliminary, phase 1 "proof-of-concept" study.

"We are not stopping," said Wolska. "We are still trying to improve the peptide so it's better and suited for the comfort of patients."

Their hope is that people living with conditions like familial hyperchylomicronemia could take the therapy as an oral pill and see their triglyceride levels fall within hours. For instances when a person needs hospital care, this type of treatment could be lifesaving.

When a person with familial hyperchylomicronemia has a severe case of acute pancreatitis and arrives at the hospital, their triglyceride levels could be at least [10 times higher](#) than normal. Triglyceride levels also

help physicians [predict](#) which patients with acute pancreatitis will experience multi-organ failure and require intensive care.

Due to extreme triglyceride levels, the pancreas starts to shut down and sets off a series of inflammatory responses. For every 10 patients with severe acute pancreatitis, about four experience organ failure. Among these patients, one may die.

"You just instantly make very high triglyceride levels that are blocking the pancreatic vascular system disappear," Devalaraja said about the best outcome for the therapy. "And then the patient survives."

Devalaraja explained that while basic scientific discoveries like these unite researchers, their real joy comes from thinking about how findings from the lab could be translated into therapies to help patients.

Especially those, like people with severe acute pancreatitis, who have limited treatment options. While larger phase 3 trials for this treatment are still years away, the researchers remain optimistic about the peptide and molecules like it.

"Our long-term goal is to make the peptide even better," said Remaley. Looking to future translational opportunities, he shared that there may even be opportunities to develop an oral peptide pill for chronic therapy, such as cardiovascular disease.

As a precursor to this research, Remaley and Wolska have been studying ways triglyceride levels could potentially improve cardiovascular disease risk predictions.

At the American Association for Clinical Chemistry's annual conference on July 25, Wolska [presented findings](#) about using a new equation that the team developed, based on the standard lipid panel, for estimating LDL triglyceride content. The equation didn't improve cardiovascular

risk predictions when added to current [10-year risk calculations](#), which includes factors, like age, sex, and [blood pressure](#). However, estimated LDL triglycerides improved predictions compared to estimated or measured LDL cholesterol levels and other lipids tested.

Statins, the go-to treatment for improving cholesterol, have been shown to reduce LDL triglyceride levels by about [30%](#). However, almost [one-third](#) of people who take statins still have elevated triglycerides. Additionally, some people may not be able to take statins or they could experience side effects, such as muscle cramps. This is where researchers see triglyceride-targeted therapies providing another option for treatment or serving as an adjunct therapy.

Yet, the group's immediate focus remains on studying how the peptide could help patients who currently need it the most.

"We aren't at the end of the journey," said Remaley. He explained false peaks or summits can often appear in research. "We can see the top of the mountain—we think."

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