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New strategy to cut heart attack risk is effective in initial test

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The first clinical trial of a new kind of drug to cut the risk of cardiovascular disease has been found safe and effective at dropping levels of “bad” low density lipoprotein (LDL) cholesterol by as much as 40 percent. High LDL levels increase the risk for heart attack and stroke.

The drug mimics the action of thyroid hormone and safely accelerates the hormone’s natural ability to rid the body of LDL. It is unrelated in structure or action to statins, the widely used class of drugs to lower cholesterol, and may offer an alternative for patients who cannot tolerate statins, according to the research team. It might also complement the use of statins to further decrease cholesterol levels, the researchers report in *The Proceedings of the National Academy of Sciences.*

Someone suffers a heart attack about every 30 seconds in the U.S., yet the best drug trials using statins show that the drugs reduce the incidence of new heart attacks and other coronary events by only about 35 percent, highlighting the need for new therapies, the scientists say.

In the clinical trial, the new drug was shown to decrease cholesterol levels in two ways: It lowers LDL levels and promotes the removal of cholesterol through the liver.

Known as KB2115, the drug was developed by Karo Bio AB, a Swedish pharmaceutical company. Scientists there are co-authors of the scientific paper reporting the finding, along with researchers at the Karolinska Institute in Sweden and at the University of California, San Francisco

(UCSF). All scientists have a proprietary interest in Karo Bio.

The results are published online in an expedited “early edition” of PNAS. The journal also is scheduled to publish an editorial on the research finding.

The Phase II trial involved 24 moderately overweight people with high LDL levels. It confirms earlier tests in animals. The animal studies also found that the drug stimulated the “good cholesterol” (HDL) pathway, which removes cholesterol from arteries and transports it into the liver, where it is converted into bile and eliminated from the body.

The animal studies also found that the drug countered both obesity and diabetes. The researchers hope to test the drug’s ability to safely treat people with these conditions too.

“In spite of today’s therapies for heart attack and stroke, there are more than a million heart attacks a year in the U.S.,” said John Baxter, MD, professor of medicine in the UCSF Diabetes Center, and senior author on the paper. “We need other types of drugs to attack this problem. Using thyroid mimics is an entirely different approach, and I think one with great promise for treating high cholesterol and probably other conditions such as obesity and diabetes.”

Baxter is former president of the Endocrine Society, a recipient of its highest honor and a member of the National Academy of Sciences.

Leaders of the study include Anders Berkenstam and Jens Kristensen at Karo Bio AB; Bo Angelin at the Kaolinska Institute in Stockholm, along with UCSF’s Baxter.

The beneficial cholesterol-lowering effects of thyroid hormone largely depend on its docking with one form of the thyroid hormone receptor in

the cell nucleus, known as the “beta” form. Until now, efforts to attack cholesterol using drugs that mimic thyroid hormone have been thwarted because the drugs stimulated not only the healthy effects of thyroid hormone made possible by the beta receptor, but also the harmful effects – such as increased heart rate – caused by docking with the second, or “alpha” form.

KB2115 binds selectively to the helpful beta receptor and is preferentially take up by the liver. It is taken up only poorly into the heart, thereby minimizing dangerous over-stimulation. The trial results show that this strategy gains the benefits of excess thyroid without the potential severe drawbacks, the researchers say.

In the early 1990s at UCSF, Baxter and Thomas Scanlan (now at Oregon Health and Science University), began efforts to develop compounds that elicit the good, but not the unwanted effects of thyroid hormone. Their work underlies the development of compounds like KB2115.

In the study, 24 people were divided into four groups. One group received a placebo, and each of the other groups received a different dose of KB2115. After two weeks, LDL levels were lowered by an average of 40 percent in the groups that took the highest doses.

Findings showed the drug was well tolerated with no detectable effects on the heart. Further clinical trials are planned.

Source: University of California - San Francisco