Researchers identify potential approach to treat heart disease through the gut

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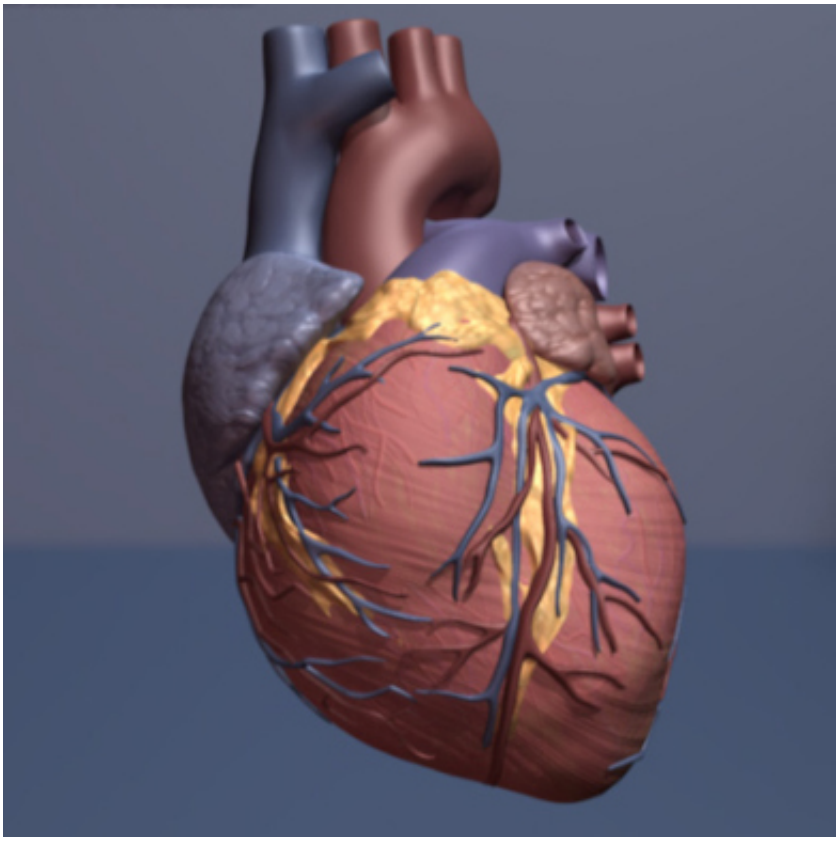


Human heart. Credit: copyright American Heart Association

Cleveland Clinic researchers have demonstrated - for the first time—that targeting microbes in the gut may prevent heart disease brought on by nutrients contained in a diet rich in red meat, eggs and high-fat dairy products.

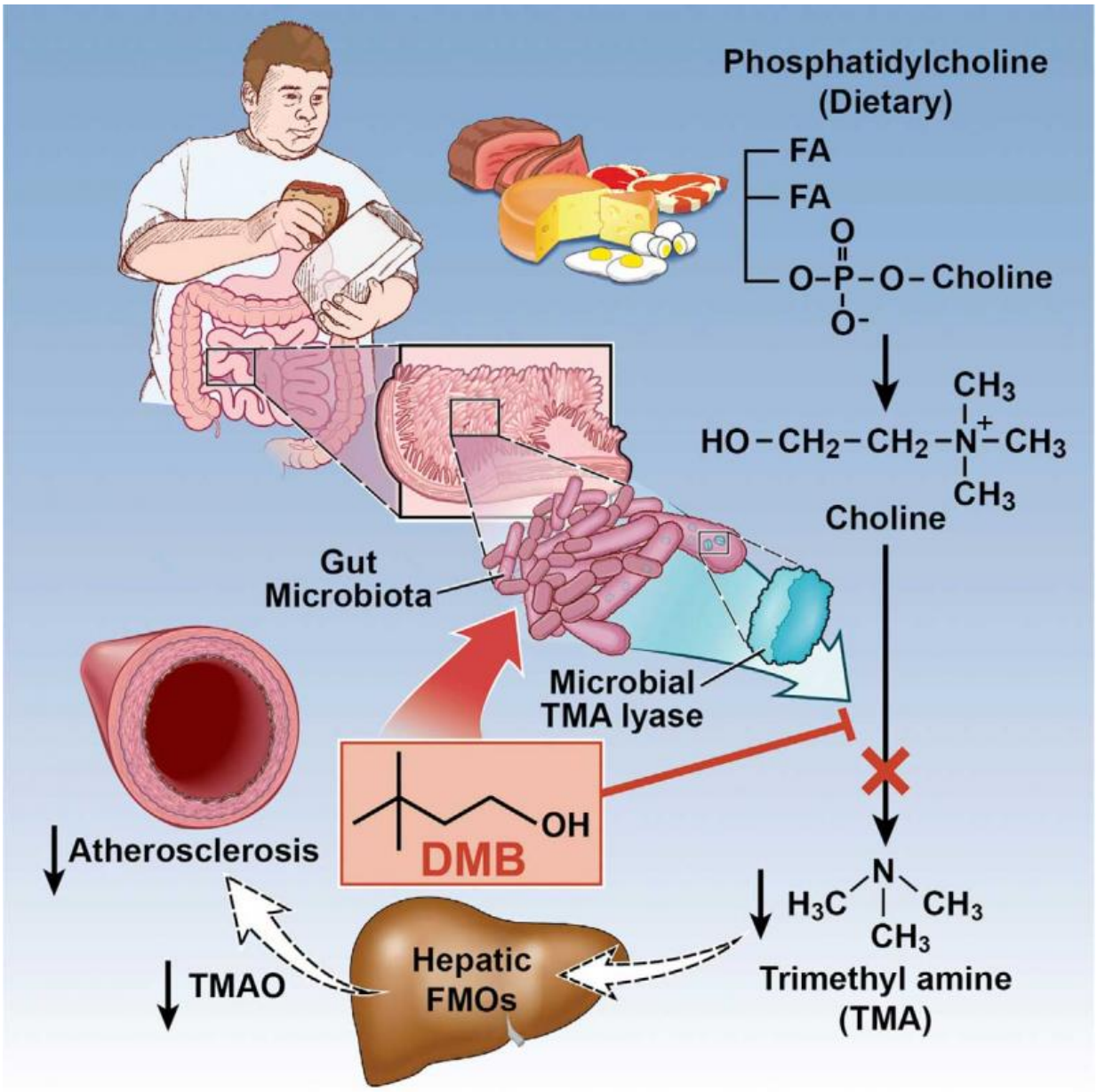
This novel approach centers around the research team's previous discovery that TMAO - trimethylamine N-oxide, a byproduct formed in the gut during digestion of animal fats - is linked to atherosclerosis and heart disease. Now, the team has identified a naturally occurring inhibitor called DMB - 3,3-dimethyl-1-butanol, found in some cold-pressed extra virgin olive oils and grape seed oils - that reduced levels of TMAO and reduced atherosclerosis in mice.

This discovery may represent a potential new therapeutic approach for the prevention of heart disease, the No. 1 killer in the United States, as well as other metabolic diseases linked to gut microbes, such as diabetes.

The current research will be published both online and in the Dec. 17 print edition of *Cell*.

The link between TMAO, gut microbes and heart disease was first discovered four years ago by the same investigative team, led by Stanley Hazen, M.D., Ph.D., Chair of the Department of Cellular & Molecular Medicine in the Lerner Research Institute and section head of Preventive Cardiology & Rehabilitation in the Miller Family Heart & Vascular Institute at Cleveland Clinic. Zeneng Wang, Ph.D., first author on the manuscript, is also a member in the Department of Cellular & Molecular Medicine in the Lerner Research Institute.

"Many chronic diseases like atherosclerosis, obesity and diabetes are linked to gut microbes," said Dr. Hazen. "These studies demonstrate the exciting possibility that we can prevent or retard the progression of diet-induced heart diseases starting in the gut. This opens the door in the future for new types of therapies for atherosclerosis, as well as other metabolic diseases."



This visual abstract depicts how drugging the gut microbiota with a nonlethal inhibitor that blocks production of the metabolite trimethylamine reduces the formation of atherosclerotic lesions and represents the first step toward treatment of cardiometabolic diseases by targeting the microbiome. Credit: Wang et al./*Cell* 2015

TMAO is a gut metabolite formed during the digestion of the nutrients choline, phosphatidylcholine (lecithin) and carnitine, which are abundant in animal products. Blood TMAO levels are associated with heightened risk of heart attacks, stroke and death in clinical studies. Carnitine is abundant in red meat and liver, while choline and lecithin are abundant in beef, lamb, liver, egg yolk and high-fat dairy products.

The present study suggests that targeted inhibition of the first step in TMAO generation, commensal microbial trimethylamine (TMA) production, can help to prevent diet-induced atherosclerosis. The research team inhibited TMA production using 3,3-dimethyl-1-butanol (DMB) in mice fed a high choline or carnitine diet. The mice treated with the inhibitor had less TMAO and developed less atherosclerosis. DMB is not an antibiotic. This important fact suggests that a treatment could target a specific microbial pathway while protecting the gut flora and avoiding antibiotic overuse and resistance, which is a worldwide health crisis.

"We were able to show that 'drugging the microbiome' is an effective way to block this type of diet-induced heart disease. The inhibitor prevents formation of a waste product produced by gut microbes, leading to lowering of TMAO levels and prevention of diet-dependent atherosclerosis." said Dr. Hazen. "This is much like how we use statins to inhibit cholesterol synthesis in human cells."

According to the Centers for Disease Control and Prevention, heart disease kills about 610,000 in the United States annually, accounting for one in every four deaths. It's the leading cause of the death in the U.S. for both men and women.

More information: Cell, Wang et al.: "Non-lethal Inhibition of Gut Microbial Trimethylamine Production for the Treatment of Atherosclerosis" dx.doi.org/10.1016/j.cell.2015.11.055

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