Novel use of existing drug could significantly cut heart attack risk

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Heart attacks have been the leading cause of death in the U.S. for a century. While most treatments for cardiac events target breaking down blood clots, Georgia Tech researchers have found a way to prevent blood

clots from even forming. Dramatically, their drug is shown to completely knock out the formation of blood clots without increasing the risks of bleeds in vivo.

This drug is both affordable and already widely available for other uses, meaning patients could experience these benefits sooner than waiting for a completely new drug to go through FDA approval. Eventually, the drug could be used to prevent second heart attacks for high-risk patients or even primary heart attacks, strokes, and other complications caused by blood clots.

The researchers presented their findings in a paper titled "N-Acetyl Cysteine Prevents Arterial Thrombosis in a Dose-Dependent Manner In Vitro and in Mice," in *Arteriosclerosis, Thrombosis, and Vascular Biology*.

How blood clots form

Most existing preventive treatments for clots involve anti-platelet drugs that can cause bad side effects for the patient.

"Doctors are between a rock and a hard place—we can give you a drug that may help prevent a second cardiac event, but it might also cause a lot of bleeding," said David Ku, Lawrence P. Huang Endowed Chair for Engineering Entrepreneurship and Regents' Professor in the George W. Woodruff School of Mechanical Engineering (ME). "These blood clots are held together by a protein called von Willebrand factor (VWF), which is a different target for drugs."

VWF is a long protein, occurring naturally in plasma, that allows blood clots to form quickly. Under normal conditions, it functions like an inert ball of yarn, but when VWF unravels, it becomes sticky and catches platelets.

"The VWF grabs platelets and the platelets activate, so they release more VWF, which grabs more platelets, creating a positive feedback loop that leads to really fast clot formation," explained Christopher Bresette, an ME postdoctoral researcher.

Breaking down blood clots

Bresette and Ku sought to break down VWF proteins using a drug already on the market, N-acetyl cysteine (NAC), typically used to treat acetaminophen overdose. Earlier researchers had tried using NAC to break down clots after formation, but Ku's team wanted to stop clots before they even started.

"We chose NAC because of its current clinical use and safety history," Bresette said. "Using an existing drug for off-label use can speed up the time it takes to start helping patients."

At the Petit Institute for Bioengineering and Bioscience, the researchers ran blood through a small channel similar to a narrowing artery that could lead to a heart attack or stroke. NAC completely prevented a clot from forming under these conditions. Next, they tested NAC in a mouse model and found comparable results. Even better, NAC's benefits lasted six hours after it left the bloodstream, keeping arteries clear for longer.

The researchers believe that the drug will be most useful if a patient has already had a heart attack but is at risk of having a second one soon after. An IV injection of NAC could lower immediate risk. Eventually, NAC derivatives could be administered orally as a daily pill to reduce heart attack risk.

Heart attacks and strokes are just the beginning. From stopping embolisms to other blockages, the future with NAC is only just beginning. The researchers are hoping to conduct a clinical trial and

receive FDA approval so NAC can help patients as soon as possible.

More information: Christopher A. Bresette et al, N-Acetyl Cysteine Prevents Arterial Thrombosis in a Dose-Dependent Manner In Vitro and in Mice, *Arteriosclerosis, Thrombosis, and Vascular Biology* (2023). DOI: 10.1161/ATVBAHA.123.319044