Gene study spots clues to heart risk for statin patients

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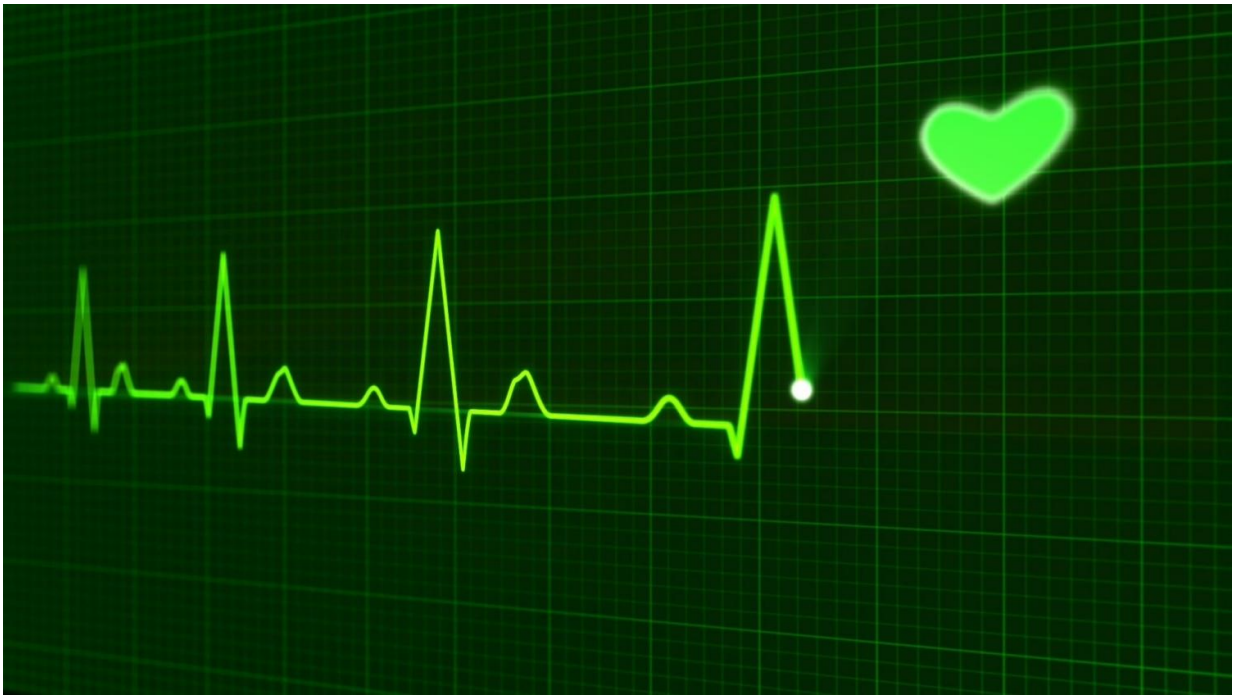

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A Vanderbilt-led research team has discovered genetic variations that increase the risk of heart attack even when patients are receiving a statin drug like Lipitor or Crestor to lower their blood cholesterol.

The finding, published by the journal *Circulation*, helps explain why some patients experience a heart attack or the need for coronary

revascularization to open blocked heart arteries while taking statins. It suggests that drugs targeting the genetic variations could lower the heart risk in these patients.

The study demonstrates the power of genome-wide association studies and longitudinal electronic health records (EHRs) to find links between genetic variation and disease, said the paper's first author, Wei-Qi Wei, MD, Ph.D., assistant professor of Biomedical Informatics in the Vanderbilt University School of Medicine.

Some of the patients were followed for heart disease for up to a decade after starting on their statin drug. The study found that the effect of the genetic variations or variants was independent of how much their cholesterol improved while taking statins.

"People with these genetic variants were at a higher risk for heart disease, even considering those who have ideal cholesterol levels on their statin," said Joshua Denny, MD, MS, Vice President of Personalized Medicine at Vanderbilt University Medical Center (VUMC) and the paper's corresponding author.

The researchers searched four sites in the Electronic Medical Records and Genomics (eMERGE) network, a nationwide consortium of experts, biorepositories and electronic medical record systems supported by the National Institutes of Health (NIH), including BioVU, VUMC's DNA databank.

They found 3,099 people who had experienced a heart attack or the need for revascularization while on statins, and compared them to 7,681 "control" patients on statins who did not experience heart events.

From this comparison, the researchers were able to identify seven genetic variations, called single nucleotide polymorphisms or SNPs, in

the LPA locus of genes that were associated with these heart events in patients receiving statin treatment.

The LPA gene encodes apolipoprotein (a), a fatty protein that binds to low-density lipoprotein (LDL), the form of blood cholesterol that is the target of statin drugs. High levels of bound LDL, called Lp(a) for short, is well known to be an independent risk factor for heart disease.

One of the SNPs was highly associated with an increased risk of heart events. When the researchers examined the full EHRs of 11,566 individuals who carried the SNP for more than 1,000 physical conditions, they found significantly higher rates of coronary heart disease and heart attack but not of other diseases.

The approach, called a phenome-wide association study, was pioneered by Denny and his colleagues at Vanderbilt.

"The study highlights the need to consider targeting Lp(a) levels as an important independent factor to reduce cardiovascular risk in patients on statin therapy," Wei concluded.

Efforts to reduce Lp(a) levels using existing or new drugs could reduce heart events in the proportion of patients on statins who carry LPA variations, he added, although clinical trials would be needed to detect potential side effects and confirm the safety of any such treatment.

More information: Wei-Qi Wei et al. LPAVariants are Associated with Residual Cardiovascular Risk in Patients Receiving Statins, *Circulation* (2018). DOI: 10.1161/CIRCULATIONAHA.117.031356

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