

Risk of cardiovascular disease and diabetes affected by PCSK9 and HMGCR genetic variations

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In a new study published in the December 1, 2016 issue of *The New England Journal of Medicine (NEJM)*, researchers at Brigham and Women's Hospital, and a collaboration of international researchers, studied variants in the genes encoding HMGCR (the target of statins) and PCSK9 (the target of PCSK9 inhibitors) that affect cholesterol levels, and found that variants that lowered LDL (or "bad") cholesterol in each gene were associated with nearly identical protective effects on the risk of cardiovascular events per unit reduction in LDL cholesterol.

"PCSK9 inhibitors are currently available, but we still await the dedicated cardiovascular outcomes trials. Our findings suggest that treatment with a PCSK9 inhibitor, used either alone or in combination with a statin, should reduce the risk of [cardiovascular events](#) to the same degree as do statins per unit reduction in LDL cholesterol," said Marc S. Sabatine, MD, MPH, Chairman of the Thrombolysis in Myocardial Infarction (TIMI) Study Group, the Lewis Dexter, MD, Distinguished Chair in Cardiovascular Medicine at Brigham and Women's Hospital, and senior author of the study.

Variants in both genes also increased the risk of diabetes, but to a lesser extent than they reduced the risk of cardiovascular events. Moreover, the risk of diabetes appeared to be restricted to those individuals who already had impaired glucose metabolism, so called "pre-diabetes."

Researchers used genetic scores consisting of independently inherited variants in the genes encoding PCSK9 and HMGCR and randomly assigned 112,772 participants from 14 studies, with 14,120 cardiovascular events and 10,635 cases of diabetes, to groups according to inherited LDL [cholesterol levels](#). The study compared the effects of lower LDL cholesterol levels that were

mediated by variants in PCSK9, HMGCR, or both, on the risk of cardiovascular events and the risk of diabetes. Genetic variants that mimic the effect of PCSK9 inhibitors and statins had remarkably similar effects as each other on the risk of cardiovascular events and similar effects as each other on the risk of [diabetes](#).

"We look forward to presenting the results of the first and largest dedicated cardiovascular outcomes trial of a PCSK9 inhibitor sometime next year. But in the meantime, these genetic data are another powerful form of evidence supporting their use as another toll in our armamentarium to lower LDL cholesterol and reduce cardiovascular risk in our patients," Sabatine said.

More information: Marc S. Sabatine et al. "Variation in PCSK9 and HMGCR and Risk of Cardiovascular Disease and Diabetes." *N Engl J Med* 2016; 375:214453. [DOI: 10.1056/NEJMoa1604304](#)

Provided by Brigham and Women's Hospital

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