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DYSLIPIDAEMIA

Predicting the benefits and risks of PCSK9 inhibition

Although inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) have been shown to reduce the levels of LDL cholesterol in clinical trials, their effect on the risk of cardiovascular events and diabetes mellitus is unclear. Now, new research shows that variants in *PCSK9* that mimic the LDL cholesterol-lowering effects of PCSK9 inhibitors are associated with a reduced risk of cardiovascular events and an increased risk of diabetes mellitus.

Using a Mendelian randomization approach, 112,772 individuals (encompassing 14,120 cardiovascular events and 10,635 patients with diabetes mellitus) were randomly assigned to groups on the basis of the number of LDL cholesterol-lowering alleles that they had in *PCSK9* and *HMGCR* (which encodes 3-hydroxy-3-methylglutaryl-coenzyme A reductase; the target of statins). Risk of cardiovascular events (first myocardial infarction or death from coronary heart disease) and new-onset diabetes mellitus (HbA_{1c} >6.5% or use of glucose-lowering drugs) was then correlated with reductions in LDL cholesterol levels mediated by variants in the two genes.

For each unit (0.26 mmol/l) decrease in the levels of LDL cholesterol, variants in *PCSK9* and *HMGCR* reduced the risk of cardiovascular events (OR 0.81 for both). Conversely, the risk of diabetes mellitus was increased by variants in *PCSK9* and *HMGCR* per unit decrease in LDL cholesterol levels (OR 1.11 and 1.13, respectively); however, this increased risk was lower in magnitude than the cardioprotective effect and was limited to those individuals who had impaired fasting glucose levels.

Overall, the findings suggest that PCSK9 inhibitors should reduce the risk of cardiovascular events by a similar extent as statins. In their report, the authors suggest that "as with statins, the reduction in cardiovascular risk with PCSK9 inhibitors should far exceed any potential increased risk of diabetes [mellitus]."

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