PCSK9

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a new target for reducing low-density lipoprotein cholesterol (LDL-C) and incident cardiovascular disease, including stroke.

It is a secretory serine protease synthesized primarily by the liver. It mainly promotes the degradation of low-density lipoprotein receptor LDL-R by binding LDL-R, reducing low-density lipoprotein cholesterol (LDL-C) clearance. In addition to regulating LDL-R, PCSK9 inhibitors can also bind Toll-like receptors (TLRs), SCARB1 scavenger receptor B (SR-B/CD36), low-density lipoprotein receptor-related protein 1 (LRP1), apolipoprotein E receptor-2 (ApoER2) and very-low-density lipoprotein receptor (VLDL-R) reducing the lipoprotein concentration and slowing thrombosis. In addition to cardiovascular diseases, PCSK9 is also used in pancreatic cancer, sepsis, and Parkinson's disease. Currently marketed PCSK9 inhibitors include alirocumab, evolocumab, and inclisiran, as well as small molecules, nucleic acid drugs, and vaccines under development [1].

Conventional lipid-lowering agents, including statins, ezetimibe, fibrates, bile acid sequestrants, nicotinic acid, bempedoic acid and Omega-3 fatty acid, are essential to the management of dyslipidemia. However, these agents have been shown to increase the level of plasma proprotein convertase subtilisin/kexin 9 (PCSK9), a serine protease associated with increased cardiovascular risk.

In community-dwelling Japanese men (n = 526) aged 46-82 years without a history of cardiovascular disease, we assessed the associations of serum PCSK9 levels with the prevalence of cerebral small vessel disease (CSVD) and intracranial artery stenosis (ICAS). using magnetic resonance imaging. CSVD included lacunar infarction, deep and subcortical white matter hyperintensity, periventricular hyperintensity, and cerebral microbleeds.

The median (interquartile range) age at baseline and serum PCSK9 levels were 69 (63 - 74) years and 240 (205-291) ng/mL, respectively. After adjusting for traditional cardiovascular risk factors including LDL-C, multivariable Poisson regression with robust error variance revealed a significant association between PCSK9 levels (per 1-SD) and ICAS (relative risks 1.18, 95% confidence intervals [CI] 1.02-1.37). Multivariable ordinal logistic regression for ICAS, with stenosis graded as mild (<50%) or moderate-severe (≥50%), revealed a similar association (common odds ratio 1.31, 95% CI 1.04-1.64). However, no significant association was observed between serum PCSK9 levels and CSVD.

Higher circulating PCSK9 levels were independently associated with an intracranial artery stenosis (ICAS) prevalence but not with a cerebral small vessel disease (CSVD) prevalence. The quantification of circulating PCSK9 levels may help to identify individuals at high risk for cerebrovascular disease in the general population [2].

A review of Luo et al. aimed to investigate the impact of commonly available conventional lipid-lowering agents on circulating PCSK9 levels and lipid profiles.

This protocol was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines. A systematic literature search will be conducted in the following databases: MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, Web of Science, SCOPUS and ScienceDirect. Additional information will be retrieved from clinical trial

registries or from reference list searches. Published and peer-reviewed randomised controlled trials with adults receiving statin, ezetimibe, fibrate, bile acid sequestrant, nicotinic acid, bempedoic acid or Omega-3 monotherapy or in combination for at least 2 weeks, with availability of plasma PCSK9 at the beginning and end of treatment or the net changes in values, will be included. Study selection, data extraction and assessment of the risk of bias will be independently conducted by two investigators. Continuous data will be presented as a standardised mean difference with 95% confidence interval (CI) and dichotomous data as risk ratios with 95% CI. Subgroup analysis and sensitivity analysis will be performed when sufficient studies are included. Publication bias will be assessed with a funnel plot and Egger's test. [3]. [4]

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