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Loss of function in PCSK9, atherogenic lipoprotein concentrations, and calcific aortic valve stenosis

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Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition reduces plasma concentrations of most atherogenic lipoproteins such as low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apoB) and lipoprotein(a) [Lp(a)]. Atherogenic lipoprotein concentrations have also been linked with calcific aortic valve stenosis (CAVS).

Purpose: 1) To determine the association between genetic variants in PCSK9 and lipoprotein-lipid levels, 2) to determine whether loss of function (LOF) in PCSK9 is associated with CAVS and 3) to evaluate if PCSK9 could be implicated in aortic valve interstitial cells (VICs) calcification.

Methods: We built a weighted genetic risk score (wGRS) using 10 single nucleotide polymorphisms at the PCSK9 locus associated with LDL-C in the Global Lipids Genetics Consortium. We determined the association between the wGRS and LDL-C, apoB and Lp(a)] in 9692 participants of the EPIC-Norfolk study using linear regression. We investigated the association between the LOF PCSK9 R46L variant and CAVS risk in a meta-analysis of published (three Copenhagen studies, 1463 cases and 101,620 controls) and unpublished studies (UK Biobank, 1350 cases and 349,043 controls, Malmö Diet and Cancer study, 682 cases and 5963 controls and EPIC-Norfolk, 508 cases and 20,421 controls) prospective, population-based studies using logistic regression adjusted for age and sex. We evaluated PCSK9 expression and localization in explanted aortic valves by capillary Western blot and immunohistochemistry in patients with and without CAVS. Von Kossa staining was used to visualize aortic leaflet calcium deposits. We also assessed VICs calcification potential under oxidative stress condition.

Results: In EPIC-Norfolk, the wGRS was significantly associated with TC, LDL-C, and apoB (all $p<0.0001$), but not with VLDL-C, HDL-C, triglycerides apoA-I, or Lp(a). Carriers of the R46L variant were at lower CAVS risk (odds ratio=0.71 (95% CI, 0.57–0.88, $p<0.001$)). Aortic valves of patients with aortic sclerosis (n=12) and CAVS (n=8) presented elevated PCSK9 levels (log2 fold change [FC]=+28.6±5.1, p=0.008 and FC=+39.3±15.2, p=0.02, respectively) compared to controls (n=4).In calcified leaflets, PCSK9 expression co-localized with calcium deposits. PCSK9 expression in VICs was induced by oxidative stress (FC=+2.3±0.4, p=0.02), and subsequent increment in calcification potential was observed.

Conclusion: PCSK9LOF variants are associated with lifelong reductions in non-Lp(a) apoB-containing lipoprotein levels and a lower risk of coronary artery disease and CAVS. PCSK9 is abundant in fibrotic and calcified aortic leaflets. Oxidative stress increases PCSK9 expression in VICs. These results support randomized clinical trials of PCSK9 inhibition in the prevention of CAVS.