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Serum PCSK9 in relation to coronary near-infrared spectroscopy-derived lipid core burden index and long-term cardiovascular outcome [ATHEROREMO-NIRS substudy]

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Background: Circulating proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme is an intensively studied target for lipid lowering therapy in cardiovascular disease. Near-infrared spectroscopy (NIRS) is an intracoronary imaging technique that is capable of identifying lipid core-containing plaques, which can subsequently be quantified as a lipid core burden index (LCBI). Clinical studies on the association between the PCSK9 level and the amount of lipid in coronary atherosclerosis as assessed by NIRS are currently lacking.

Purpose: The aim of this study was to provide additional insight into the pathophysiology of PCSK9 in coronary atherosclerosis by investigating the association between the serum PCSK9 level with NIRS-derived LCBI. Furthermore, the predictive value of the PCSK9 level for the occurrence of major adverse cardiac events (MACE) during long-term follow-up was assessed.

Methods: Serum PCSK9 levels were measured in 581 patients who underwent diagnostic coronary angiography for stable angina pectoris (SAP) or acute coronary syndrome (ACS) between 2008 and 2011. NIRS imaging of a non-culprit coronary artery segment was performed in a subset of 203 patients and NIRS-derived LCBI was assessed. Follow-up for MACE (a composite of all-cause mortality, nonfatal ACS or unplanned coronary revascularization) was registered in all 581 patients during a median of 4.7 years. Linear regression and Cox regression analyses were used.

Results: In the NIRS cohort, mean age was 63.4 years and 72.9% were men. The median [IQR] PCSK9 level was 278 μg/L [218–344] μg/L, and levels ranged from 91 to 804 μg/L. In univariate analysis, a higher serum PCSK9 level was significantly associated with a higher LCBI (Beta: 0.051 ln(μg/L) per SD increase in LCBI; 95% CI: 0.001–0.101, p=0.047). This association persisted after multivariable adjustment for cardiac risk factors, statin use and baseline serum LDL cholesterol level (Beta: 0.060 ln(μg/L) per SD increase LCBI; 95% CI: 0.004–0.116, p=0.037). During a median follow-up of 4.7 years [IQR: 4.2–5.6] years, 155 patients (27%) experienced MACE. After adjustment for cardiac risk factors, statin use and baseline serum LDL cholesterol level, serum PCSK9 level above versus below the median was significantly associated with MACE (HR[95% CI]: 1.52 [1.10–2.11], p=0.012), as well as with the composite of death or ACS (HR[95% CI]: 1.66 [1.10–2.49], p=0.015). There was also a trend towards a linear association between serum PCSK9 level and MACE after multivariable adjustment (HR[95% CI]: 1.60 [0.96–2.65] per ln(μg/L), p=0.071), and a borderline linear association between serum PCSK9 level and the composite of death or ACS (HR[95% CI]: 1.87 [0.99–3.51] per ln(μg/L), p=0.053).
Conclusion: The serum PCSK9 level is associated with the amount of lipid core in coronary atherosclerosis as assessed by NIRS, as well as with long-term clinical outcome after CAG, independently of cardiac risk factors, statin use and LDL cholesterol level.