RELATIONSHIP BETWEEN PLASMA LEVELS OF PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9(PCSK9), VASCULAR EVENTS AND MARKERS OF SUBCLINICAL ATHEROSCLEROSIS: RESULTS FROM THE IMPROVE STUDY

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Background and aims: The role of PCSK9in atherosclerosis development is still matter of debate. This paper reports the results of an analyses on baseline data of the IMPROVE study aimed at identifying the major determinants of PCSK9.

Methods: The IMPROVE study involved 7centres in 5European countries (Finland, France, Italy, Netherlands, and Sweden). Collected variables included clinical, biochemical, genetic, socioeconomic, psychological, nutritional, and educational data, personal and family history of diseases, drug intake, and physical activity. Ultrasonographic variables (cIMT, plaques size and ICCAD) have been measured on ultrasonic scans stored in the IMPROVE imaging-bank. Circulating PCSK9was measured on plasma aliquots collected after an overnight fasting by using a commercial ELISA kit.

Results: In a crude analysis, carried out in 3.703subjects (54-79years; 48% men), plasma concentration of PCSK9was greater in women than in men ($p<0.0001$) and negatively correlated with latitude and age ($p\leq0.003$). In a partial correlation analysis, adjusted for such variables, plasma levels of PCSK9were significantly associated with some dysmetabolic diseases (hypercholesterolemia, hypertriglyceridemia, hypoalphalipoproteinemia), with different family histories (FH of CVD, dyslipidemia, hypertension and diabetes), with several vascular risk factors (DB-pressure, smoke-duration, packyears, cigarettes/day, total-cholesterol, triglycerides, HDL-C, LDL-C, uric acid, blood-glucose, white blood cells count) nutritional variables (wine, milk, tea and eggs) and some pharmacological treatments (statins, fibrates, and antiplatelet). In a multiple regression analysis, independent predictors of PCSK9concentrations were hypercholesterolemia, HDL-C, blood-glucose, packyears, hip, wine, statins, and fibrates (β-values ranging from 0.26to 79.03). In the same analysis, independent predictors inversely associated to PCSK9were latitude, sex, diabetes, use of oestrogen, uric acid, and fish consumption (β-values ranging from -23.2to -2.8). The association between PCSK9and the different ultrasonographic variables of subclinical atherosclerosis was evaluated by general linear models. The analyses were adjusted for age, sex, latitude plus all the covariates that in the multiple regression analysis were significantly associated with both PCSK9and the ultrasonographic variable of interest, i.e. IMT_{mean}, IMT_{max}, $IMT_{mean-max}$, $CC\text{-}IMT_{mean}$ measured in plaque free areas and inter-adventitia common carotid artery diameter (ICCAD). Among all the variables considered, only ICCAD was weakly but significantly associated with PCSK9($\beta=-0.0003$; $p=0.018$).

Conclusions: Beyond to associations with many VRFs, the only index of subclinical atherosclerosis associated with plasma levels of PCSK9was the inter-adventitia common carotid artery diameter measured in plaque free areas, i.e. an index of functional arterial damage. By contrast, all the ultrasonographic variables indexing a morphological damage (e.g. IMT plaque size etc.) were not associated with PCSK9.

Key words: circulating PCSK9, atherosclerosis