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PCSK9 as a predictor of cardiovascular events in atrial fibrillation: role of platelet activation

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BACKGROUND High circulating levels of proprotein convertase subtilisin/kexin 9 (PCSK9) were shown to be predictive of cardiovascular events (CVEs) in patients with atrial fibrillation (AF). Because high PCSK9 plasma levels were significantly correlated with 11-dehydro-thromboxane B2 (11-dh-TxB2), a marker of platelet activation, it is conceivable to hypothesize a direct effect of PCSK9 on platelet activation but the mechanism is still unclear.

PURPOSE We evaluated the association between PCSK9 and platelet activation in FA patients and investigate the possible molecular mechanism involved.

METHODS According to our previous prospective study, we conducted a post-hoc analysis including 50 patients with baseline PCSK9 below and 50 above the median value of 1200pg/ml. The two groups were balanced for age and sex. In vivo platelet activation was assessed by aggregation (PA), recruitment, plasma thromboxane B2 (TxB2) formation and sPselectin levels. As markers of oxidative stress we used sNox2-dp, H2O2 production, urinary isoprostanes and oxLDL. To asses the role of PCSK9 in platelet activation, we performed an in vitro study with platelets from healthy subjects (n=5) added with PCSK9 concentrations achievable in human circulation (1000pg/ml and 2000pg/ml) measuring PA, TxB2, isoprostanes production, Nox2 activation, H2O2 production, oxLDL, p38, p47 and PLA2 phosphorylation. RESULTS We observed an increased of platelet activation and oxidative stress in patients with PCSK9 levels above median (1200pg/ml) compared to those below (p<0.05). A significant correlation between plasma levels of PCSK9 and markers of platelet activation and markers of oxidative stress were found. In vitro study demonstrated that PCSK9, at the concentration similar to that of patients with CVEs, was able to increase platelet activation act by binding oxLDL receptor. PCSK9 dependent platelet activation is mediated by p47 phosphorylation, a key step in Nox2 activation and is mediated by the PLA2 phosphorylation.

CONCLUSIONS PCSK9, at concentration achievable in patients with CVEs, increased platelet aggregation via oxLDL receptor with a pathway involving Nox2 activation.