C-REACTIVE PROTEIN AND IMMATURE PLATELET FRACTION CONTRIBUTE TO POOR RESPONSIVENESS TO LOW-DOSE ASPIRIN AND PERSISTENT *IN VIVO* PLATELET ACTIVATION IN POLYCYTHEMIA VERA

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Introduction: Polycythemia Vera (PV) is a myeloproliferative neoplasm (MPN) characterized by peripheral erythrocytosis and increased thrombotic risk affecting morbidity and mortality. Low-dose aspirin once-daily (od) is currently recommended for primary and secondary cardiovascular prevention in PV. However, it has been recently suggested that low-dose aspirin should be used twice-daily (bid) in PV patients at intermediate-to-high cardiovascular risk, based on pharmacodynamic studies in essential thrombocythemia. However, pharmacological or clinical data supporting bid aspirin in PV are missing.

Materials and methods: We studied the platelet responsiveness to standard aspirin (100 mg od) in PV patients, assessed at the end of the 24-hour dosing interval. PV patients diagnosed according to the WHO 2008criteria, on standard aspirin underwent a run-in phase (7-10 days) during which aspirin intake was synchronized at breakfast. Routine hematochemistry, genotype and allelic burden, clinical characteristics, history and medications were recorded. We measured serum thromboxane B_2($sTXB_2$) as *ex vivo* biomarker of aspirin pharmacodynamics, urinary 11-deidro-TXB_2(TXM) as *in vivo* index of platelet activation, the major urinary prostacyclin metabolite, 2,3dinor 6-keto-$PGF_{1\alpha}$ (PGIM), the urinary isoprostane 8-iso-PGF_{2a} and plasma salicylic acid esterase activity.

Results: Fifty patients (aged 67[48-83] years, median and IQR, 16females) on aspirin for ≥1month gave their informed consent; compliance and non-steroidal anti-inflammatory drug intake were checked by phone calls and patient's interview on the day of the visit; 36patients were on phlebotomy, 30 were on hydroxyurea. Hematocrit averaged 44[37-49]%, platelets 342[177-728] 10^3/uL, immature platelets 9.1[3.5-29.5] 10^3/uL. The median $sTXB_2$value was 8.4[2-49] ng/ml, urinary TXM 509[207-1312] pg/mg creatinine, urinary 8-iso-PGF_{2a} 729[240-1653] pg/mg creatinine, urinary PGIM 172[120-275] pg/mg creatinine, plasma esterase activity 62[44-88] μmol/L salycilic acid/min. $sTXB_2$significantly ($p<0.01$) correlated with total and immature platelets (rho=0.1and 0.53, respectively), C-reactive protein (CRP) (rho=0.41) and urinary TXM (rho=0.51). By multivariable analysis, $sTXB_2$was independently predicted by CRP and immature platelets, and urinary TXM was independently predicted by sTXB2and CRP levels (all $p<0.05$). Plasma esterase activity correlated with hemoglobin levels (rho=0.33, $p=0.04$), but not with the hematocrit, urinary TXM or $sTXB_2$.

Conclusions: A fraction of PV patients characterized by high immature platelet and CRP levels have a reduced response to a standard regimen of low-dose aspirin, which may contribute to persistently enhanced *in vivo* platelet activation. An improved antiplatelet regimen should be tested in these patients.