PII-8

CASTRATION REDUCES HUMAN PLATELET TXA_2 RECEPTOR DENSITY AND AGGREGABILITY. A. A. Ajayi, MD, PhD, P. V. Halushka, PhD, MD, Texas Southern University, Medical University of South Carolina, Houston, TX.

BACKGROUND: Exogenous testosterone T upregulates platelet TXA_2 receptors and enhances aggregation response to TXA_2 mimetics in healthy men.

AIM: Investigate the impact of reduction in plasma testosterone on platelet $TXA_{2\ receptors}$.

METHODS: Design A cross sectional study. Subjects : surgically castrated men with prostate cancer n= 8, aged 71±8yrs and age-matched urologic cases n=7, 67±9yrs, Setting : tertiary referal hospital Radioligand binding studies for platelet TXA_2 receptors using ^{125} I-BOP, and platelet aggregation studies using I-BOP and thrombin were undertaken.

RESULTS: Castrated patients had reduced plasma T,16 ± 5, compared to controls 308 ng/dl ($p< 0.001$). Platelet TXA_2 receptor B_{max} but not K_d was reduced in castrated (0.50±0.12 pmol/mg protein) compared to controls(1.01±0.17pmol/mg protein) $p = 0.03$. The E_{max} of platelet aggregation but not EC_{50} to 1-BOP was reduced in the castrated (53±2%) compared to control patients (63±2%) [p=0.003ANOVA. *In vitro,* hydroxyflutamide at high concentration 100uM, did not affect I-BOP binding, but competitively inhibited U46619 aggregation ($p< 0.05$ ANOVA).

CONCLUSION: Endogenous testosterone genomically regulates human platelet TXA_2 B_{max} and aggregation response to TXA_2 mimetic I-BOP, and thrombin. Inhibition of androgen production or receptor blockade may reduce platelet aggregation. There is indirect evidence that there are functional androgen receptors on human platelets, which regulate TXA_2 receptor expression.

PII-9

PHARMACODYNAMICS (PD) OF CLOPIDOGREL IN PATIENTS WITH ACUTE CORONARY SYNDROMES UNDERGOING PERCUTANEOUS INTERVENTIONS (PCI). I. Fuchs, MD, M. Frossard, MD, A. Laggner, MD, A. Spiel, MD, E. Wohlschläger, MD, B. Jilma, MD, Department of Clinical Pharmacology and Dept. of Emergency Medicine, Medical University, Vienna, Austria.

BACKGROUND/AIMS: Little is known about the PD of clopidogrel in patients suffering from acute coronary syndromes (ACS) undergoing PCI. We hypothesized that the high degree of platelet activation in ACS patients may impede the PD effects of clopidogrel early after onset of ACS.

METHODS: ACS patients (n=200), who presented to the University Hospital, were included into a prospective trial. Patients received a loading dose of clopidogrel (300 mg) followed by 75mg/d clopidogrel up to 12 months. Platelet function was assessed by the collagen adenosine diphosphate closure time (CAPD-CT) with the FDA approved platelet function analyzer (PFA-100). The single nucleotide polymorphism (SNP) i-744 of the purinergic receptor P2Y12 was determined by Taqman technology.

RESULTS: Baseline CAPD-CT averaged 99s (CI: 90-110), and a 10% increase in CADP-CT was observed only after a time-lag of 7 days (p=0.03). Maximum effectiveness was observed only after period of 3 months on therapy [CADP-CT: 154s (138-169); p<0.0001]. The diagnosis of myocardial infarction and high plasma levels of von Willebrand Factor levels predicted decreased responsiveness to clopidogrel therapy, whereas the assessed P2Y12R SNP had no impact.

CONCLUSIONS: Our pharmacodynamic data indicate that ACS patients could profit from higher clopidogrel dosages particularly in the early weeks after PCI, and dose finding studies appear recommendable.

PII-10

EFFICACY AND SAFETY OF CONTROLLED-RELEASE ISOSORBIDE-5-MONONITRATE FOR PATIENTS WITH STABLE EFFORT ANGINA PECTORIS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY. K. Shimada, MD, S. Sunayama, MD, K. Nakazato, MD, H. Satoh, MD, H. Daida, MD. PhD, Department of Cardiology, Juntendo University, Tokyo, Japan.

BACKGROUND: A major limitation of the use of nitrates is the development of "nitrate tolerance". The widely accepted treatment of preventing tolerance is to provide a period of "low nitrate interval". Then, a new controlled-release isosorbide-5-mononitrate (I-CR) has been developed.

METHODS: We conducted a randomized, double-blind, placebo-controlled study, which investigated the efficacy and safety of I-CR for 30 outpatients with stable angina pectoris. After consecutive exercise tests (ETs) for ascertaining the reproducibility of exercise tolerance during the placebo run-in period, patients were randomly assigned to either I-CR (40 mg once daily) or placebo groups (2:1) for 2 weeks. ETs were performed at 5, 12 and 24 hours after dosing on the final day. The primary efficacy variable was the change in exercise time to moderate angina from the baseline.

RESULTS: The changes of exercise time to moderate angina were prolonged at 5 hours but not shortened at 24 hours. The subgroup analysis suggested that presence of concomitant use of insulin affected on this result. Headaches were the most frequent adverse effect but self-control levels in the I-CR group. The plasma concentration of I-CR at 24 hours was less than 100ng/mL.

CONCLUSION: These results suggest that I-CR improves exercise tolerance during the daytime and can be well tolerated in patients with stable effort angina without increasing adverse effect.

Change in exercise time to moderate angina from baseline (seconds)

	Treatment	N	5 hours	12 hours	24 hours
All patients	I-CR	21	39.1 14.7~63.6	−7.5 −29.7~14.8	27.5 4.2~50.9
	placebo	9	26.8 −16.6~70.1	−17.2 −61.7~27.3	65.4 26.1~104.8
Without insulin concomitant	I-CR	16	52.9 28.0~77.9	5.0 −19.2~29.2	38.8 13.7~63.9
	placebo	8	21.9 −26.8~70.5	−24.5 −72.4~23.4	65.4 19.7~111.1

Data are presented as mean values (95% confidence interval).