Netherlands; [2] Good Biomarker Sciences, Leiden, The Netherlands; [3] Bristol-Meyers Squibb, New York, USA; [4] Departments of Physiology and Pulmonary Diseases, Institute for Cardiovascular Research, VU University Medical Center, Amsterdam, The Netherlands; [5] Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

Aim: Treatment of chronic myeloid leukemia patients with the second and third generation BCR-ABL1 tyrosine kinase inhibitors (TKIs) increases cardiovascular side effects including myocardial infarction. We investigated the effect of these TKIs on cardiovascular risk factors (plasma lipids, blood pressure, inflammation markers, endothelial dysfunction) and development of atherosclerosis, in a translational model for atherosclerosis, the APOE3*Leiden.CETP mouse.
Methods: First, dose and dosage interval were determined by PK analysis to reach similar plasma concentrations as in patients. Next, mice were treated for sixteen weeks with imatinib (150 mg/kg BID), nilotinib (30 mg/kg QD) or ponatinib (10 mg/kg QD), as representatives of the first, second and third generation TKIs. Cardiovascular risk factors were analyzed throughout, and histopathological analysis of atherosclerosis and gene expression and pathway analysis in the liver as predictor tissue were performed.
Results: Imatinib and ponatinib decreased plasma cholesterol (-69%, $P<0.001$ and -37%, $P<0.001$) and atherosclerotic lesion area (-78%, $P<0.001$ and -48% $P=0.001$), which were not affected by nilotinib. In addition, imatinib reduced inflammation markers and increased plaque stability. Ponatinib increased E-selectin levels (161%, $P<0.05$) and the urinary albumin:creatinin ratio (13-fold, N.S.). All three TKIs decreased pro-inflammatory Ly6Chigh monocytes, consistent with the mode of action of TKIs. Gene expression pathway analysis confirmed our findings on decreased cardiovascular risk by imatinib and increased risk by ponatinib.
Conclusions: Imatinib showed a beneficial cardiovascular risk profile and nilotinib had no adverse cardiovascular effects, whereas ponatinib despite favorable effects on plasma lipids and atherosclerosis increased the cardiovascular risk through increased inflammation and endothelial activation.

SAG004.
ROLE OF PLATELET SURFACE RECEPTOR EXPRESSION AND BLOOD GROUP IN PREDIC7NG RISK OF BLEEDING WITH ASPIRIN

Rana Khalil[1], Eimear Dunne[2], Dermot Kenny[3]. [1] *School of Medicine, RCSI, Dublin, Ireland;* [2] *Department of Molecular and Cellular Therapeutics, RCSI, Dublin, Ireland;* [3] *RCSI Clinical Research Centre, Dublin, Ireland*

Aim: Aspirin (ASA) is the first-line therapy for the secondary prevention of cardiovascular events(1). Platelet response to ASA is highly variable between individuals, and is associated with varying risks of bleeding. This study aimed to examine the role of platelet surface receptors and blood group in determining this risk of bleeding attributable to ASA.
Methods: Platelet GPIb-IX-V receptor binds VWF and initiates platelet aggregation by capturing platelets to damaged subendothelium. GPIIb/IIIa receptor binds fibrinogen and is essential in the formation of a primary platelet plug by mediating cross-linkage of platelets. We recruited 20 healthy volunteers and administered 300mg ASA. We evaluated the standard response of ASA to Arachidonic Acid- induced platelet aggregation using Light Transmission Aggregometry. Plasma TxB2 (product of activated platelets) and Glycocalicin (soluble GPIb normally found in plasma) were measured using ELISA. The surface expression of GPIIB/IIIa and GPIb were measured using flow cytometry.
Results: LTA and post-ASA TxB2 demonstrated standard effects of ASA on platelet aggregation ($p<0.0001$, student t-test, $n=19$ and $p<0.0001$, student t-test, $n=20$ respectively). Donors with blood group O had significantly less surface expression of GPIb counts compared to non-O donors ($p=0.0288$, student t-test, $n=10$). Interestingly, both groups had almost identical Glycocalicin post- ASA, suggesting that the reduced GPIb expression in blood group O can't be explained by shed plasma GPIb.
Conclusions: Our results suggest for the first time that blood group plays a crucial role in platelet GPIb-IX-V receptor expression, independent of plasma Glycocalicin levels. This can be used to possibly determine the individual risk of ASA bleeding.

SAG005.
PREDICTIVE VALUE OF CIRCULATING MICROVESICLES IN CORONARY ARTERY BYPASS GRAFT PATENCY

Marta Brambilla[1], Paola Canzano[1], Laura Rossetti[1], Chiara Zara[1], Laura Cavallotti[1], Alessandro Parolari[2,3], Fabrizio Veglia[1], Elena Tremoli[1,2,3,4], Marina Camera[1,2,3,4]. [1] *Centro Cardiologico Monzino IRCCS, Milan, Italy;* [2] *Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, Milan, Italy;* [3] *IRCCS Policlinico San Donato, San Donato Milanese, Italy;* [4] *Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, Milan, Italy*

Aim: Graft patency is one of the major determinant of long-term outcome following coronary artery bypass grafting (CABG). The identification of predictors of graft patency after CABG has been addressed by several studies but none has assessed the potential involvement of microvesicles (MVs). MVs are biomarkers of vascular injury and inflammation in several cardiovascular diseases including atherothrombosis. The aim of the study was to elucidate whether a specific "signature" of MVs is associated with CABG occlusion.
Methods: MVs were analyzed in platelet free plasma (PFP) collected from 179 patients the day before elective surgical myocardial revascularization (T0). At 18 month-follow-up, a 64-rows CT scan evaluation of graft patency was performed. The number of MVs, their cell origin and the expression of platelet activation markers (P-selectin, CD40L, TF) were evaluated by flow cytometry.
Results: Analysis of MV signature at T0 indicated that patients that would have occluded bypass at follow-up had higher number of CD41pos, Psel/CD41pos and CD40L/CD41pos MVs. No significant differences were observed when monocyte-, granulocyte- and endothelium-derived MVs were analyzed. Of interest, TF/CD41pos MVs were increased in occluded compared to patent graft patients (64 ± 40 vs 17 ± 7 MVs/μl, $p=0.0002$). ROC curve analysis confirmed the predictive value of TF/CD41pos MV-signature in the assessment of CABG occlusion (AUC: 0.81; $p<0.0001$).
Conclusions: These data show that patients that would have occluded bypass-graft had a significant higher number of MVs compared to patients with patent graft. Moreover these data provide the evidence that the signature of MVs before CABG surgery has a predictive value of graft patency.

SAG006.
EFFECTS OF PCSK9 INHIBITORS ON PLATELET FUNCTION IN ADULTS WITH HYPERCHOLESTEROLEMIA

Cristina Barale, Katia Bonomo, Fabio Noto, Monica Traversa, Franco Cavalot, Mirko Iozzia, Chiara Frascaroli, Angelo Guerrasio, Isabella Russo. *Internal Medicine and Metabolic Diseases, Department of Clinical and Biological Sciences, University of Turin, Orbassano, Italy*

Aim: Proprotein Convertase Subtilisin/Kexin 9 (PCSK9) plays a major role in the regulation of LDL-receptor function and therapy with PCSK9 inhibitors have shown efficacy in reducing LDL-cholesterol levels whereas their effects on platelets are unknown.
Aim of the study was to evaluate, in adults with hypercholesterolemia, the effects of therapy with monoclonal antibody anti-PCSK9 on platelet function.
Methods: 21 subjects with hypercholesterolemia (14M/7F, age 56.2 ± 11.5 years, BMI 25.5 ± 4.5 kg/m2) were enrolled and most of them ($n=14$) were on acetylsalicylic acid (ASA). At baseline and after a 8-week treatment with the PCSK9 inhibitors Alirocumab or Evolocumab, we evaluated lipid profile and the folllowing platelet parameters: i)aggregation in platelet-rich plasma(PRP) and whole blood(WB) to agonists, ii)adhesion and

aggregation under elevated shear stress condition(PFA-100), iii)membrane expression of the activation marker CD62P (cytofluorimetric assay).
Results: A 8-week treatment with anti-PCSK9 therapy reduced total-cholesterol by 41±5% (p<0.001), LDL-cholesterol by 55±4% (p<0.001), and triglycerides by 15±2% (p<0.01). In ASA-treated subjects, we found: a decrease of platelet aggregation in PRP to ADP (-33±2%, p<0.01), and collagen (-27±5%, p<0.001); an increase of closure time of PFA-100 (+70±7%, p<0.02); a decrease of CD62P expression (-49±8%, p<0.03); in non-ASA treated subjects: a decrease of aggregation in PRP to ADP (-24±6%, p<0.05), and collagen (-31±4%, p<0.05); a decrease of aggregation in WB to ADP (-51±9%,p<0.04), and collagen (-44±2%,p<0.02); a decrease of CD62P expression (-47±3%,p<0.003).
Conclusions: In adults with hypercholesterolemia, a 8-week treatment with monoclonal antibody anti-PCSK9 significantly improved lipid profil, reduced platelet reactivity to agonists and increased platelet sensitivity to the inhibitory effects of aspirin.

SAG007.
RELATIONSHIP OF PLATELET THROMBOXANE INHIBITION BY ASPIRIN AND ALL-CAUSE MORTALITY IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE

Luis R. Lopez[1], Anupama Vasudevan[2], Mohanakrishnan Sathyamoorthy[2], Jeffrey M. Schussler[2], Carlos Velasco[2], Caren Swift[3], Raphael Schiffmann[3], Teodoro Boittiglieri[3], Peter A. McCullough[2]. [1] *Corgenix, Inc., Broomfield, USA;* [2] *Baylor Heart and Vascular Institute, Dallas, USA;* [3] *Baylor Research Institute, Dallas, USA*

Aim: Anti-platelet therapy with aspirin (ASA) reduces nonfatal myocardial infarction, stroke, and cardiovascular death by irreversibly inhibiting platelet COX-1 and TxA2 production. However, variable TxA2 inhibition is common. We studied the relationship of urinary 11dhTxB2, an inactive TxA2 metabolite, with all-cause mortality in stable coronary artery disease (CAD) patients on ASA treatment.
Methods: CAD patients (n=449) taking ASA from Baylor Heart and Vascular Hospital and Texas Heart Hospital Baylor Plano were studied.
Results: There were 73% males and 27% females with a mean age of 66.5±10 and 65±10.2, respectively. A positive linear trend for age (p=0.01), chronic obstructive pulmonary disease (p=0.0003), heart failure (p=0.003), and oxidative stress (p<0.001) was observed among 11dhTxB2 tertiles. There were more females (p=0.001) in the upper tertiles. There was no difference in ASA dosage and P2Y12 antagonist use (p=0.53) between 11dhTxB2 tertiles (p=0.22). 14.9% patients died over a median follow-up of 3 years with 87.5% deaths from cardiovascular causes. 38.8% non-survivors received P2Y12 antagonists compared to 42.2% survivors (p=0.61). The mortality rate in the upper tertile was 8.1 compared to 5.1 and 0.7 in middle and lower tertiles (p<0.001). By stepwise Cox hazard analysis, patients in the middle (HR=7.14; 95% CI:2.46-20.68) and upper 11dhTxB2 tertiles (HR=9.91; 95%CI:3.45-28.50) had a higher risk for mortality after adjusting for age and co-morbidities.
Conclusions: Urinary 11dhTxB2 is a strong independent risk factor for all-cause mortality among stable CAD patients on ASA therapy. These results suggest that inadequate response to ASA may prompt additional anti-platelet therapy in these high risk patients.

SAG008.
ROLE OF STRAIN RATE IMAGING IN THE DETECTION OF SIGNIFICANT CORONARY ARTERY STENOSIS

Abdallah Almaghraby, Gehan Magdy, Mohamed Sadaka, Tarek Elzawawy. *University of Alexandria, Alexandria, Egypt*

Aim: To assess the possibility of using the novel strain rate imaging method in the detection of significant regional myocardial ischemia caused by significant coronary artery disease in patients with stable coronary artery disease.
Methods: Thirty patients with SCAD and significant single vessel left anterior descending (LAD) coronary artery stenosis, diagnosed by invasive coronary angiography, undergoing elective percutaneous coronary intervention (PCI) of the LAD lesion with no significant lesions in the other coronary vessels, left circumflex (LCX) and right coronary artery (RCA). Patients with diabetes, regional wall motion and reduced left ventricular systolic function were excluded.
Regional systolic strain and strain rate was measured in the ischemic LAD segments which are six, apicoseptal, mid anteroseptal, basal anteroseptal, apicoanterior, mid anterior and basal anterior, and measured in the non-ischemic LCX and RCA segments, before elective PCI of LAD and three months later.
Results: By comparing the strain and strain rate of the ischemic segments before and after PCI there was significant improvement of the systolic strain while there were non-significant changes in the non-ischemic segments.

	Peak systolic strain (%)		P value	Peak systolic strain rate (1/s)		P value
	Before PCI	After PCI		Before PCI	After PCI	
Ischemic segments	-8.11 ± 3.31	-12.81 ± 3.27	<0.001*	-0.66 ± 0.27	-0.90 ± 0.29	<0.001*
Non-ischemic segments	-10.54 ± 3.25	-11.26 ± 6.46	0.061	-0.84 ± 0.26	-0.90 ± 0.56	0.069

SAG008

Conclusions: Tissue Doppler strain and strain rate imaging during resting echocardiography can be used to detect regional myocardial ischemia in patients with significant coronary artery stenosis.

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SAG009.
NEURONAL GUIDANCE CUES AND THEIR ROLE IN PREMATURE ATHEROSCLEROSIS

Caroline Bruikman[1], Dianne Vreeken[2], J.C. van Capelleveen[1], S.J. Pinto-Sietsma[1], G.M. Dallinga-Thie[1,3], J.M. van Gils[2], G. Kees Hovingh[1]. [1] *Department of Vascular Medicine, AMC, Amsterdam, The Netherlands;* [2] *Department of Internal Medicine, Einthoven Laboratory of Experimental Vascular Medicine, LUMC, Leiden, The Netherlands;* [3] *Department of Experimental vascular Medicine, AMC, Amsterdam, The Netherlands*

Aim: Neuronal guidance cues (NGCs) are known for controlling neuronal migration and vascular patterning through a complex interplay of signals. It has been shown that NGCs and their receptors play an important role in the regulation of the adhesion of monocytes to the vascular endothelium and their subsequent proatherogenic actions. However, the role of NGCs in human atherosclerosis is not well studied.Because we know that monocyte adhesion and the vascular endothelium permeability play an important role in the atherosclerotic process, we hypothesize that a dysfunctional NGC pathway contribute to this in patients with premature atherosclerosis (PAS) and no cardiovascular risk factors.