Venous thromboembolism (VTE) is a multicausal disease. The risk of VTE is dependent upon the number and severity of risk factors present in an individual person. The most important circumstantial risk factors are advancing age, surgery and trauma, oestrogen intake, pregnancy, and certain medical illnesses including heart failure and cancer. Gain of function mutations (factor V Leiden or the pro-thrombin mutation) and natural coagulation inhibitor (antithrombin, protein C and protein S) deficiencies are the most important inherited risk factors for a first VTE. Risk factors for a first VTE are not necessarily associated with a high risk of recurrence. We were the first to demonstrate that the heterozygous carrier state of either factor V Leiden mutation or the prothrombin mutation does not confer an increased risk of recurrent VTE. Conversely, patients with high factor VIII or hyperhomocysteinemia have an increased risk of recurrence. Nevertheless, thrombophilia screening, i.e. measurement of laboratory risk factors of VTE, has a low predictability with regard to the likelihood of recurrence in an individual patient and has therefore been widely abandoned. The risk of recurrence is increased among patients with more than one episode of VTE, unprovoked VTE, proximal VTE, pulmonary embolism at manifestation or cancer. For instance, patients with proximal deep-vein thrombosis and/or pulmonary embolism have a recurrence risk as high as 30% after 5 years. Hence, these patients are good candidates for indefinite anticoagulation regardless of the presence or absence of laboratory risk factors of VTE.
bibilized from the flowing blood onto the site of injury. Under high shear conditions further accrual of newly arriving platelets again requires VWF, which has to bridge platelets not only to the exposed collagen but also to each other by being sand-wiched between the multiple platelet layers of the hemostatic plug. Signaling pro cesses and engagement of further receptors secures firm adhesion and formation of a hemostatic plug or thrombus.

SY2-3
Assessment of platelet function in the laboratory
Harrison P1
1Department of Clinical Pharmacology, Medical University of Vienna, Austria

Platelet function testing is essential for the diagnosis of congenital/acquired bleeding disorders and may be useful for the prediction of surgical bleeding. Nowadays there is also much interest in monitoring the efficacy of anti-platelet therapy and measuring platelet hyper-function. However, this often presents clinical laboratories with significant challenges as platelet function tests are complex, poorly standardized, time consuming and quality assurance is not straightforward. There are also few comprehensive modern guidelines available and many recent published surveys have revealed poor standardization between laboratories. Up until the late 1980’s the traditional clinical platelet function tests that were available were the bleeding time (BT), light transmission (LTA) and whole blood aggregometry (WBA) and various biochemical assays. These were also usually performed within specialized research and clinical laboratories. Since the last BCSH guidelines were published in 1988 a variety of new platelet function tests have become available. These include flow cytometry and an ever increasing choice of new commercial instruments. Although the potential clinical utility of the new assays is emerging some have not yet entered into routine clinical practice. It is encouraging that a number of standardization committees (e.g. CLSI, BCSH and ISTH Platelet Physiology SSC) are now beginning to produce new platelet function testing guidelines and this will hopefully improve clinical practice, quality assurance and result in less variability between different laboratories.

SY3 Mecha-nisms of Vascular Disease

SY3-1
Role of von Willebrand factor in vascular disease
Paulinka P1, Spiel A1, Linke B1
1Department of Clinical Pharmacology, Medical University of Vienna, Austria

Plasma levels of von Willebrand factor (VWF) are increased in patients with cardiovascular risk factors. Various studies were aimed to elucidate the relation of VWF with thromboembolic cardiovascular events, ischemic stroke as well as with peripheral arterial occlusive disease. In the general population, there is only a weak association between VWF levels and future cardiovascular events or stroke. In contrast, VWF levels are predictive in patients with documented vascular disease. Those patients with increased VWF suffer a higher incidence of major adverse cardiac events including death. The extent of the VWF release and its levels independently predict clinical outcome in patients with acute coronary syndromes. Elevated VWF levels have also been observed in patients with atrial fibrillation compared to controls and predict outcome. This may at least in part be attributable to the association of VWF with underlying cardiovascular risk factors. Hence, VWF correlates with Framingham and CHADS2 stroke risk stratification score and can be used as a biological marker in patients with A.F. However, VWF is not only a predictor; it also plays a crucial role in thrombogenesis. This fact has made VWF a promising target for research into new anti-platelet therapies that specifically inhibit VWF. This review focuses on the role of VWF in ACS, ischemic stroke and peripheral arterial disease and outlines the relevance of therapeutic interventions targeting VWF for ACS patients.

SY4 Inflammation in the Vessel Wall

SY4-2
Key transcriptional regulators of the vasoprotective effects of shear stress
Horrocks AJ1, Born RI2
1Utrecht University Medical Center, Amsterdam, The Netherlands
2University of Oxford, Oxford, UK

Atherosclerotic plaque rupture and subsequent thrombosis is the main cause of sudden coronary death. Remarkably, atherosclerosis only develops in certain pre-disposed areas of the vasculature. Endothelial cells in these pre-disposed areas experience low or oscillatory shear stress, which activates the pro-inflammatory and pro-coagulant transcription factors activator protein 1 (AP-1) and nuclear factor κB (NFκB), thus inducing a pro-inflammatory, pro-coagulant surface. In contrast, healthy endothelial cells that are exposed to prolonged high laminar shear stress, express anti-inflammatory and anti-coagulant genes. The key shear stress-induced transcription factors that govern the expression of these genes are K-rüppel-like factor 2 (KLF2) and nuclear factor erythroid 2-like 2 (Nrf2). Together KLF2 and Nrf2 govern ~70% of the stress-elicited gene sets. Nrf2 potently induces anti-inflammatory/antioxidant enzymes, while KLF2 induces anti-inflammatory and anti-coagulant proteins, most specifically endothelial Nitric Oxide Synthase (eNOS), and Thrombomodulin (TM). KLF2 also inhibits pro-inflammatory and anti-fibrinolytic genes through inhibition of proinflammatory transcription factors AP-1 and NFκB. The wide-spread beneficial effects of the key transcription factors KLF2 and Nrf2 on endothelial phenotype, holds the promise that their targeted modulation might lead to a whole new class of cardiovascular drugs.

SY4-3
Immune modulation by natural antibodies to prevent vessel wall inflammation
Binder C1
1GMM Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria

This review focuses on the role of VWF in ACS, ischemic stroke and peripheral vascular disease and outlines the relevance of therapeutic interventions targeting this protein for research into new anti-platelet therapies that specifically inhibit VWF.

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Wien 2009
**SY6-1**

**Obesity and vascular risk**

Linnen F1

1Center for Molecular and Vascular Biology, Leuven, Belgium

**Objectives:** To study the role of the fibrinolytic and matrix metalloproteinase (MMP) systems in development of adipose tissue and to evaluate obesity as a prothrombotic risk.

**Methods:** A nutritionally induced obesity model was used in transgenic mice with deficiency or overexpression of components of both proteolytic systems. Venous and arterial thrombosis models were applied to lean and obese mice.

**Results:** Tissue-type plasminogen activator (t-PA) deficient mice, kept on high fat diet, had higher body weight and adipose tissue mass than wild-type controls. However, development of obesity was impaired in plasminogen deficient mice. The role of plasminogen activator inhibitor-1 (PAI-1) in development of obesity remains controversial. Stromelysin-1 (MMP-3) deficiency promoted adipose tissue development, whereas deficiency of tissue inhibitor of mmP-1 (TIMP-1) induced impaired adipose tissue development associated with adipocyte hypertrophy. A administration to wild-type mice kept on a high fat diet of broad-spectrum or relatively gelatinase-specific MMP inhibitors resulted in moderate to significant reduction of adipose tissue weight. In an inferior caval vein thrombosis model obese mice showed an increased thrombus weight as compared to lean controls. In a femoral arterial thrombosis model obese mice showed a shorter occlusion time and lower total blood flow.

**Conclusion:** Studies in transgenic mice support a role of the fibrinolytic and MMP systems in development of obesity. Studies in venous and arterial thrombosis models confirm a prothrombotic risk associated with obesity.

**SY6-3**

**Fibrin in angiogenesis and wound healing**

De Maat M1

1ErasmusMC, Rotterdam, The Netherlands

Fibrinogen and fibrin play an important role in blood clotting, fibrinolysis, cellular and matrix interactions, inflammation, wound healing, angiogenesis, and neoplasia. The contribution of fibrinogen to these processes largely depends not only on the characteristics of the fibrinogen itself, but also on interactions between specific binding sites on fibrinogen, pro-enzymes, clotting factors, enzyme inhibitors, and cell receptors. Fibrinogen contributes to cutaneous wound repair via these molecular and cellular mechanisms. More specifically, the outcome of wound healing depends largely on the fibrin structure, such as the thickness of the fibers, the number and density of branch points, the porosity, and the permeability. Furthermore, the binding of fibrinogen to hemostasis proteins and platelets as well as several different cells such as endothelial cells, smooth muscle cells, fibroblasts, leukocytes, and keratinocytes is indispensable for the process of wound repair. High molecular weight and low molecular weight fibrinogen, two naturally occurring variants of fibrin, are important determinants of angiogenesis and differ in their cell growth stimulation, clotting rate, and fibrin polymerization characteristics. Fibrin sealants have been investigated as matrices to promote wound healing. These sealants may also be an ideal delivery vehicle to deliver extra cells for the treatment of chronic wounds.

**SY7**

**Hemostasis in Major Surgery**

**SY7-2**

**How much blood transfusion is needed in major surgery?**

Gombotz H1

1Department of Anesthesiology and Intensive Care, General Hospital Linz, Austria

**Objectives:** To measure and to assess measures were the amount of intra- and postoperative blood components transfused and intercenter variability of transfusion rate. Secondary outcome measures were prevalence of preoperative anemia, calculated perioperative blood loss, and lowest measured perioperative hemoglobin (Hb) level.

**Methods:** A total of 777 patients undergoing primary unilateral total hip replacement (THR, n = 1401), primary unilateral knee replacement (TKR, n = 1296), and coronary artery bypass graft (CABG) surgery were enrolled. There was a large intercenter variability in the percentage of patients who received transfusions: THR 16 to 85 percent, TKR 12 to 87 percent, and CABG 37 to 63 percent. In the patients who received transfusions, the number of red blood cells (RBC) units transfused varied significantly. There was also a considerable intercenter variability in RBC loss. The prevalence of preoperative anemia was 19 percent and identical in both sexes. The incidence of preoperatively untreated anemia was three times higher in patients who received transfusions compared to those who did not.

**Conclusion:** This study demonstrates a high intercenter variability in RBC transfusions and RBC loss in standard procedures. Whereas the variability in blood loss remains largely unexplained, the main predictors for allogeneic RBC transfusions are preoperative and nadir Hb and surgical RBC loss.

**SY7-3**

**Use of recombinant factor VIIa in the perioperative period**

Levi M1

1Department of Medicine and Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Recombinant activated factor VII (factor VIIa) is a pro-hemostatic agent that can be used for patients with hemophilia and inhibiting antibodies towards a coagulation factor. Recombinant factor VIIa is, however, increasingly used for several other indications, including patients who experience serious and life-threatening bleeding. In addition, recombinant factor VIIa has been evaluated for the prevention of major blood loss in patients undergoing surgical procedures that are known to be associated with major blood loss. In this manuscript we review the available data on efficacy and safety of recombinant factor VIIa in the prevention of excessive blood loss and transfusion requirements in the perioperative period. We conclude that recombinant factor VIIa is a promising agent for perioperative prevention of major blood loss but that its efficacy will probably vary between specific clinical settings.

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**Congress Program:** 53rd Annual Meeting - Society of Thrombosis and Haemostasis Research Tagungsprogramm: S3. Jahrestagung der Gesellschaft für Thrombose- und Hämostaseforschung e.V. - GTH
Cancer-associated thrombosis: predictive parameters, data from the Cancer and Thrombosis Study (CATS)

Ay C1, Vormittag PJ, Pabinger I1
1Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Medical University of Vienna, Austria

Patients with cancer have a high risk to develop venous thromboembolism (VTE), which leads to additional morbidity and increased mortality of cancer patients. The management of cancer patients could be improved, if VTE could be reliably predicted by clinical or laboratory parameters. A high platelet count was reported to be associated with cancer-associated VTE. Recently a risk scoring model for chemotherapy-associated thrombosis incorporating known clinical and laboratory parameters was developed by Khorana et al to define high-risk patients and predict VTE in the ambulatory setting. In 2003 we have initiated the Vienna Cancer and Thrombosis Study (CATS) to define predictive parameters for occurrence of VTE in cancer patients. Over 1000 patients have been included in the ongoing CATS. The cumulative probability of developing VTE in the whole study population was 5.7% after six months and 7.9% after one year. At present, four laboratory parameters were identified to significantly increase the risk for VTE in cancer patients: A high platelet count (>95th percentile of the total study population) was associated with an increased hazard ratio (HR) of 5.5 (95% CI: 2–13.5) for VTE. Elevated soluble P-selectin (>75th percentile of the total study population) increased the VTE risk with an HR of 2.6 (1.4–4.9). Furthermore, the multivariable HR of VTE in patients elevated D-Dimer (1.8 [1.0–3.2]) and elevated F1+2 (2.0 [1.2–3.6]) were statistically significantly associated with VTE. Strong predictive risk factors for VTE were also surgery and radiotherapy, whereas chemotherapy could not be shown to increase the risk. In conclusion, certain clinical and laboratory parameters would help identify cancer patients at increased risk for VTE. The benefit of prophylactic anticoagulant treatment needs to be evaluated in appropriately designed randomized interventional studies considering these new laboratory risk factors.

Microparticles in Hemostasis and Thrombosis

Microparticles and female issues
Toth B1
1Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, Klinikum der Universität München-Campus Großhadern, Munich, Germany

Emerging evidence suggests that circulating, cell-derived microparticles (MP) play a role in various physiological and pathophysiological processes. MPs are involved in coagulation, inflammation and transport. The role of circulating MPs in the field of obstetrics and gynaecology has been investigated only recently. Healthy women show menstrual cycle-specific differences in circulating MPs which differ significantly from age-matched men. With regard to obstetrics, MPs were elevated in subgroups of patients with miscarriage or preeclampsia. Whether MPs contribute to the pathogenesis of the diseases themselves is part of ongoing research. Moreover, recent studies indicate MP levels parallel tumor invasiveness in breast cancer patients and show similar sensitivity-specificity profiles than established biomarkers.

Pathophysiological significance of procoagulant microvesicles in cancer disease and progression
Castellana D1,2, Kunzelmann C1, Freyssinet L1
1U770 INSEMM, Le Kremlin-Bicêtre, France; Université Paris-Sud, Faculté De Médecine, Le Kremlin-Bicêtre, France; Université Louis Pasteur, Faculté De Médecine, Strasbourg, France; 2Universität Heidelberg, Experimentelle Onkologie, Tumorzellbiologie, Heidelberg, Germany

Microvesicles (MV) are submicrometric membrane fragments (0.1 to 1µm), released from the plasma membrane of activated or apoptotic cells. They are characterized by most of the antigenic profile of the cells they originate from, and by the presence of procoagulant phospholipids at their surface. MV are detectable in the peripheral blood of mammals and considered as efficient effectors in the haemostatic or thrombotic responses, able to remotely initiate or amplify beneficial or deleterious processes, depending on the circumstances. Variations in their level and phenotype make them relevant pathogenic markers of thrombotic disorders and vascular damage. To date, MV are recognized as mediators of communication allowing cells to influence a target present in the local microenvironment as well as to distant sites. The mechanisms by which MV interact with target cells are still unclear, but a number of studies suggest involvement of MV-cell fusion or ligand-receptor interactions. More importantly, MV have been shown implicated in horizontal transfer of genetic material. This review focuses on the role of MV in the context of cancer, and their possible part in cancer associated thrombosis.