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Abstracts of the
24th Biennial International Congress on Thrombosis – EMLTD Congress 2016
4–7 May, 2016, Istanbul, Turkey

Guest Editors:
Ahmet Muzaffer Demir, Turgut Ulutin, Reyhan Küçükkaya

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Founded by A.L. Copley

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Thrombosis Research is an international journal with a goal of rapid dissemination of new information on thrombosis, hemostasis, and vascular biology to advance science and clinical care. The journal publishes peer-reviewed original research, along with reviews, editorials, and opinions and critics. Both basic and clinical studies are published. Publication of research which will lead to novel approaches in diagnosis, therapy, prognosis and prevention of thrombotic and hemorrhagic diseases is given high priority. Rapid communication and high visibility is facilitated by on-line submission, processing, and dissemination through Science Direct with powerful on-line links to other journals and sources.

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24th Biennial International Congress on Thrombosis - EMLTD Congress 2016
4–7 May 2016, Istanbul, Turkey

Welcome

Dear Colleagues,

On behalf of the Congress Executive Board, the local Organizing Committee and the Council of the European and Mediterranean League against Thrombotic Diseases, it is with great pleasure and privilege to invite you to the 24th International Congress on Thrombosis to be held in Istanbul, Turkey on May 4-7, 2016.

This will be the third ICT Congress held in Turkey. The first two were held in 1974 and 2008 by Prof. Dr. Orhan N. Ulutin who was a founding member of many international organizations, including EMLTD and the Hemostasis and Thrombosis Congresses in Turkey.

The Scientific Programme of the upcoming Congress will cover topics ranging from various fields of clinical and laboratory issues on thrombosis and related scientific issues. The Congress will feature contemporary lecture topics, evidence-based hematology sessions, and satellite symposia covering the latest developments on thrombotic diseases. The education program of the Congress will strike a balance between the needs of both basic and clinical issues. We took great care in designing a program that caters to the needs of younger attendees through discussions that foster scientific exchange, presentations, awards and special social functions.

The cultural program also promises to be appealing, and will highlight Istanbul's proud culture and national heritage. Istanbul's history dates back to the end of the 4th century B.C., and relics from the Hellenic, Roman, Byzantine and Ottoman periods are scattered throughout the city. The Hagia Sophia, Basilica Cistern, Blue Mosque, Grand Bazaar, Topkapı Palace and Turkish Baths, all contribute to Istanbul's unique experience as an open-air museum. You will have the opportunity to discover Turkish music, art and architecture, enjoy delicious Turkish and Ottoman cuisines, and experience world renowned Turkish hospitality. Istanbul's unique geography at the crossroads of Europe and Asia, allows the world "to meet where the continents meet".

The Haliç Congress Center will be the venue for the Congress. The Haliç Congress Center is ideally situated along the shores of the Golden Horn. The Center is easily accessible from hotels and via public transportation to and from the entire city.

Once again, on behalf of the Executive Board of EMLTD and of the Organizing Committee, I would like to invite you to the 24th International Congress on Thrombosis. I sincerely believe that you will enjoy both the scientific and cultural aspects of the programme, and the pleasure of spring time in Istanbul.

I look forward to personally welcoming you to Istanbul in May, 2016!

Ahmet Muzaffer Demir, M.D.
President of 24th International Congress on Thrombosis

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24th Biennial International Congress on Thrombosis – EMLTD Congress 2016 4–7 May 2016, Istanbul, Turkey

ORAL COMMUNICATIONS

Angiogenesis and Vascular Biology

C0299
CANCER PROCOAGULANTS PROMOTE TUMOR GROWTH AND ANGIOGENESIS IN BREAST CANCER PROGRESSION; AN IN VIVO BIOMARKER STUDY

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Background: Hemostatic elements involved in coagulation and fibrinolysis are increasingly recognized as supporters of the progression of breast cancer from the initial stage to the metastatic condition. Coagulation activation is known to be an important regulator of tumor angiogenesis, metastasis and malignant transformation. This study aims to investigate the interrelation between cancer procoagulants and the histologic/nuclear stage of breast cancer in women.
Methods: We used ELISA to obtain patterns of procoagulant factors and regulator proteins from plasma samples of 24 healthy volunteers and 30 patients with breast cancer, 28 of whom were diagnosed with invasive ductal carcinoma, and 2 with invasive mix carcinoma. Tissue Factor (TF), protease activated receptor-2 (PAR-2), which are pro-coagulation factors, interleukin-8 (IL-8), a chemokine, and FXa and FXa-PAR-2 complexes, which are regulator proteins, were examined to study the potential role of procoagulants in cancer progression. For histologic/nuclear studies, tissues were subdivided and fixed in formalin for paraffin embedding and stored at -80 °C for subsequent immunohistology.
Results: A strong relationship was found between the synthesis of TF, IL-8, FXa, FXa-PAR-2 and PAR-2 as cancer procoagulants, and the histologic/nuclear stage of breast cancer. TF levels were increased with breast cancer prognosis ($p<0.001$). FXa, PAR-2 and FXa-PAR2 complex levels were both significantly elevated ($p<0.001$). Chemokine IL-8 levels also rose significantly depending on the intensity of cancer prognoses ($p<0.001$).
Conclusions: Activation of all biomarkers have been correlated with the production tumor promoting molecules, primary tumor growth and tumor angiogenesis.
Acknowledgment: This study was supported by a grant from Marmara University, Research Foundation (Project no: SAG-B- 200611-0191).

Animal, cellular and molecular research in thrombosis

C0037
EXOPOLYPHOSPHATASE BASED STRATEGIES FOR INTERFERENCE WITH PROCOAGULANT POLYPHOSPHATE ACTIVITIES

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Background: Polyphosphates are inorganic polymers composed of linear linked orthophosphate units that critically contribute to thrombosis. Exopolyphosphatases are enzymes that bind and degrade polyphosphates. Here, we report specific strategies based on polyphosphate-degradation or binding, to interfere with procoagulant activities of the polymer *in vitro* and *in vivo*.
Methods: We analysed recombinant expressed exopolyphosphatase (PPX) mutants for interference with polyphosphate using in vitro clotting assays in human plasma, thrombus formation under flow in full blood, murine arterial thrombosis models, a model of pulmonary venous thrombosis in transgenic mice and an array of bleeding models.
Results: Full size PPX bound to and degraded polyphosphates but not nucleotides, heparin or ATP, while PPX lacking domains 1 and 2 (PPX_Δ12) bound to but was unable to degrade the polymer. Both PPX and PPX_Δ12 dose dependently interfered with polyphosphate- but not tissue factor-driven thrombin and clot formation in plasma in a factor XII-dependent manner and abolished procoagulant platelet-driven plasma clotting. PPX and PPX_Δ12 dose-dependently interfered with thrombus formation both under arterial and venous flow. Electron microscopy revealed that PPX and PPX_Δ12 treatment reduced fibrin formation but not fibrin fiber thickness of formed thrombi. PPX and PPX_Δ12 prolonged time to carotid artery occlusion in wild-type mice and protected animals from platelet-driven lethal pulmonary embolism. Despite providing thromboprotection PPX and PPX_Δ12 infusions did not interfere with haemostasis and did not prolong bleeding time nor increase blood loss from injury sites.
Conclusions: We show that targeting polyphosphates is a safe and potent novel strategy for anticoagulation that is not accompanied by an increase in bleeding.

C0258

INVESTIGATION OF THE ANTITHROMBOTIC AND ANTIPLATELET EFFECT OF A NEW UREA ANALOG, ON CAROTID ARTERY THROMBOSIS IN RABBITS

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Background: The $P2Y_{12}$ ADP receptor plays a key role in platelet aggregation and thrombus formation. Elinogrel is a selective and reversible $P2Y_{12}$ antagonist that has a urea residue in its structure. *In vitro* studies of our laboratory that investigated the antiplatelet effect of a series of synthetic urea analogs on human platelets led to the development of a strong human platelet activation inhibitor, GVMF160. The aim of the present study was to investigate the effect of GVMF160 on rabbit platelet aggregation *in vitro* and *ex vivo* as well as its antithrombotic effect on rabbit carotid artery thrombosis, *in vivo*.
Methods: Experiments were conducted on male New Zealand white rabbits. The *in vitro* effect of GVMF160 on rabbit platelet aggregation was studied in platelet-rich plasma (PRP) using 500μM arachidonic acid (AA) or 20μM ADP as agonists. For the investigation of its effect on carotid artery thrombosis, *in vivo*, GVMF160 was administered intravenously at doses of 2.5, 5 or 15mg/Kg body weight. Thrombus formation was induced 45min after administration, by applying 7.5% $FeCl_3$ on the carotid artery. Blood flow was monitored for 50min after thrombus formation, using the flow probe QuickFit Pro 1.5mm. Blood samples were collected before and 45min after the administration of each GVMF160 dose for the determination of *ex vivo,* platelet aggregation to AA or ADP, in PRP.
Results: GVMF160 significantly inhibited rabbit platelet aggregation *in vitro* induced by AA (IC_{50}=236μM) or ADP (IC_{50}=400μM). GVMF160 administration *in vivo* at 5mg/Kg inhibited only ADP-induced platelet aggregation *ex vivo*, whereas at 15mg/Kg it inhibited both, ADP- and AA-induced platelet aggregation *ex vivo*. Importantly, GVMF160 exhibited a strong antithrombotic effect on the experimentally-induced carotid artery thrombosis, since it significantly inhibited thrombus-induced carotid blood flow reduction and maintained the flow by 50% at 5mg/Kg and 62% at 15mg/Kg, 50min after thrombus formation.
Conclusions: The synthetic urea analog GVMF160 may represent a novel antiplatelet agent that inhibits platelet aggregation and can effectively prevent thrombus formation and carotid artery occlusion in a rabbit model of arterial thrombosis.

Anticoagulant drugs

C0068

DABIGATRAN TROUGH AND PEAK LEVELS IN "REAL-LIFE" PATIENTS WITH ATRIAL FIBRILLATION

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Background: In patients with atrial fibrillation treated with dabigatran dosing recommendation is based on specific clinical characteristics without routine coagulation monitoring. However plasma concentrations achieved vary widely. The aim of our study was to assess the effect of dosing recommendation on dabigatran levels in patients treated with dabigatran 150 mg (D150) or 110 mg (D110) twice daily and explore the potential relationship between dabigatran concentration and adverse events.
Methods: In this prospective study we included 44 patients who stated treatment with dabigatran 150 mg (D150) or 110 mg (D110) twice daily. Through and peak blood samples that were collected 2-4 and 6-8 weeks after dabigatran initiation. Plasma levels of dabigatran were assessed by LC-MS/MS and coagulation tests: activated partial thromboplastin time (aPTT), Hemoclot thrombin inhibitor assay (HTI) and ecarin chromogenic assay (ECT).
Results: Patients receiving D110 (n= 21) were older (74±7 vs 68±6 years), had lower eGFR (68±21 vs 92±24 mL/min) and higher $CHADS_2$ score (1.8±0.9 vs 1.0±0.7) compared to D150 patients (all p<0.01). However average dabigatran levels were similar on D110 and on D 150 in trough samples: LC-MS/MS (87±70 vs 72±50 μg/l, p=0.18), HTI (107±91 vs 88±54 μg/l, p=0.33), ECT (106±100 vs 86±69 μg/l, p=0.42) and aPTT (55.4±12.6 vs 54.2±7.6 s, p=0.98) as well as in peak samples: LC-MS/MS (173±111 vs 170±92 μg/l, p= 0.77), HTI (206±108 vs 198±108 μg/l, p=0.63), ECT (211±130 vs 213±132 μg/l, p=0.95) and aPTT (67.7±15.1 vs 70.1±15.5 s, p=0.74).
During the 12-month follow-up 6 patients on D110 and 4 on D150 suffered minor bleeding. There was no major bleeding or thromboembolic event. Patients with bleeding had significantly higher average trough dabigatran levels: LC-MS/MS (93±36 vs 72±62 μg/L, p=0.02), HT (120±62 vs 86±72 μg/L, p=0.03), and ECT (119±61 vs 85±89 μg/L, p=0.05), than patients without bleeding, while aPTT trough levels were not significantly different. Peak dabigatran values had no predictive value.
Conclusions: Our date show that guidelines-based dabigatran dosing in real-life resulted in similar trough and peak dabigatran levels in patients treated with D150 or D110. High trough dabigatran levels may predispose patients to the risk of minor bleeding.

C0140

THROMBIN GENERATION (TG) POTENTIAL IN PATIENTS ON CHRONIC ORAL ANTICOAGULANT THERAPY (OAT)

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Background: Atrial fibrillation (AF) and cardiac valvular prosthesis (CVP) are two conditions that expose patients to vascular complication and risk of stroke that contribute to their morbidity and mortality. It is well confirmed that oral anticoagulation with vitamin K antagonists (i.e. Warfarin) improve outcomes despite increase the risk of fatal bleeding also in patients with Prothrombin-International Normalized Ratio (PT-INR) in therapeutic range. This suggests that PT-INR doesn't always reflect the real bleeding or thrombotic risk and that different assays might be useful to provide information about global hemostatic capacity. Among these, TG potential measured by the calibrated automated thrombogram (CAT), seems to be promising. This prospective study aims to characterize TG potential in a group of patients on OAT with Warfarin in order to investigate whether a correlation exists between TG and PT-INR and whether TG might be useful to identify subjects at increased bleeding risk.
Methods: Twenty patients (13 AF/7 CVP) with 100% in range PT-INR in the last 3 months were enrolled after informed consent at OAT unit of Bergamo Hospital and prospectively followed for one year. CAT assay with 5pM TF was performed in platelet-poor plasma collected at the same day of PT-INR control (13 samples/each patient). Activated protein C (APC) resistance was evaluated by CAT in presence of 10 pM TF +2 nM APC. Normalized APC sensitivity ratio (nAPCsr) was calculated. 20 healthy subjects acted as control group.
Results: TG potential was significantly lower in patients compared to controls at any time points, particularly in CVP subjects. Significant correlations (p<0.01) were found between PT-INR and TG parameters, independently to age. Interestingly, patients with similar PT-INR showed different TG values. The nAPCsr, which was equal to 1 in controls, was significantly (p<0.01) reduced in patients (0.59±0.14), suggesting that they were more sensitive to the anticoagulant activity of APC. During follow-up,

bleeding complications were registered in four patients (one major) with *in range* PT-INR, but very low TG potential.
Conclusions: The wide variability of TG values in patients with similar INR and the occurrence of bleeding complications in patients on therapeutic PT-INR but low TG values, suggests that CAT assay can be more sensitive in detecting a hemorrhagic phenotype. This might be useful in monitoring those patients initiating and/or receiving multiple antithrombotic drugs.

C0152
IMPACT OF RENAL IMPAIRMENT ON PLATELET REACTIVITY AND CLINICAL OUTCOMES DURING CHRONIC DUAL ANTIPLATELET THERAPY FOLLOWING CORONARY STENTING

M.H.Kim[1], L.Z.Guo[2], C.H.Shim[2], S.Y.Choi[2], V.L.Serebruany[3]
[1]Cardiology, Global Clinical Trial Center, Dong-A University Hospital (Busan) Korea; [2]Dong-A University Hospital (Busan) Korea; [3]HeartDrug Research Laboratories, Johns Hopkins University (Baltimore) USA

Background: Clinical utilization of dual antiplatelet therapy (DAPT) in patients with renal impairment (RI) following percutaneous coronary interventions (PCI) represents an urgent, unmet need choosing optimal agents, duration of treatment, and potential dose/regimen adjustment. Lack of any large randomized trials specifically in RI patients, and absence of the uniformed clinical data reporting policy clouds the reality. Moreover, triaging RI patients is problematic due to ongoing kidney deterioration, and the fact that RI patients are prone to both vascular occlusions and bleeding.
Methods: 701 Korean patients receiving DAPT with aspirin 100 mg/daily and clopidogrel 75 mg/daily after PCI were prospectively enrolled in the study. Patients were dichotomized into 5 groups according to RI: estimated glomerular filtration rate (eGFR)> 90 mL/min/1.73m^2 (RI1), 60 - 89 mL/min/1.73m^2 (RI2), 30 - 59 mL/min/1.73m^2 (RI3), < 30 mL/min/1.73m^2 (RI4), and undergoing dialysis (RI5). Major adverse clinical event (MACE) (cardiovascular death, myocardial infarction, stent thrombosis and stroke) were collected for 1 year. Platelet reactivity by Verify*Now*™ assay and eGFR were simultaneously assessed at 1 month after maintenance DAPT.
Results: Patients with RI exhibited gradual significant increase of residual platelet reactivity during DAPT, dependent on eGFR deterioration [191± 72PRU (RI1) vs. 216± 78PRU (RI2) vs. 248± 80PRU (RI3) vs. 264±70PRU (RI4) vs. 317± 96PRU (RI5), p<0.001] being the highest in the dialyses group. Declined eGFR has been gradually associated with advancing age (OR=1.03, 95% CI=1.00–1.05; p=0.032), female gender (OR=1.7, 95% CI=1.1–2.5; p=0.01), diminished smoking rates (OR=0.6, 95% CI=0.37–1.00; p=0.05), hypertension (OR=1.8, 95% CI=1.3–2.5; p<0.001); diabetes (OR=1.5, 95% CI=1.1–2.1; p=0.007), and MACE (HR=13.9; CI=1.6-124.3;p=0.02 for RI4; and (HR=31.9; CI=2.9-351.9;p=0.005 for dialysis), but not for bleeding (p=0.143). MACE risks still remained significant for RI4 (p=0.027), and RI5 (0.002) by multivariate Cox hazard regression estimates.
Conclusions: RI is strongly associated with gradual elevation of residual platelet reactivity while on DAPT, enhanced MACE risks, but not bleeding events. These data should be confirmed in a large randomized outcome-driven trial, and may justify future maintenance phase DAPT regimen/dose adjustment in RI patients.

C0201
CLINICAL PERSPECTIVES ON THE MANAGEMENT OF SEVERE BLEEDING IN PATIENTS TREATED WITH ORAL ANTICOAGULANTS IN SPAIN. RESULTS OF THE DECOVER STUDY (DELPHI IN ORAL ANTICOAGULATION AND ACTION REVERSAL)

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Background: Oral anticoagulants are prescribed in patients with atrial fibrillation to prevent stroke. Bleeding is the most common complication of oral anticoagulation. The rate of major bleeding has been significantly reduced with the use of the direct anticoagulants (DOAC) (apixaban, dabigatran, edoxaban and rivaroxaban). However guidelines for bleeding management in patients on DOAC are not well detailed, due to the lack of evidence on the efficacy and safety of current alternatives. The aim of the study is to understand the level of agreement among treating physicians on bleeding management in anticoagulated patients.
Methods: A panel composed of 15 hematologists and 17 emergency physicians distributed across Spain were asked to share their perspective on the best practice in anticoagulated patients who suffer bleeding and specific recommendations to revert the action of anticoagulant activity, following the DELPHI methodology. Two rounds of interviews were conducted between April and September 2015. Consensus in round 2 was attained if ≥75% of respondents agreed on a particular question item
Results: Experts agreed that hemodynamic control (100%), tests of basic coagulation and renal function tests (93.8%), complete blood count (93.8%), endoscopy/interventional radiology (87.5%), blood products (87.5%), transfusion of blood cells (84.4%), activated prothrombin complex concentrate (aPCC) (84.4%) local hemostasis measures (81.3%), surgery need assessment (78.1%), and non-activated PCC (78.1%) are priority measures in case of severe bleeding. Non-activated PCCs are the only treatments that were thought to be effective for rivaroxaban and apixaban, while there was no therapy considered effective for dabigatran. No existing alternative was considered safe for any DOAC. Reversal agents were considered useful in case of severe bleeding (96.9%) but would require a good organization between health care professionals and centers for patients to have access to the reversal agent (81.3%). There was consensual agreement on ranking specific reversal agents as #1 in reversal therapies of DOAC activity in case of severe bleeding, with no difference between specialists
Conclusions: This DELPHI study suggests the clinical availability of specific reversal agents should change substantially the treatment algorithm of DOAC-anticoagulated patients who suffer from a severe bleeding event and become the therapy of choice when such events happen.

C0233
DABIGATRAN ETEXILATE TREATMENT OF PATIENTS WITH SEVERE BURN INJURY IN THE OPERATING PERIOD

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Background: Explore the possibility of using oral anticoagulant dabigatran etexilate (Prodaxa®) as a means of prevention of venous thrombosis in patients with severe burn injury requiring surgical treatment
Methods: The study included 30 burn patients. Inclusion criteria: damage area is not less than 30% of the surface of the body, the patient's age no older than 75 years, weight from 50 to 100 kg. Patients received dabigatran etexilate (Prodaxa®) at a dosage of 220 mg/day. All patients underwent surgery: necrectomy (at least 10% pt) in the period from 5 to 14 days after injury. In the preoperative period, all patients were divided into 2 groups: I group - 15 patients, who Prodaxa®) canceled 24 hours prior to surgery. Group II - 15 patients, who Prodaxa®) canceled 48 hours prior to surgery. The patients did not differ in principle by age, sex and the nature of the burn injury. Laboratory parameters were monitored: aPTT, PTI, INR, thrombin time, fibrinogen. The effectiveness of the proposed schemes was evaluated to identify thrombosis on ultrasonography veins of the lower limbs and the absence of hemorrhagic complications during surgery (increased bleeding wound surface, the low efficiency of local and systemic hemostatic agents, timing advance stability hemostasis).
Results: Patients in both groups showed no thrombosis, suggesting a high preventive efficacy of dabigatran etexilate (Prodaxa®). In a blood test there were no significant fluctuations in laboratory parameters. During the operation, the patients in group I marked the most significant bleeding from the wound surface, and the use of tranexamic acid intravenously and the use of local hemostatic agents were not as effective as in patients of Group II. Dates of the onset of stable hemostasis from wounds in patients in group I ranged 18-24 hours, in patients of group II 10-12 hours.
Conclusions: Operating period in patients with burn injury is extremely dangerous for the risk of hemorrhagic and thrombotic complications and require careful monitoring of the hemostatic system. Dabigatran etexilate (Prodaxa®) is effective in the prevention of thrombosis in patients with burns. If you plan to necrectomy recommended removal of the drug Prodaxa® 48 hours, followed by the appointment of 24 hours after the operation.

C0327
DIRECT FACTOR XA INHIBITORS FOR PULMONARY EMBOLISM IN PATIENTS INITIALLY ADMITTED TO SUB INTENSIVE CARE UNIT FOR INTERMEDIATE HIGH RISK INDEX EVENT

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Background: Pulmonary Embolism (PE) is a potential life-threating cardiovascular emergency with an early mortality rate varying from 0.2 up to 25% depending on the severity of presentation. Direct Oral Anticoagulants (DOACs) including Direct Factor Xa Inhibitors (DFXaI) have been developed to address limitations associated with traditional anticoagulant therapy. Anyway due to the scarce representation of intermediate high risk patients in clinical study, traditional anticoagulant therapy, that involves parenteral anticogaulants overlapping with oral vitamin k antagonists, still represents the mainstay of treatment in many Sub Intensive Care Unit (SICU). The aim of our pivotal register is to obtain a reliable estimate of the risks and benefits of DFXaI treatment in intermediate high risk PE patients initially admitted to SICU.
Methods: Patients admitted to the two different SICU of our hospital for intermediate high risk PE in the last 12 months were evaluated for starting oral anticoagulant after a variable course of parenteral therapy by an expert physician in DOACs of our Thrombosis Centre. To all the patients with a favorable evolution without other contraindications it was proposed to start DFXaI. Follow up visits were planned prior to discharge and after 3 and 6 months from the hospital admission.
Results: During the last 12 months, 37 patients were admitted to the two SICU of our hospital due to intermediate high risk PE: the mean age at the time of the index event was 71.7 (SD±17.3) with a mean Creatinine Clearance of 76.3 ml/min (SD±22.0). The mean PESI (Pulmonary Embolism Severity Index) scored 115.3 (SD±43.7) at the admission and actually 5 patients died during hospital stay confirming the intermediate high risk mortality predicted (14.2%).
Of the 31 patients discharged, 18 patients started Rivaroxaban and 6 Apixaban at the dose suggested by 2014th European Society of Cardiology guidelines after a period variable from 0 to 18 days of parenteral therapy. Moreover 4/24 patients were thrombolysed before starting any other therapy.
Up to January 10th 2016 no recurrent venous thromboembolic and major bleeding event was observed in the 21/24 patients discharged on DFXaI therapy who completed the planned 3 months follow up visit.
Conclusions: DFXaI appear to be a reasonable alternative for patients admitted to SICU for intermediate high risk PE after an initially favorable evolution. Single drug approach and switch therapy are both consistent option in clinical practice.

C0331
EFFICACY AND SAFETY OF NEW ORAL ANTICOAGULANTS IN TREATMENT OF PATIENTS WITH ATRIAL FIBRILLATION AND VENOUS THROMBOEMBOLISM. DATA FROM LJUBLJANA REGISTRY

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Background: In recent years, new oral anticoagulants (NOAC) can be used both for patients with non-valvular atrial fibrillation (NVAF) and patients with venous thromboembolism (VTE).
Methods: Data for patients treated with NOAC in the last three years was retrospectively analysed. Incidences of bleeding, thromboembolic events and treatment-related death were calculated per 100 patient-years.
Results: During the last three years, 1,863 patients with NVAF and 954 patients with VTE were treated with NOAC. The incidence of major bleeding in patients with NVAF was 1.65 and 2.67 per 100 patient-years for dabigatran and rivaroxaban, respectively. In patients with VTE, the incidence of major bleeding was 1.4 per 100 patient-years for rivaroxaban.
In patients with NVAF, the incidence of thromboembolic events was 1.65 and 3.45 per 100 patient-years for dabigatran and rivaroxaban, respectively. In patients with VTE, the incidence of thromboembolic events was 0.7 per 100 patient-years for rivaroxaban.
8 patients with NVAF and 1 patient with VTE died due to either thromboembolic or bleeding complications of NOAC treatment.
Conclusions: Our real-life data is similar to data reported in large randomised controlled trials.

C0333
SENSITIVITY OF LOCAL DRVTT SCREEN AND CONFIRM REAGENTS TO RIVAROXABAN AND APIXABAN

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Background: Dilute Russel's Viper Venom Time (dRVVT) is an essential and widely used test for the diagnosis of lupus anticoagulants. As recently has been demonstrated that the sensitivity of dRVVT to direct oral

anticoagulants is even higher than that of prothrombin and activated partial thromboplastin time, the aim of this study was to evaluate the sensitivity of local dRVVT towards rivaroxaban and apixaban.

Methods: Sensitivity of local Screen and Confirm dRVVT reagents (LA1 and LA2, Siemens Healthcare Diagnostics, Marburg, Germany) towards rivaroxaban and apixaban was investigated on the BCS-XP analyzer, by analyzing pooled normal plasma spiked with increasing rivaroxaban (29, 121, 346 and 734 μg/L) and apixaban (33, 164, 398 and 737 μg/L) concentrations, corresponding to through, peak and supratherapeutic levels. Ratios of LA1 (LA1-R) and LA2 (LA2-R) test results for each concentration divided by LA1 and LA2 results in the normal pooled plasma samples were calculated, whereas LA ratios (LA-R) were calculated by dividing individual LA1 and LA2 results.

Results: A dose-dependent prolongation of both LA1 and LA2 results was observed for rivaroxaban and apixaban, being more pronounced for the Screen dRVVT reagent. Higher LA1-R were obtained for rivaroxaban (1.37, 2.26, 3.63 and 4.66) than for apixaban (1.15, 1.44, 2.11 and 3.04), whereas similar LA2-R were obtained for rivaroxaban (1.17, 1.57, 2.09 and 2.93), and apixaban (1.17, 1.52, 2.14 and 2.97). Increasing rivaroxaban concentrations resulted in increasing LA-R ranging from 1.33 to 1.98, whereas this was not observed for apixaban, as similar LA-R, ranging from 1.05-1.13 were obtained with increasing apixaban concentrations.

Conclusions: According to results obtained in this study, both local Screen and Confirm dRVVT reagent was found to be sensitive to rivaroxaban and apixaban. Screen dRVVT was found to be more sensitive to rivaroxaban than to apixaban, whereas the Confirm dRVVt reagent showed similar sensitivities to both drugs. By performing both dRVVT assays and using the LA-R, it was even possible to distinguish between rivaroxaban and apixaban. Confirm dRVVT seems to be a promising qualitative test, especially to the presence of apixaban, as widely used PT reagents has low sensitivity to apixaban.

C0377
IDARUCIZAMAB, A SPECIFIC ANTIDOTE FOR DABIGATRAN, CROSS-REACTS WITH MELAGATRAN AND MAY ALSO INTERACT WITH OTHER BENZAMIDINE-CONTAINING COMPOUNDS

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Background: Idarucizamab (Praxbind) is produced by Boehringer-Ingelheim for the specific neutralization of dabigatran and is recently approved by the US FDA for the control of bleeding associated with dabigatran. Dabigatran etexilate is a prodrug which is converted into the active agent dabigatran endogenously. Idarucizamab is an anti-dabigatran Fab fragment which specifically binds to the benzamidine group on dabigatran and inhibits its anti-thrombin activity. Benzamidine represents a commonly used pharmacophore which is present in a variety of drugs, mainly serine protease inhibitors and related agents.

Methods: In order to test the specificity of the inhibitory effects of idarucizamab, such antithrombin agents as argatroban, melagatran, hirudin, and bivalirudin were tested in plasma-based anticoagulant assays including thrombin time, PT, and aPTT. In addition, other antithrombin agents such as human antithrombin, thrombomodulin, heparin cofactor II, and heparin-AT complexes and synthetic FXa inhibitors such as rivaroxaban, apixaban and DX-9065a were also tested. Idarucizamab itself at a concentration of up to 1 mg/ml did not produce any effect on plasma clotting profile.

Results: The antibody showed strong specificity for the inhibition of dabigatran and did not affect the anticoagulant effect of the other synthetic and natural thrombin and FXa inhibitors with the exception of melagatran, which was strongly inhibited by this antibody. Dabigatran and melagatran contain benzamidine moieties in their structures, which is primarily responsible for the inhibition of thrombin. The benzamidine group on dabigatran is also primarily responsible for its interaction with anti-dabigatran Fab fragment idarucizamab.

Conclusions: Therefore, the cross reactivity between idarucizamab, dabigatran, and melagatran may involve the benzamidine pharmacophore. These results suggest that while idarucizamab does not inhibit the currently available antithrombin agents, it inhibits the action of melagatran, therefore it may also modulate the action of drugs which contain benzamidine moieties. Thus, these observations warrant a systemic screening of idarucizamab for its potential interactions with drugs containing benzamidine moieties.

Antithrombotic drugs

C0176
A MULTINATIONAL, MULTICENTRE, RANDOMIZED, OPEN-LABEL, PARALLEL GROUP STUDY ON THE EFFICACY AND SAFETY OF ONCE DAILY BEMIPARIN COMPARED TO TWICE DAILY ENOXAPARIN IN THE TREATMENT OF ACUTE DEEP VEIN THROMBOSIS

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Background: Scientific guidelines consider low molecular weight heparins (LMWH) as first choice medicines for the acute treatment of deep vein thrombosis (DVT), but there are very few head-to-head comparisons of the efficacy and safety between them. Bemiparin is a second-generation LMWH with mean molecular weight of 3.6 kDa, half-life of 5.2-5.4 h and anti-Xa/anti-IIa activity ratio of 8:1.

Methods: This was a phase III, multicentre, prospective, randomized, open-label, parallel group study in symptomatic patients with proximal DVT to demonstrate the therapeutic non-inferiority of Bemiparin 115 IU/kg/24 h s.c. compared to Enoxaparin 1 mg/kg/12 h s.c. Both LMWHs were administered for 7±2 days and oral warfarin (adjusted to INR=2-3) was added on Day 2 up to Visit 3 (Day 83). The primary efficacy endpoint was the percentage of patients with an improvement in thrombotic burden after 3 months, defined as a ≥4-point reduction in an ultrasound (US) based thrombus score (or at least half of the thrombus score in the case the total score is ≤ 6) without confirmed symptomatic extension of recurrence of DVT, confirmed symptomatic PE, or VTE-related death. Compression US was performed according to a standardized protocol and centrally assessed by independent blinded readers. Non-inferiority margin was set as Δ= -0.15 with a 1-sided α-level of 2.5%.

Results: Twenty one sites from the Russian Federation and Georgia randomized 312 patients with proximal DVT to Bemiparin (n=162) or Enoxaparin (n=150). The primary endpoint was achieved by 78.2% (111/142) patients in the Bemiparin group and 80.8% (97/120) patients in the Enoxaparin group (per protocol population), and non-inferiority was demonstrated (difference Bemiparin vs Enoxaparin= -2.66 [97.5% CI: -12.39; ∞). At Visit 3, mean (SD) decrease of thrombus score from baseline was 8.7 (6.70) and 8.4 (6.61), in the Bemiparin and Enoxaparin groups, respectively (full analysis set population). No cases of recurrent DVT occurred during the study. Non-fatal pulmonary embolism was reported for one patient in each treatment group. No treatment-emergent major bleedings were reported. Three patients from each arm discontinued due to non-tolerable adverse events. There were no deaths in the study.

Conclusions: Once daily administration of Bemiparin was demonstrated to be non-inferior to twice daily administration of Enoxaparin in the treatment of acute proximal deep vein thrombosis. Both LMWHs exhibited a favourable safety profile.

C0177

ASSESSMENT OF BLEEDING RISK IN ELDERLY AND PATIENTS WITH RENAL IMPAIRMENT UNDER BEMIPARIN PROPHYLACTIC DOSES FOR MORE THAN 3 WEEKS

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Background: Careful management of LMWH is needed in elderly and patients with renal impairment (RI) due to increased risk of bleeding events. Clinical trials do not usually include enough number of patients from these special populations and therefore aggregating data from clinical trials (CT) is a useful way for evaluating the safety of a drug in these subgroups at higher risk of adverse reactions.
Methods: Aggregated data were obtained from selected CTs of the Rovi's Bemiparin Clinical repository according to predefined criteria: Randomized-controlled clinical trials evaluating in patients (i.e. excluded healthy volunteers) the subcutaneous administration of Bemiparin for more than 3 weeks at prophylactic doses (≤3500 IU/day). RI was classified by 3 subgroups according to creatinine clearance values by Cockcroft-Gault equation: mild (≥50 y ≤80 ml/min); moderate (≥30 y <50 mL/min) and severe (<30 mL/min). Elderly were older than 65 years. Bleeding Rates and relative risk reduction (RRR) with confidence interval (CI) at 95% was calculated for Bemiparin and Placebo.
Results: Data from 6 randomized CTs were aggregated, from which 720 patients received Bemiparin and 599 Placebo, being elderly 17.8% and 15.6%, respectively. Mean (SD) treatment time was 56.69 (34.02) days on Bemiparin and 36.05 (36.81) days on Placebo. Seven hundred and two patients had normal renal function and 617 some degree of RI: 36.7%/39.2% mild RI, 7.1%/9.8% moderate RI and 1%/0.2%, severe RI in Bemiparin/Placebo groups.
The bleeding rates according to renal function and age groups were:

	Bemiparin	Placebo	RRR (CI 95%); p-value
Normal Renal Function	2.3%	4.3%	0.47 (-0.22-0.77); 0.097
Mild RI	3.4%	3.4%	0 (-1.55-0.61); 0.598
Moderate RI	3.9%	0%	N/A; 0.216
Severe RI	0%	0%	N/A
>65 y	3.4%	1.9%	-0.75 (-4.06-0.39); 0.216
≤65 y	2.1%	4.4%	0.53 (-0.02-0.78); 0.039

N/A=not applicable

Conclusions: Aggregated data from 6 randomized CTs showed a similar incidence of bleeding rates in patients under prophylactic doses of Bemiparin for more than 3 weeks than patients under Placebo regardless of the renal function or age subgroups.

Arterial thrombosis and atherosclerosis

C0189

CORONARY THROMBUS CHARACTERIZATION: NATIVE CORONARY THROMBOSIS AND IN-STENT THROMBOSIS

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Background: The clinical impact of in-stent thrombosis is high because it is associated with a high percentage of mortality and 20% of the patients that suffer a first episode of in-stent thrombosis will suffer a recurrent event within the 2 following years. In this context, the aim of this study has been to characterize by differential proteomics in-stent thrombi in comparison to thrombi developed on native coronary arteries in order to identify their molecular signature.
Methods: The study included 20 patients treated to guidelines that were subjected to thromboaspiration (within the first 6 hours after the onset of the event). Ten patients were subjected to primary percutaneous intervention because of an in-stent thrombosis (IST) and ten because of the formation of a thrombus on native coronary arteries (CT). Cardiovascular risk factors and Troponin I and CPK levels were similar between the groups. CRP levels were significantly higher in IST patients than in CT patients. All patients had TIMI flow grade 0 before PCI. Once aspirated, thrombi were frozen and then characterized by a differential proteomic approach (2-DE+MALDI-TOF/TOF).
Results: Among the identified proteins, IST samples depicted a coordinated change in the proteomic distribution of several cell stress-related proteins and chaperones. Specifically, IST samples showed a 2-fold increase in the intensity of Hsp 60kDa mitochondrial and Hsp A8 ($P<0.05$) and a 6-fold increase in the aryl-hydrocarbon-interacting protein-like 1 which is involved in apoptosis ($p<0.05$). The most important change was detected in 26S protease regulatory subunit 7 that showed a mean 19-fold increase in IST samples ($P<0.05$).
Conclusions: Our results demonstrate an important increase in stress-related proteins and chaperones in thrombi developed in a stented artery in comparison with thrombi developed in native coronary arteries. The coordinated changes observed in chaperones and proteasome regulatory proteins reflect the activation of intracellular protection mechanisms to maintain protein integrity in the in-stent thrombi. This is possibly the response against the increased cellular stress in this type of thrombi growing on rigid stented arteries and in a more inflammatory milieu when compared to thrombi formed on native coronary arteries that may have higher distensibility to encompass the growing thrombotic mass.

C0263

NEUTROPHIL EXTRACELULAR TRAPS IN PATIENTS WITH ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME ARE ASSOCIATED WITH MARKERS OF PLATELET ACTIVATION

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Background: Neutrophil extracelular traps (NETs) are formed by activated neutrophils when they release their nuclear DNA decorated with histones and granular proteins. These NETs, besides having antimicrobial activity, are able to activate platelets and induce thrombotic processes. Although the mechanisms involved in the formation of NETS are not well known, it has been described recently that NETs formation requires participation of the platelet P-selectin [1].
Aims: To evaluate the presence of NETs in patients with ST-segment elevation acute coronary syndrome (STEMI), and its possible relationship with markers of platelet activation.
Methods: 145 patients with STEMI were included. Blood samples were obtained prior, 30 min after and 24 hours after stent implantation. As markers of NETS we measured circulating DNA and nucleosomes. Platelet activation was evaluated by P-selectin exposure, platelet-leukocyte aggregates and GPIIbIIIa activation by flow cytometry. 17 healthy subjects without any medication were used as controls. Patients were followed-up for a period of 1 year.
Results: DNA and nucleosomes are elevated in patients on admission as compared with healthy subjects (DNA: 28.12±19.66 vs. 19.66±2.70 $p<0.000$; nucleosomes: 0.31±0.21 vs. 0.15±0.03 $p<0.000$), as well as platelet-leukocyte aggregates and P-selectin exposure. After stent implantation, these values were greatly increased in an important percentage (58%) of patients. Interestingly, this increase was not observed in those patients treated with bivalirudin *vs*. patients treated with heparin. At 24 hours NETs remain increased in patients. We observed a strong correlation between NETs and markers of platelet activation, especially with platelet-leukocyte aggregates and P-selectin exposure. Importantly, elevated NETs in the first 48 hours after the onset of the event were associated with an increase in the risk of MACE at one year.
Conclusions: 1) We report for the first time that NETs are elevated in STEMI patients, especially after stent implantation, although the increase is lower in patients treated with bivalirudin *vs*. heparin. 2) NETs are strongly

associated with platelet-leukocyte aggregates and P-selectin exposure in STEMI patients. 3) A higher NETs formation is associated with a worse clinical outcome at 1 year follow-up in STEMI patients.

Reference:

[1] Etulain J Blood 2015. Grants: FIS13/00016; Red Cardiovascular [RD12/0042/0003]; FETH to AL; Sociedad Valenciana Cardiología; Hexacath.

Atrial fibrillation

C0039
RELATION BETWEEN SYNTAX SCORE AND NEW-ONSET ATRIAL FIBRILLATION IN PATIENTS WITH ACUTE CORONARY SYNDROMES

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Background: The new onset atrial fibrillation is associated with a worse prognosis at follow up patients with ACS. Predicting and prevention new onset AF is therefore a crucial step in improving prognosis of patients with ACS. The purpose of present study was to investigate the association between SxScore and new onset AF in patients with ACS

Methods: Two hundred fifty one patients with first time diagnosis of acute coronary syndromes (ACS) were enrolled consecutively. Syntax score (SxScore) was calculated by a computer software. New onset AF was defined by developing AF during the hospitilisation.

Results: Forty nine patients developed AF. Patients with AF had higher SxScores (21 ± 6.2 vs 13 ± 7.4, p<0.001) (Table 1). In univariate analyse, age (p<0.001), diabetes (p= 0.012), diagnosis of STEMI (p<0.001), female gender (p<0.001) and SxScore (p<0.001) were significantly associated with new onset AF. Multivariate analyse demonstrated age (95% confidence interval, CI, 1.008–1.0.88, p = 0.017, ST Segment Elevation Myocardial Infarction (STEMI) (95% CI, 2.34–14.68, P < 0.001), and SxScore (95% CI, 1.038–1.159, P < 0.001) as an independent determinant of new onset AF. Analysis using the receiver operating characteristic curve has demonstrated that SxScore of 22 constitutes the cut-off value for the development of AF with 75% sensitivity and 82 % specificity (area under the curve: 0.782, 95% confidence interval 0.534-0.986)

Table 1
Clinical and laboratory characteristics of subjects in groups with and without new onset AF

Variables	No AF (n = 202)	New-onset AF (n = 49)	P value
Age, years	62 ± 12	70 ± 11	<0.001
Female gender, n (%)	50 (25)	25 (50)	0.001
Smoking, n (%)	53 (26)	14 (28)	0.19
Diabetes, n (%)	41 (20)	20 (41)	0.03
Dyslipidemia, n (%)	25 (12)	23 (47)	0.55
Hypertension, n (%)	155 (77)	49 (100)	<0.001
STEMI, n (%)	86 (42)	41 (84)	<0.001
Number of diseased vessels	1.7 ± 0.03	2.1 ± 0.4	0.06
SyntaxScore	13 ± 7.4	21 ± 6.2	<0.001

Conclusions: We have found SxScore as an independent determinant of mew onset AF in ACS patients. SxScore may have clinically meaningful in terms of predicting new onset AF that was associated with increased in-hospital and long-term mortality rates.

C0211
RELATIONSHIP OF THE SAME-TT2R2 SCORE TO ANTICOAGULATION QUALITY IN ATRIAL FIBRILLATION

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Background: The efficacy and safety of vitamin K antagonists (VKAs) therapy strongly depends upon the quality of anticoagulation control, as reflected by the average time spent in the therapeutic range (TTR) of international normalized ratio (INR). A simple clinical tool (the SAMe-TT_2R_2 score) for identifying patients with atrial fibrillation (AF) who would do well on VKAs has been proposed to help when choosing between VKAs and non-vitamin K oral anticoagulants. The aim of this study was to determine the value of the SAMe-TT_2R_2 score (sex-female, age < 60 years, medical history [more than two comorbidities], treatment [interacting drugs, e.g., amiodarone], tobacco use [doubled], race [doubled]) for prediction of anticoagulation quality with VKA in patients with non-valvular AF.

Methods: In a cohort of 518 consecutive AF patients on VKA, seen in our anticoagulation clinic between September 2006 and September 2015, we retrospectively calculated the TTR (using the Rosendaal method) and the SAMe-TT_2R_2 score. The predictive value of the SAMe-TT_2R_2 score was evaluated using the TTR of 70% as a cut-off point. The C statistic, a measure of the area under the receiver operating characteristic (ROC) curve, quantified the predictive validity of the SAMe-TT_2R_2 score and tested the hypothesis that the score performs significantly better than chance (indicated by a C statistic > 0.5).

Results: Of 518 patients (mean age 71.97 ± 8.35 years), 55.78% were male. The median follow-up was 756 (112 – 42,241) days, and the mean TTR was 54.46% ± 17.57%. No significant differences in sex, age, clinical characteristics or CHA_2DS_2-VASc score values were found between the group with a TTR value of ≥ 70% (n = 97, 18.73%) and the group with a TTR < 70% (n = 421, 81.27%). Of patients who achieved a TTR ≥ 70%, 84.54% had a SAMe-TT_2R_2 score of ≤ 2. The score had a modest predictive value for a TTR of ≥ 70% (c-statistic 0.57; 95% CI, 0.51 - 0.63, $p = 0.043$).

Conclusions: Our results show a moderate predictive ability of the SAMe-TT_2R_2 score for identification of patients who would do well on VKAs in a cohort of AF patients with relatively poor overall quality of anticoagulation with VKAs.

C0245
GUIDELINE ADHERENCE OF NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANT THERAPY: RESULTS FROM RAMSES STUDY

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Background: Ischemic stroke is one of the feared complication of atrial fibrillation (AF). Oral anticoagulant therapy is indicated for stroke prevention in patients with AF if the risk of stroke is moderate or high assessed by CHA_2DS_2VASc score. The availability of high and low dose of non-vitamin K antagonist oral anticoagulants (NOACs) have led to a probable misuse of these drugs. In this study we aimed to investigate guideline adherent use of NOAC doses in patients with non-valvular AF (NVAF).

Methods: Real-life Multicenter Survey Evaluating Stroke prevention strategies (RAMSES study) was across-sectional, observational study. Patients were excluded if they had valve replacement or mitral stenosis. A total number of 6273 NVAF patients were enrolled in RAMSES study and 2086 patients who were on NOACs (dabigatran, rivaroxaban, apixaban) were included to the current analysis. Patients were divided into two groups according to 2012 European Society of Cardiology AF guideline recommendation as "high" and "low" dose of NOAC recommended. Than study patients were divided to undertreatment, overtreatment and appropriate treatment groups.
Results: High dose of the drug was recommended to 1557 (74.6%) and low dose was recommended to 529 (25.3%) patients according to ESC guideline. Of the high dose recommended patients 634 (40.7%) were on undertreatment and of the low dose recommended patients 205 (38.75%) were on overtreatment. Low dose of NOACs were chosen for elder patient with low creatinine clearance. There was no association among comorbid diseases and guideline adherence. However CHA_2DS_2VASc score was higher in the undertreatment group (3.4±1.3 vs. 3.1±1.3 p<0.001) and HAS-BLED was higher in the overtreatment group (2.5±1.02 vs. 2.3±1.1 p=0.041). Undertreatment was most prevalent for dabigatran, (57.5%) followed by rivaroxaban, (29.1%) and apixaban, (17.6%) whereas overtreatment was most common for rivaroxaban, (52.4%) followed by apixaban, (40.0%) and dabigatran (27.8%).

Table 1

	NOAC high dose rec (n = 1557)			NOAC low dose rec (n = 529)		
	Undert. (n = 634)	GB (n = 923)	P	GB (n = 324)	Overt. (n = 205)	P
Male, n (%)	264 (41.6)	418 (45.3)	0.161	103 (31.8)	60 (29.3)	0.563
Age, mean±SD	71.4±8.9	67.5±9.3	<0.001	77.1±7.9	73.9±8.3	<0.001
Comorbidity						
CHF, n (%)	116 (18.3)	157 (17.0)	0.542	74 (22.8)	42 (20.5)	0.590
HT, n (%)	426 (67.3)	669 (72.5)	0.032	249 (76.9)	157 (76.6)	1.000
DM, n (%)	149 (23.5)	235 (25.5)	0.402	73 (22.5)	52 (25.5)	0.462
VD, n (%)	145 (22.9)	179 (19.4)	0.099	105 (32.4)	60 (29.3)	0.500
CHD, n (%)	153 (24.1)	193 (20.9)	0.137	111 (34.3)	61 (29.8)	0.296
Stroke history, n (%)	70 (11.0)	126 (13.7)	0.140	78 (24.1)	54 (26.3)	0.606
Bleeding history						
Major bleeding, n (%)	20 (3.2)	29 (3.1)	1.000	20 (6.2)	14 (6.8)	0.856
Minor bleeding, n (%)	78 (12.3)	111 (12.1)	0.875	50 (15.4)	35 (17.1)	0.628
Creatinine clearance, mL/min	75.4±23.1	83.6±25.9	<0.001	54.3±21.6	62.6±34.1	0.002
CHA_2DS_2VASc score, mean±SD	3.4±1.3	3.1±1.3	<0.001	4.3±1.4	4.2±1.3	0.355
HASBLED score, mean±SD	1.3±0.6	1.3±0.7	0.108	2.3±1.1	2.5±1.0	0.041
NOAC						
Dabigatran, n (%)	418 (57.5)	309 (42.5)		208 (72.2)	80 (27.8)	
Rivaroxaban, n (%)	177 (29.1)	732 (70.9)	<0.001	110 (47.6)	121 (52.4)	<0.001
Apixaban, n (%)	39 (17.6)	182 (82.4)		6 (60.0)	4 (40.0)	

Conclusions: We evaluated guideline adherence of NOACs in a multicenter epidemiological study and found that nearly 40% of patients were on undertreatment or overtreatment. Undertreatment was more common in high stroke patients and overtreatment was more common in high bleeding risk patients. Guideline adherent management of NOACs has been associated with better outcomes thus there is a need for greater adherence to the guidelines.

Coagulation and Tissue factor

C0343
DOXORUBICIN-INDUCED MDR1/P-GP IN MCF7 BREAST CANCER CELLS WAS ASSOCIATED WITH TISSUE FACTOR OVEREXPRESSION AND THROMBIN GENERATION

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Background: Acquisition of properties rendering cancer cells resistant to the chemotherapy agents is among the main causes of treatment failure. Epithelial carcinoma breast cancer cells MCF7 are usually sensitive to several chemotheurapetic agents, but they can develop chemoresistance after prolonged exposure to cytostatic drugs, acquiring a more aggressive phenotype.
Methods: Pre-treatment of MCF7 cells for several weeks with increasing concentrations of doxorubicin, renders them chemo-resistant. Tissue factor (TF) and MDR1/P-gp expression by MCF7 cells were assessed by flow cytometry and western blot assays. Reverse transcriptase-polymerase chain reaction (RT-PCR) for TFmRNA and electrophoretic analysis in agarose gels was also performed. TF activity (TFa) from cancer cells was measured with a clotting based assay (Diagnostica Stago). Thrombin generation of normal platelet poor plasma (PPP) in the presence of MCF7 cells was assessed with the CAT assay (Diagnostica Stago).
Results: The acquisition of the chemo-resistance phenotype by MCF7 was correlated with a significant acceleration of thrombin generation. Chemo-resistant MCF7 cells expressed higher amounts of TF and showed marked TFa activity as compared to nonresistant cells. Expression of TF by chemo-resistant MCF7 was correlated with the expression of the MDR1/P-gp.
Conclusions: Our results demonstrate that the acquisition of the chemo-resistance phenotype by the breast cancer cells is associated with enhancement of their procoagulant properties which are principally mediated by the TF expression.

Coronary, cerebrovascular and peripheral vascular disease

C0290
ASSESSMENT OF PAR-1 MRNA EXPRESSION IN PLATELETS AND LEUKOCYTES OF PATIENTS WITH ISCHEMIC STROKE

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Background: Ischemic stroke is associated with abnormal platelets reactivity, leukocytes activation and platelet-leukocytes aggregates formation. One of the key links that affects multiple interactions of platelets, leukocytes and endothelial cells in acceleration of thrombus formation and stroke development is thrombin. Growing body of evidence shows that high expression of thrombin receptor - protease-activated receptor-1 (PAR1), encoded by F2R is associated with severity of neuronal damage. In order to check the role of PAR-1 in intravascular events we assessed the PAR-1 mRNA expression in blood cells among patients with ischemic stroke.
Methods: In this pilot study the PAR-1 mRNA expression was detected by RT-PCR method in isolated platelets and leukocytes of 10 patients (males, 54±2.3 years old) with ischemic stroke, confirmed by neuroimaging methods, at the moment of hospital admission. All patients received treatment according to the ESO Guidelines for Management of Ischaemic Stroke and had the same functional outcome. 10 healthy volunteers were taken as a control group. The results were assessed using MedCalc software.

Results: Expression of PAR-1 in leukocytes was not detectable both in stroke and control groups. High diversity of the PAR-1 mRNA concentration in platelets under stroke was found. It varied more than 10 times among patients with ischemic brain injury. We did not find associations of the PAR-1 mRNA concentration with blood pressure, size of brain damage and neurological deficits estimated by using NIHS scale. Variability of platelets' PAR-1 expression was determined with bimodal character of distribution of data: the most of observed patients had low level of the PAR-1 mRNA concentration 0.031±0.005 (versus 0.067±0.01 in control; $p<0.001$), whereas 3 patients demonstrated extremely high level of F2R expression. Two of them suffered with recurrent cerebral ischemia, and one patient had myocardial infarction previously.
Conclusions: These results indicate the low expression of PAR-1 mRNA in platelets of patients with primary ischemic stroke that could be considered as a compensatory mechanism preventing propagation of thrombus formation. However discovered association between recurrent ischemic events were associated and high F2R expression stimulates for further investigation of PAR-1 role in stroke development and complications.

C0342
DESMOTEPLASE FOR ACUTE ISCHEMIC STROKE: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: There is an unmet need to develop better treatments for acute ischemic stroke (AIS). Desmoteplase is a vampire bat saliva-derived analogue of human tissue plasminogen activator (tPA). Compared to human tPA, desmoteplase has higher fibrin selectivity, lower morbidity, and longer half-life. There is a lack in class one evidence about the safety and efficacy of Desmoteplase for AIS. Therefore, we performed this meta-analysis to synthesize evidence from published randomized controlled trials (RCTs) about the safety and efficacy of Desmoteplase in AIS.
Methods: We searched PubMed for RCTs assessing the safety and efficacy of desmoteplase, against placebo, for AIS. Records were screened for eligibility and data were extracted and analyzed by RevMan software. Reperfusion at 4 to 8 hours, improvement in national institute of health stroke scale (NIHSS), and modified Rankin scale 0-2 were pooled as odds ratio (OR) between the two groups. Adverse events of symptomatic intracranial hemorrhage, asymptomatic intracranial hemorrhage, and mortality were pooled as risk ratio (RR) between the two groups. Heterogeneity was assessed by chi-square and I-square tests.
Results: Four RCTs (n=383 patients) were pooled in the final analysis. The overall effect size favored desmoteplase in terms of reperfusion 4-8 hours (OR 2.52, 95% CI [1.21 to 6.34]). While the pooled effect size did not favor either of the two groups in terms of good clinical outcome at 90 days (OR 1.16, 95% CI [0.71 to 1.92]), modified Rankin scale (OR 0.99, 95% CI [0.58 to 0.1.70]), or NIHSS (OR -0.02, 95% CI [-0.16 to 0.11]). In terms of safety, neither of the adverse events was significantly higher in the desmoteplase group (symptomatic Intracranial hemorrhage: RR 1.40, 95% CI [0.38 to 5.17]; symptomatic intracranial hemorrhage: RR 1.21, 95% CI [0.89 to 1.66]; major hemorrhagic events: RR 1.02, 95% CI [0.39 to 2.68]; and Mortality within 90 days: RR 1.41, 95% [0.63 to 3.14]). No significant heterogeneity was found for all outcomes.
Conclusions: Current evidence suggests that treatment with desmoteplase (up to 125 μg/kg) within 3 to 9 hours after AIS was safe and achieve reperfusion within 4 to 8 hours. However, desmoteplase did not alleviate the severity of stroke or improve the quality of life. Further research and development are needed to translate this successful reperfusion into better clinical outcome and better quality of life for AIS patients.

Deep vein thrombosis and PE

C0057
HIGH PREVALENCE OF PULMONARY EMBOLISM IN PATIENTS HOSPITALIZED FOR SYNCOPE

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Background: All patients referred to 11 hospitals in Italy with a first episode of syncope had a systematic work-up for pulmonary embolism, irrespective of the presence of alternative explanations for syncope. The presence of pulmonary embolism was excluded in patients with unlikely clinical probability in combination with negative D-dimer. In all other patients, computed tomography pulmonary angiography or ventilation/perfusion scanning was performed.
Methods: The prevalence of pulmonary embolism among patients with syncope is not well documented, and current guidelines pay little attention to a diagnostic work-up for pulmonary embolism in these patients.
Results: We included 560 patients (mean age, 76). In 330 (58.9%), pulmonary embolism was excluded based on the combination of an unlikely clinical probability and negative D-dimer. In the remaining 230 patients, pulmonary embolism was found in 97 (42.2%, 95% confidence intervals, 35.8 to 48.6). In the entire cohort, the prevalence of pulmonary embolism was 17.3% (14.2 to 20.5). In 65 patients, the most proximal location of the embolus was in the main pulmonary or lobar arteries, or the perfusion defect was larger than 50%. Pulmonary embolism was found in 45 of the 355 patients (12.7%) with an alternative explanation for syncope, and in 52 of the 205 (25.4%) without one.
Conclusions: Pulmonary embolism was found in nearly 1 in every 6 patients hospitalized for a first episode of syncope.

C0058
A PROSPECTIVE ALGORITHM INCORPORATING LIMITED AND WHOLE-LEG ASSESSMENT OF THE DEEP VENOUS SYSTEM IN SYMPTOMATIC OUTPATIENTS WITH SUSPECTED DEEP VEIN THROMBOSIS (THE PALLADIO STUDY)

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Background: In a multicenter, prospective cohort study, consecutive outpatients with suspected DVT underwent D-dimer (DD) measurement and pre-test clinical probability (PTP) assessment. DVT was ruled out without further testing if PTP was unlikely and DD negative (group 1). Patients with PTP likely or positive DD underwent limited CUS only (group 2), whereas patients with PTP likely and positive DD underwent extended whole-leg CUS (group 3). All patients in whom DVT was ruled out underwent a 3-month follow-up, and the primary outcome was the incidence of objectively documented venous thromboembolism (VTE) in this patient group. A sample of 1100 patients was calculated on the assumption that

the primary outcome would not exceed 1%, and the upper limit of the 95% confidence intervals (CI) would not exceed 2%.
Methods: Compression ultrasonography (CUS) is the mainstay for the diagnosis of deep vein thrombosis (DVT) of the lower limbs. CUS can be extended to the entire deep venous system or limited to the proximal veins only. The two approaches were shown to be clinically equivalent. We assessed the diagnostic accuracy of an algorithm combining whole-leg and limited CUS.
Results: Of 1162 recruited patients (median age 66 years, 60% females), 351 were in group 1, 401 in group 2, and 410 in group 3. Limited CUS was positive in 12 patients (3%) in group 2; extended CUS was positive in 200 patients (48%) in group 3; 38% of diagnosed DVT were isolated distal DVT. The three-month incidence of VTE in untreated patients after a negative diagnostic strategy was 0.87% (95% CI, 0.44-1.70).
Conclusions: An algorithm combining limited and whole-leg CUS is a reliable, safe and convenient tool for the diagnostic management of outpatients with clinically suspected DVT.

C0059
THE VALUE OF COMPUTED TOMOGRAPHY FOR THE DETECTION OF OCCULT CANCER IN PATIENTS WITH UNPROVOKED VENOUS THROMBOEMBOLISM (D'ACQUAPENDENTE STUDY)

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Background: We performed a randomised multicenter trial to assess if in patients with unprovoked VTE, a computed tomography (CT)-based diagnostic strategy including thoracic, abdominal and pelvic CT in association with hemoccult yields a higher cancer detection rate than a non-standardised testing approach based on physicians' clinical judgment and patients' preferences. Cancer-free patients were followed up for up to 24 months.
Methods: Patients with unprovoked venous thromboembolism (VTE) may harbour occult cancer. Whether an aggressive diagnostic work-up for cancer has additional value over a more limited screening for detection of underlying malignancy in these patients is controversial.
Results: Of the 195 consecutive patients with unprovoked VTE who were eligible for this investigation, an occult cancer was identified in 10 of the 98 patients (10.2%) randomised to the CT-based strategy, and in 8 of the 97 (8.2%) allocated to the personalised strategy (absolute difference, 2.0%; 95% CI, -7.2 to 11.1; p=0.81). During follow-up, cancer was identified in additional 2 patients in each group. Overall, 7 (7.1%) patients of the CT-based strategy died, as compared to 11 (11.3%) of the personalised strategy, with 2 and 4, respectively, due to cancer.
Conclusions: A CT-based strategy in association with hemoccult does not provide a clinically significant benefit over more limited cancer screening for detecting occult cancer in patients with unprovoked VTE.

C0060
THE IMPACT OF RESIDUAL OBSTRUCTION ON THE LONG-TERM OUTCOME OF PATIENTS WITH PULMONARY EMBOLISM

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Background: In a nationwide, multicentre study 653 consecutive patients with a first, objectively confirmed acute PE, with or without simultaneous deep vein thrombosis (DVT) of the lower extremities, received a perfusional lung scanning after six months, and were then followed up prospectively for up to three years. The presence of RPO was evaluated using the Meyer score. The primary study outcome was to assess the impact of RPO on the combined incidence of recurrent VTE and CTEPH, defined according to widely accepted criteria.
Methods: Whether the persistence of residual pulmonary obstruction (RPO), as shown by perfusion lung scanning six months after an episode of acute symptomatic pulmonary embolism (PE), plays a role in the development of recurrent venous thromboembolism (VTE) and of chronic thromboembolic pulmonary hypertension (CTEPH) is unknown.
Results: The perfusion lung scanning showed the persistence of RPO in 329 of the 653 patients (50.4%; 95% CI, 45.0 to 56.1). Objectively proven recurrent VTE developed in 30 of the 329 patients (9.1%) with RPO, and in 16 of the 324 (4.9%) without RPO. CTEPH developed in 11 (3.3%) and in none, respectively. After adjusting for age, sex, modality of PE presentation (unprovoked or secondary), severity of PE and contemporary DVT as simple covariates, and for the duration of anticoagulation as time-dependent covariate, the hazard ratio (HR) of developing subsequent recurrent VTE and/or CTEPH in patients with as compared to those without RPO was 2.70 (95% CI, 1.24 to 5.89).
Conclusions: In patients with acute symptomatic PE, the persistence of residual obstruction, as shown by perfusion lung scanning six months after the index episode, is a powerful and independent predictor of unfavourable outcome.

C0067
TRENDS IN MORTALITY AFTER ACUTE DEEP VEIN THROMBOSIS

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Background: A comprehensive evaluation of temporal trends in short-term mortality of patients with deep vein thrombosis (DVT) is important for identifying modifiable factors that may contribute to the trends.

Methods: We identified adults with acute DVT enrolled in the RIETE registry between 2001 and 2014. We assessed temporal trends in length of hospital stay and use of pharmacological and interventional therapies. Using multivariable regression, we examined temporal trends in risk-adjusted rates of all-cause, PE-related, and bleeding-related death to 30-days after diagnosis.
Results: Among 26,695 patients with DVT, mean length of stay decreased from 9.0 days to 7.6 days over time (16% relative reduction, P < 0.01).For initial treatment, the use of unfractionated heparin did not significantly changed over time, whereas the use of low-molecular weight-heparin decreased from 98% to 90% (P < 0.01 for trend). Direct oral anticoagulants use increased from 0.5% in 2010 to 13.4% in 2014 (P < 0.001 for trend). Local thrombolytic therapy use increased from 0.2% to 4.7% (P < 0.001 for trend) and filter insertion increased from 1.5% to 2.5% (P < 0.01 for trend). Risk-adjusted rates of all-cause mortality decreased from 3.9% in the first period 2001-2005 to 2.7% in the last period 2010-2014(adjusted rate ratio per year, 0.84; 95% confidence interval [CI], 0.74 to 0.96; P < 0.01 for trend). Rates of bleeding-related mortality decreased over time, with a risk-adjusted rate of 0.5% in 2001-2005 and 0.1% in 2010-2014 (adjusted rate ratio per year, 0.55; 95% CI 0.40 to 0.77; P < 0.01 for trend).
Conclusions: This temporal analysis in the large international RIETE registry found a decreasing trend in adjusted death rate for acute DVT.

C0083
INCIDENCE OF HOSPITAL-ACQUIRED VENOUS THROMBOEMBOLIC DISEASE AMONG CLINICAL AND SURGICAL INPATIENTS

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Background: Venous thromboembolism (VTE) is still a common, sometimes fatal, and potentially preventable medical problem in hospital settings. Our aim was to estimate the crude incidence rate (IR) and adjusted by standardization of VTE developed during hospitalization, in clinical and surgical inpatients.
Methods: Prospective cohort of all adult clinical and surgical inpatients, admitted to the hospital between 2006 and 2013. VTE incident cases were captured prospectively from the Institutional Registry of Thromboembolic Disease in a tertiary hospital care in Buenos Aires. Follow-up was until discharge or death. The IR was calculated for inpatients according to the number of incident cases of an initial VTED episode per 1,000 person-days. The rates were adjusted by direct standardisation to the age and sex distribution of the populations of Argentina and Buenos Aires according to the 2010 Census, as well as in relation to the European standard population. We also conducted a Poisson regression model to evaluate the determinants of VTE and adjusted for the following variables: age category, sex and surgical admissions. Incidence rate ratios (IRRs) were obtained for this model with 95% confidence intervals.
Results: The crude incidence rate of VTE for clinical patients was 0.49 (CI95% 0.45-0.55) per 1,000 person-days, and IR adjusted for Argentina was 0.23 (CI95% 0.20-0.27). The crude IR of VTE for surgical patients was 0.25 (CI95% 0.23-0.27), and IR adjusted for Argentina was 0.14 (CI95% 0.10-0.17). The IR ratio for VTE when adjusted for age category, sex and surgical admissions: Surgical admissions reduce the IRR by 40%; and the thrombosis rate risk increases across age categories, being 8 times higher for older than 80 years than <29 years age category.
Conclusions: This study demonstrates, consistent with the literature, the high risk of VTE in hospitalized patients, which is still a health major problem.

C0084
CLINICAL COURSE OF PATIENTS WITH VENOUS THROMBOEMBOLISM (VTE) AND INFERIOR VENA CAVA FILTER (IVCF): COHORT STUDY

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Background: Despite the current growing use of inferior vena cava filters in patients with venous thromboembolism (VTE), there is little data on the evolution of these patients, and how this is influenced by concomitant anticoagulant therapy. The aim was to describe the evolution and filter retrieval of patients with acute episode of symptomatic VTE requiring IVCF, according subgroup of concomitant therapy received.
Methods: Retrospective cohort of all patients with acute symptomatic VTE and IVCF, included in the Institutional Register of Thromboembolism (Institutional Registry of Thromboembolic.-ClinicalTrials.gov, NCT01372514) between 2006 and 2014, in the Hospital Italiano, Buenos Aires, Argentina. Outcomes measures at followed up were filter retrieval, VTE complications and death. We modeled the cumulative incidence of filter retrieval in the presence of competing event death, estimated with competitive risk regression, according to the type of treatment (no treatment, prophylaxis or anticoagulation). Crude (HRc) and adjusted sub hazard ratios (HRa) were reported.
Results: We included 321 patients with VTE and FVCI. The main indications for placement were absolute contraindication to therapeutic anticoagulation (41%), and need to suspend anticoagulation for invasive procedure (35%). The overall mortality was 47%, being higher in those without treatment and lowest in the anticoagulation group (70 vs. 36%, p 0.01). The main complications during follow-up were recurrence of VTE (16%) and bleeding (11%), with no difference between groups. The cumulative filter retrieval in the presence of competing event death at 30 and 90 days were: 6% and 8% for no treatment, 30% and 38% for prophylaxis, and 40% and 50% for anticoagulation group. The retrieval rate was higher in patients who were receiving anticoagulation, and lower in patients with cancer compared with no treatment group. The hazard for filter retrieval in the presence of competing event death compared with no treatment group were: HRc 7.09 (CI95%2.5-20.11) and HRa 6.70 (CI95%2.35-19.06) for prophylaxis group, HRc 10.48 (CI95%3.86-28.45) and HRa 9.82 (CI95%3.60-26.76) for anticoagulation group.
Conclusions: Mortality in this group of patients was high. Failure to filter removal was associated with concomitant cancer and no anticoagulation.

C0110
EFFECTS OF INFERIOR VENA CAVA FILTER IN PATIENTS WITH THROMBOEMBOLIC RECURRENCES ON ANTICOAGULANT THERAPY

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Background: The effectiveness of inferior vena cava filter (IVC) use among patients with recurrent symptomatic venous thromboembolism (VTE) while on anticoagulation therapy remains unclear.
Methods: In this prospective cohort study patients with acute VTE identified from RIETE registry, we assessed the association between IVC filter insertion placed for recurrent VTE on the first 3 months of anticoagulation therapy and the outcomes of all-cause mortality, pulmonary embolism (PE)-related mortality and VTE rates through 30 days after diagnosis of recurrence. We

used propensity score matching to adjust for the likelihood of receiving a filter.

Results: Of the 606 patients with a recurrent VTE while anticoagulation, 21 underwent filter placement because of recurrent deep vein thrombosis (DVT) and 54 underwent filter placement because of recurrent PE. For DVT recurrences, 17 patients treated with a filter were matched with 49 patients treated without a filter. In patients who recurred as DVT, propensity-score-matched groups showed a non-statistically significant increase in death for filter compared with no insertion (odds ratio [OR] 1.49; 95% confidence interval [CI], 0.39 to 5.67; p=0.56). Risk-adjusted recurrent VTE rates did not significantly differ for filter insertion than no insertion (11.8% vs 4.1%, p=0.29). For PE recurrences, 48 patients treated with a filter were matched with 91 patients treated without a filter. Propensity score-matched pairs showed a significant lower risk of all-cause death for filter insertion compared with no insertion (2.1% vs 25.3%, p=0.002). The risk adjusted PE-related mortality rate was lower for filter insertion than no insertion (2.1 vs 17.6%, p=0.08). Risk-adjusted recurrent VTE rates did not differ for filter insertion than no insertion (4.2% vs 2.2%, p=0.55).

Conclusions: In patients with recurrent VTE on anticoagulation, IVC filter insertion did not show a survival effect in patients who recurred as DVT while it was associated with a significant lower risk of all-cause death in patients who recurred as PE.

C0113
VENOUS THROMBOEMBOLISM PREVENTION IN ONCOLOGY PATIENTS WITH RADIATION THERAPY (VERT STUDY)

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Background: Venous thromboembolism (VTE) prevention in oncology patients during radiation therapy (RT) is the challenging question. Nowadays there are no clear evidence is the RT an independent VTE risk factor or not.

Methods: In retrospective analysis 360 patients (25 - 76 y.o., mean – 54), received in 2014-2015 RT or chemotherapy were included. All patients were stratified in 3 groups: group I (n=120) 3D-conformal RT for brain tumors or brain metastasis; group II (n=120) 3D-conformal RT for body tumors (abdominal, retroabdominal, pelvic, chest); group III (n=120) was control – brain and body tumors on chemotherapy. Mean fraction numbers were 25 (11 - 32), mean total dose – 52 Gy (22 - 66). VTE diagnostic algorithm based on clinical data, D-dimer, venous ultrasound examination (US) and chest CT. All patients received LMWH in prophylactic dose and elastic compression.

Results: We haven't detected any cases of pulmonary embolism. Deep vein thrombosis (DVT) has developed in 4 patients (1.67%): 3 from group I (right parietal area astrocytoma, brain trunk tumor, skull basis cancer) – 2.5%; 1 in group II (rectal cancer) – 0.86%. In control group 1 DVT was detected (0.86%). In all 4 cases DVT was unilateral, involving common femoral vein and non-occlusive. These patients were switched on high LMWH doses. 2 patients were available for long-term outcomes assessment (12 months after radiation therapy). During 1-year period we haven't detected thrombosis recurrence. Posthrombotic disease was developed but without severe venous insufficiency. One patient on 11th follow-up month was exposed with repeated course of RT without any complications. During statistical analysis we have calculated VTE risks (95% CI). Absolute risk for groups I and II was 0.017. Risks difference was 0,008 (sensitivity 0.8; specificity 0.335). Relation was minimal and insignificant (p>0.05)

Conclusions: Heparinoprophylaxys in adequate dosage regime characterized by low VTE incidence in patients during radiation therapy. Based on study results analysis we suggest that for generate serious evidence the unmet need is the organizing strong trial with high statistical power and a huge number of patients. Since Dec 1st 2015 we are starting the restrospective evaluation of our Oncology center data - about 6000 patients with radiation therapy (2009-2015) and will communicate results as soon as possible.

C0368
MULTILOCUS GENETIC RISK SCORE: A NEW METHODOLOGY FOR THE EVALUATION OF THE RISK FOR IDIOPATHIC VENOUS THROMBOEMBOLISM

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Background: In the development of venous thromboembolism (VTE) genetics contribute in a relevant manner. In clinical routine the presence of two mutations Factor V Leiden (FVL) and G20210A Prothrombin (PT) are analysed to evaluate this genetic contribution. However, the sensitivity of FVL and PT is very low. New algorithms combining clinical data with genetic variables like TiC have demonstrated higher sensitivity.

To evaluate whether the use of Genetic Risk Scores (TiC) provides a better assessment of the VTE risk than a model based only on FVL-PT in a population of French patients with unprovoked idiopathic VTE.

Methods: The VTE predictive capacity of FVL+PT and TIC panels were compared. For each panel a multi-locus GRS was computed for each individual as the sum of the number of risk alleles, after weighting them by its effect size. A population of 103 idiopathic unprovoked VTE (35 males, 68 females; 47.5±13.9 years old) and 248 controls (109 males, 139 females; 49.0±14.9 years old) was used.

The predictive capacity was assessed by calculating the c-statistic (AUC-ROC); sensitivity, specificity Positive and Negative Likehood ratios and OR of a positive test result. Informed consent was obtained and the studies were approved by recognised ethics committees.

Results: When compared to FVL+PT, the use of TIC panel significantly improved the capacity to discriminate VTE (AUC-ROC: 0.613 vs 0.712, p=0.01). Moreover, clinical sensitivity (number of cases where the score of the panel was higher than the cut-off) increases very significantly in relation to FVL+PT (21.36% vs 96.12%, p< 0.001). Specificity was higher with FVL+PT (93.55 vs 59.68, p< 0.001).

Table 1

Variant (presence)	Controls (%)	Cases (%)	p value	OR	+Likehood ratio (p=0.7)	-Likehood ratio (p=0.001)
FVL (rs6025)	2.02	1.94	0.7			
F2 (rs17999639)	2.82	4.85	0.5			
AB0-A1	35.7	31.07	0.4			
F12 (rs1801020)	2.02	5.82	0.12			
F13 (rs5985)	56.5	92.23	<0.0001			
SERPIN A10 (rs22232698)	1.61	0	0.45			
SERPIN C1 (rs121909548)	0.40	0.97	0.89			
TiC panel				17.71	2.38	0.06
FVL+PT panel				3.71	3.31	0.84

Conclusions: TIC panel significantly improves the predictive capacity of VTE risk when compared to FVL+PT. Thus, our study suggests that the use of algorithms with a set of confirmed susceptibility loci (TIC) improves disease risk assessment and could be also an aid in the prevention, diagnosis and treatment of VTE disease.

Diagnostic and laboratory methods

C0234
CONTROL OF CHANGES OF A HEMOSTASIS AT BURN PATIENTS WHEN CARRYING OUT SURGERIES

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Background: To estimate a condition of system of a hemostasis at patients with extensive burns by means of a new method of research of system of a hemostasis during performance of bloody nekrektomiya.
Methods: Research included 20 patients with extensive burns to which the nekrektomiya on the area from 7 to 15% of a surface of a body was carried out. The total area of burn wounds averaged 39.1% of the item of t. (from 18 to 65% of the item of t.). Operations were executed after stabilization of a condition of patients on average for the 8th days from the moment of receiving a trauma. Intraoperative blood loss averaged 240 ml. Age of victims from 19 to 71 year (on average 39 years). In the preoperative period patients received therapy by not fractional heparin with cancellation it in 12 hours prior to operation. For an assessment of coagulation used the test of a trombodinamika based on video microscopic supervision of distribution of a fibrinous clot in not mixed plasma layer activated by the immobilized fabric factor. Key parameters of test of a trombodinamik: time of a growth inhibition of a fibrinous clot (Tlag), initial growth rate of a clot (Vi) and stationary growth rate of a clot (Vs). Analyses did in 3 key points: for an hour before operation, in an hour and in a day after completion of operation.
Results: In 5 cases from 20 in a point 2 initial speed decreased concerning value of parameter to operation, in a day value of parameter came back to initial, that is the undergone operation led to shift of a hemostasis in hypocoagulation area. It should be noted that in these cases there were greatest burns on the area. Other patients have changes of value of initial growth rate within the normal range of values of parameter. Stationary growth rate of a clot (norm 20 – 30mkm/mines) changed the identically initial. Emergence of spontaneous clots was noted at 5 patients in a point 2.
Conclusions: The obtained data say that 50% operated have expressed changes of system of a hemostasis which can lead to development venous the tromboembolicheskikh of states. At patients with extensive burns in the preoperative period monitoring of a condition of a hemostasis is necessary for individual selection of means of antikoagulyantny therapy, and also its adjustments for the purpose of achievement of adequate effect.

Genetics and genomics in thrombosis and Hemostasis

C0229
DESIGN AND APPLICATION OF A TWENTY-THREE-GENE PANEL BY NEXT-GENERATION SEQUENCING FOR INHERITED COAGULATION BLEEDING DISORDERS

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Background: Molecular testing of Inherited bleeding coagulation disorders (IBCDs) not only offers confirmation of diagnosis, but also aids in genetic counseling, prenatal diagnosis and in certain cases genotype–phenotype correlations are important for predicting the clinical course of the disease and to allow tailor-made follow up of individuals. Until recently, genotyping has been mainly performed by Sanger sequencing, a technique known to be time consuming and expensive. Currently, Next-Generation Sequencing (NGS) offers a new potential approach that enables the simultaneous investigation of multiple genes at manageable cost. The aim of this study was: To design and to analyze the applicability of a 23-gene NGS panel in the molecular diagnosis of patients with IBCDs.
Methods: We enrolled a total of 20 patients (13 males and 7 females; median age, 24 years, ranging from 1 to 61 years old), with previously confirmed deficiencies of coagulation factors. Twenty patients with an IBCDs phenotype were studied using NGS technology. A custom target enrichment library was designed to capture twenty-three genes known to be associated with IBCDs. Probes were generated for 296 targets to cover 86.3 kb regions (all exons and flanking regions) of these genes. Sanger sequencing was performed to validate all causative variants identified by NGS.
Results: The use of this 23-gene panel approach allowed us to identify the causative variants of the IBCDs in all patients. Overall, Twenty-one pathogenic variants were found, including six novel mutations affecting *F8, FGA, F11, F10* and *VWF* genes and fifteen previously reported variants were detected. Of the 21 alterations, 18 were missense and 3 were frameshift changes due to micro deletions. NGS and Sanger sequencing were 100% concordant.
Conclusions: Inherited coagulation disorders could be successfully molecularly characterized by using our 23-gene Next Generation DNA Sequencing panel. This approach allowed the diagnosis of the disease at a molecular level in all patients, and the identification of novel genetic variants in 30% of the cases included. Our results demonstrate that this approach could be an accurate, reproducible, and reliable tool in the rapid genetic diagnosis of IBCDs.

Hemostasis and inflammation

C0151
SIGNIFICANCE OF ENDOGENOUS THROMBIN POTENTIAL (ETP) IN ASSESSMENT OF COAGULATION DISORDERS AND DEVELOPMENT OF SEPSIS

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Background: During the development of sepsis endothelial activation, as well as activation of coagulation system are in complex relationship with systemic inflammation. Data from literature bring evidence that markers of coagulation activation and endothelial dysfunction could be useful in prediction of sepsis development and progression. The aim of our study was to determine whether the use of endogenous thrombin potential (ETP) as specific marker of pro- and anticoagulant events is associated with more severe form of sepsis and whether its levels correlate with widely used APACHE II (Acute Physiology and Chronic Health Evaluation) and SOFA (Sequential Organ Failure Assessment) score.
Methods: 150 patients with sepsis were included in our study. Prognostic scores (APACHE II and SOFA) associated with prediction of multiorgan failure and outcome of critically ill septic patients were calculated. ETP levels were determined within first 24 hours of the onset of the disease. Correlations between APACHE II and SOFA scores and ETP levels on the first day of sepsis development were assessed by SPSS 20,0 software- Kendall`s tau correlation, since data were not normally distributed. Data are expressed as mean± standard deviation. All P-values were two-sided and statistical significance was set at a value of 0.01.
Results: Out of 150 patients that were included in the study, 59.33 % were males and 40.66% females, between the ages of 18 to 87 years. Levels of ETP (AUC %) (77.37±34.52) significantly correlated with both APACHE II (15±7.54; p=0.00; correlation coefficient -2.63) and SOFA (5.73±34.52, p=0.00; correlation coefficient -3.46) scores on the first day of sepsis onset.
Conclusions: Negative correlation of ETP levels with prognostic APACHE II and SOFA scores may imply that there is significantly lower thrombin generation in patients with more severe form of sepsis. Our results also suggest that measuring ETP could contribute to global assessment of coagulation disorder and prediction of worse outcome in patients with sepsis.

C0153
EVALUATION OF THROMBOELASTOGRAPHY (TEG) IN PATIENTS WITH MYELOPROLIFERATIVE NEOPLASM: PLATELET COUNT >600 (X109/L) ASSOCIATED WITH PROTHROMBOTIC PARAMETERS

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Background: Myeloproliferative disorders (MPN), such as polycythaemia rubra vera and essential thrombocythaemia, are independent risk factors for cardiovascular and thrombotic events. However, there currently remain no routinely available laboratory tests to evaluate these risks. Global coagulation assays such as thromboelastography (TEG) may be a better surrogate measure of these individual's thrombosis risk.
Methods: Individuals with existing MPN regardless of treatment status were recruited. All samples were citrated and underwent TEG 5000 analysis within 4 hours of collection, using standard manufacturer guidelines. Routine TEG parameters including R (mins), K (mins), maximum amplitude (mm), α-angle (°) and LY30 (%) were recorded. Results were compared to locally recruited normal controls.
Results: 29 MPN patients (15 F, 14 M) with median age of 67 (45-82) were recruited. 21 had essential thrombocythaemia (ET) and 7 with polycythaemia rubra vera (PRV); 24 were JAK2V617F positive, 4 calreticulin (CALR) positive and 1 was both JAK2 and CALR negative. No differences were seen between ET and PRV. When compared to age-matched normal controls, MPN patients with platelet count >600 (x10^9/L) had more thrombotic parameters (see Table 1).
Interestingly, and contrary to other prothrombotic markers, LY30, a marker of clot breakdown at 30 minutes post maximum clot strength, was significantly higher (3.05% vs 0.3%, p<0.001). These changes were independent of aspirin use. Similarly, patients with at least 2 TEG parameters within the top quartile of the age-matched normal control range, had higher platelet counts (588 x10^9/L vs 429 x10^9/L, p=0.01), thrombin generation (760 dynes/cm^2 vs 687 dynes/cm^2, p=0.03), higher lymphocyte count (2.1 x10^9/L vs 1.4 x10^9/L, p=0.01) and more likely to be on cytoreductive therapy (68% vs 27%, p=0.03).

Table 1

TEG parameter	MPN with plts >600 (x10^9/L)	Normal controls	p-value
R time (mins)	6.04	6.3	p=0.38
K time (mins)	2.08	2.1	p=0.78
α-angle (°)	62.6	61.3	p=0.84
MA (mm)	65.1	60.5	p=0.03
LY30 (%)	2.87	0.3	p<0.01
Thrombin generation (dynes/cm^2)	790	743	p=0.03

Conclusions: This pilot study suggests that MPN patients with platelets >600 (x10^9/L) have more prothrombotic TEG parameters. Similarly, the presence of 2 or more "prothrombotic" TEG parameters, when compared to age-matched controls, predicts for thrombocytosis, use of cytoreductive therapy and higher thrombin generation. Further studies evaluating TEG® parameters in MPN patients is warranted.

Heparins and heparin induced thrombocytopenia

C0324
ANALYSIS OF HEPARIN INDUCED THROMBOCYTOPENIA SCREENING TESTS IN CRITICAL CARE UNITS AT KING FAISAL SPECIALIZED HOSPITAL AND RESEARCH CENTER

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Background: Heparin induced thrombocytopenia (HIT) occurs in 1 of 5000 hospitalized patients or in 0.1-0.5% individuals exposed to heparin. Recent publications have shown increased in HIT among critically ill individuals. This study estimates the HIT burden in our intensive care unit (ICU) in relation to whole institute and international figures.
Methods: A retrospective observational study reviewed 1,238 HIT screening tests for patients receiving unfractionated heparin (UH) or low molecular weight heparin (LMWH) with clinical suspicion of HIT by two screening methods from 2011-2014.
Results: There were 340 tested samples from patients in ICU with age ranging from 1 week to 111 years (median, 62 years). Out of those samples, 12.94% were positive by one or both used methods. In this cohort, 232 patients were exposed to UH, 31 to LMWH and 77 to both medications. The tests reported positive for HIT 16.81% in patients exposed to UH and 6.49% for patients who received both medications and none tested positive for those who received LMWH alone. The reported prevalence of HIT positivity in all requested tests (1,238) was 7.35%. The expected number of patients

needed to develop one event of HIT is approximately 500 individuals as 43,123 individuals were exposed to heparin during study period.
Conclusions: These results are in concordance with what has been reported as an increase incidence of HIT among critically ill patients. UH is more associated with developing HIT when compared with LMWH administration. This could be used as a surrogate indicator for quality assurance in HIT awareness among ICU physicians.

Microparticles

C0141
THROMBIN-INDUCED PLATELET ACTIVATION AND MICROVESICLE RELEASE: PROTEOMIC SIGNATURE OF PLATELET-DERIVED MICROVESICLES

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Background: Platelets play a fundamental role in the acute coronary syndromes (ACS). Platelet-derived microvesicles (pMVs) are found elevated in the circulation of ACS patients. However, MV protein composition remains poorly defined. pMV phenotype, rather than quantity, may help to better understand the pathophysiology of atherothrombosis. The present study aimed to characterize the proteomic signature of pMVs released by thrombin-activated platelets.
Methods: Washed platelets of healthy donors were treated *in vitro* with 0.5uNIH/mL thrombin (3 min at 37ºC) (T) or with placebo buffer (C). pMVs were obtained by differential centrifugation and characterized by flow cytometry using Annexin V and CD41. Proteomic studies were performed by bidimensional (2D) electrophoresis and mass spectrometry (MALDI-ToF-ToF). Proteins were identified using Swiss-Prot database. Differences in the protein patterns were analyzed using specific data analysis software (PDQuest) and proteins were identified using Swiss-Prot database.
Results: Flow cytometric characterization revealed that pMV from control platelets (C-pMV) have binding capacity for annexin V, express high levels of CD41 and low levels of P-selectin and PAC1. After thrombin activation (T-pMV), P-selectin and PAC1 levels were significantly increased. The proteomic analysis showed that a total number of 337 protein spots were found in each group in all experiments (N=5). By 2D-electrophoresis 382±9 different proteins features were detected in thrombin-activated pMPs (T-pMV) and a total of 73 protein spots were differentially altered in T-pMVs compared to C-pMVs. Differential proteins were related to cytoskeleton/cell organization, signal transduction, metabolism, and vesicle-mediated transport. Top connecting networks assessed by Ingenuity Pathway Analysis demonstrated the association of coagulation system for these differential regulated proteins (P<0.0001).
Conclusions: Thrombin-induced platelet activation triggers the release of pMVs with a complex proteomic profile that transfer proteins in blood and mobilize proteins to distal vascular cells facilitating cellular crosstalk. T-pMVs proteins seem to have functional involvement in occlusive thrombus formation and the progression of atherosclerosis.

Platelets and Megakaryocytes

C0092
DIFFERENTIAL PLATELET ACTIVATION AFTER P2Y12 INHIBITION

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Background: Some patients on P2Y12 inhibitors still develop thrombosis or bleeding complications. Tailored antiplatelet therapy, based on platelet reactivity testing, might reduce these complications. Several tests have been used for this purpose, but failed by lack of sensitivity or specificity. This could be due to the narrowness of current platelet reactivity tests, which merely focus on the platelets capacity to form aggregates. To establish a deeper understanding of the effect of P2Y12 inhibitors on platelet activation, we studied the effect of P2Y12 inhibition on several platelet activation pathways and markers.
Methods: The effect of in vitro and in vivo P2Y12 inhibition on αIIbβ3 activation, P- selectin and CD63 expression, aggregate and platelet-leucocyte complex formation, PF-4, -TG, RANTES and PDGF-AB release from the alpha granules and ATP/ADP release from the dense granule was assessed, after stimulation of different platelet activation pathways. Platelet reactivity measured by flow cytometry in 73 patients on P2Y12 inhibitors was compared to the results of VerifyNow (current gold standard) testing.
Results: Inhibition of the P2Y12 receptor, has major impact on aIIbb3 activation, platelet aggregation and platelet thrombus formation under physiological flow conditions, while it only mildly inhibits P-selectin expression, platelet-leukocyte interaction, CD63 expression and ADP/ATP release after stimulation with PAR-1 agonist, PAR-4 agonist and CRP-xl. P2Y12 inhibition on platelets stimulated with ADP almost completely blocked the ADP dependent platelet activation. Little agreement was observed between the results of VerifyNow and platelet reactivity assessed with flow cytometry.
Conclusions: Our findings indicate that P2Y12 blockade selectively inhibits platelet thrombus formation, while it has minor impact on alpha- and dense-granule release. Accurate platelet reactivity testing should therefore assess different platelet activation pathways and markers.

C0125
INCREASED PLATELET ACTIVATION AND P-SELECTIN IN OBSTRUCTIVE SLEEP APNEA SYNDROME

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Background: OSAS (obstructive sleep apnea syndrome) is a syndrome that which is characterized by recurrent apneas and hypopneas, and decreasing blood oxygen saturation level during this attacks. We intended to shed light the association of severity of OSAS related to platelet activation and P-selectin which is not apparently explained.
Methods: 59 patients has been included in the study as a group of 4 according to Polysomnography (PSG). Platelet functions were examined by aggregometry and flow cytometer (FC). The rates of platelets including CD62P (P-selectin), CD41b, CD42b molecules were determined with FC.
Results: Significant increase were detected in the severe OSAS group compared to the simple and light group of platelet aggregation (p<0.05). The ratio of CD41b in Moderate and severe OSAS groups and the ratio of CD42b in the severe OSAS group were detected as lower than that of the other groups; CD41b-CD62P+ platelet ratios were detected as higher than in the moderate and severe OSAS groups. As a result, smoking, age and gender independent P-selectin levels were detected as high in patients with moderate and severe OSAS group.
Conclusions: This finding show that platelet activation and aggregation in moderate and severe OSAS group were more active than that of the other groups. Similarly it was reported that platelet activation increased in some diseases like diabetes, atherosclerosis, asthma to favorably effect the development of disease. In accordance with our assessment, especially patients with moderate and severe OSAS may predispose to cardiovascular and cerebrovascular diseases and platelet activity may provide a significant contribution to this process.

C0204
SURFACE EXPRESSION OF TYRO3, AXL AND MER RECEPTORS ON PLATELETS IN PATIENTS WITH TYPE 2 DIABETES

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Background: Several reports revealed that Growth Arrest-Specific 6 (Gas6), a newly discovered vitamin K dependent protein, has been involved in the regulation of immunity/inflammation, which is related to the pathogenesis of type 2 diabetes. It seems like that Gas6 and its receptors (TAM receptors) represent an important mechanism for diabetes mellitus and its complications. The objective of this study is to quantify TAM receptors (Tyro3, Axl, Mer) on platelet surface in patients with type 2 diabetes, for the first time, and compare the results with the control.
Methods: 24 patients with type 2 diabetes and 21 healthy volunteers were enrolled in this study. None of the study participants were on anticoagulation therapy or vitamin K supplementation. Platelets were isolated from citrated blood samples and then the density of TAM receptors on platelet surfaces (resting and ADP-activated) were analyzed by flow cytometry and quantified by QIFI kit using specific antibodies against each receptor.
Results: The density of the each TAM receptors on platelet surfaces was found in resting platelets: Tyro3 (Sky) =9,308±4,261, Axl Median=8,378 (25. percentiles=6,145-75. percentiles=10,624), Mer Median=8,539 (6,339-9,737) in healthy controls (n=21); Tyro3 (Sky) Median=6,312 (5,251-9,983), Axl Median=6,902 (6,051-13,982), Mer Median=7,338 (5,708-8,908) in diabetic group (n=24). In the control group, the receptors Tyro3 (Sky) and Mer increased significantly after activation of platelets with ADP ($p<0.05$). In the diabetic group, activation of platelets with ADP did not cause any significant increase in the three types of receptors ($p>0.05$). When the diabetic group was compared with the control in respect to Tyro3 (Sky), Axl and Mer, there was no significant difference for resting platelets and also after activation with ADP ($p>0.05$). A high correlation was observed between fasting plasma glucose levels and the receptor Axl on activated platelets from diabetic patients ($r=0.855$).
Conclusions: This preliminary study, for the first time, showed that some changes of the density of the TAM receptors on platelet surfaces in patients with type 2 diabetes when platelets were activated by ADP. Gas6/TAM signalling may play a potential role in the pathogenesis of micro- and macro-complications of type 2 diabetes. Further studies are required to elucidate the role of Gas6/TAM signalling in complications of diabetes.

C0224
TOLERABILITY AND EFFICACY OF ELTROMBOPAG IN CHRONIC IMMUNE-MEDIATED THROMBOCYTOPENIA: META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: Immune thrombocytopenia (ITP) is a condition of increased platelet destruction and defective platelet production. The primary goal of therapy is to minimize the risk of bleeding by increasing platelet count to a safe level. Eltrombopag is an oral thrombopoietin-receptor agonist that stimulates the production of normally functioning platelets. The aim of this meta-analysis is to synthesize evidence from published randomized controlled trials (RCTs) about the safety and efficacy of Eltrombopag for ITP patients.
Methods: We searched PubMed, Web of Science, and Cochrane Central for RCTs evaluating the safety and efficacy of Eltrombopag for ITP patients. Data were extracted and analyzed using Review Manager 5.3. Overall platelet response, risk of significant bleeding (WHO grade II to IV), risk of any bleeding, number of cases needed to rescue treatment, and common adverse events were pooled as relative risk (RR) in the meta-analysis model. Heterogeneity was measured by I-square and Chi-square tests. We performed subgroup analysis to investigate if treatment effect varies significantly between adults and children. In case of significant heterogeneity, a random effect model was used. Otherwise, a fixed effect model was employed. An alpha level below 0.05 was considered significant.
Results: Five RCTs (n=588 patients) were included in the final analysis. The overall effect estimates favored Eltrombopag group in terms of: overall platelet response (RR 3.32, 95% CI 2.44 to 4.52, $P<0.0001$); incidence of significant bleeding (WHO grade II to IV) (RR 0.56, 95% CI 0.41 to 0.77, $P=0.0004$); number of cases needed to rescue treatment (RR 0.45, 95% CI 0.32 to 0.65, $P<0.0001$); and incidence of any bleeding (RR 0.74, 95% CI 0.66 to 0.83, $P<0.00001$), pooled studies were homogenous ($P>0.1$). For subgroup analysis, the efficacy of Eltrombopag did not differ significantly between children and adults except for incidence of any bleeding (RR 0.83 vs 0.51, respectively, $P=0.008$). None of the adverse events were significantly higher in Eltrombopag group than placebo group: sever adverse events (RR 0.73, 95% CI 0.35 to 1.51, $P=0.39$); headache (RR 0.85, 95% CI 0.62 to 1.17, $P=0.33$), diarrhea (RR 1.33, 95% CI 0.67 to 2.64, $P= 0.42$), and upper respiratory tract infection (RR 1.84, 95% CI 0.94 to 3.63], $P=0.08$).
Conclusions: This study provides class one evidence that Eltrombopag is a tolerable and effective drug for the management of chronic Immune thrombocytopenia in children and adults.

C0261
USE OF ELTROMBOPAG IN IMMUNE THROMBOCYTOPENIA IN TURKEY

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Background: Immune thrombocytopenia (ITP) is a disease in which count of platelets is persistently or transiently below 100 x 10^9/L due to immune mediated destruction. There is no standard approach currently in the cases recurring following splenectomy (refractory ITP). Being introduced recently following better understanding of pathophysiology of the disease, the thrombopoetin receptor agonists seem to be an efficient treatment for the refractory patients.

Methods: The present study included 249 cases (162 females, 87 males) with ITP receiving treatment with eltrombopag for diagnosis of refractory ITP in 50 study centers from several parts of Turkey. Median age at the time of diagnosis of ITP was 43 years (range: 26.5-58 years). For purpose of evaluating therapeutic response, the patients with platelet counts (per mm^3) below 30,000 were considered to have no response, those with platelet counts of between 30,000 and 100,000 and platelet counts doubled compared to the baseline were considered to have response, and those with the platelet counts above 100,000 as complete response. For the first-line therapy, IVIG was used in only one patient and corticosteroids were used in all of the remaining patients. One-hundred and fifty five (65.7%) patients had complete response and 53 (22.5%) had response while 28 (11.9%) patients had no response. During the therapy, median platelet count (per mm^3) was 11,000 at baseline, 35,000 on week 1, 48,750 on week 2, 58,000 on week 3, 73,000 one week 4, and 114,000 on week 8. Median duration of follow-up period was 18 (6-28.25) months. Platelet counts during follow-up of treatment with Eltrombopag is given in Table 1.

Table 1
Characteristics of the patients and platelet counts following Eltrombopag treatment, response to and follow-up of Eltrombopag treatment

Female/Male	162/87
Age	43 (26.5-58)
Platelet count at the time of diagnosis	8,000 (5,000-15,250)
Platelet count before Eltrombopag treatment	11,000 (5,000-18,000)
Eltrombopag week 1	35,000 (18,000-77,000)
Eltrombopag week 2	48,750 (20,000-157,750)
Eltrombopag week 3	58,000 (24,000-146,250)
Eltrombopag week 4	73,000 (31,000-157,000)
Eltrombopag week 8	114,000 (46,750-214,000)
Overall rate of response	n =208 (% 88,2)
Complete response	n = 155 (% 65.7)
Response	n = 53 (% 22.5)
No response	n =28 (% 11.9)
Time during which platelet count was above 50,000 (days) (median)	14 (8-30)
Eltrombopag follow-up period (months)	18 (6-28.25)

Results: Response was achieved in 88.2% (208/249) of the patients with refractory ITP on the second week of Eltrombopag treatment and platelet values could be maintained during follow-up period. Response could be achieved by increasing dose or adding low-dose corticosteroid in the patients with no response at the baseline. Side effects, toxicity, and adverse event during treatment are given in Table 2.

Table 2
Side effects and toxicity

Side effects	Number of cases
Headache	10
Fatigue	4
Nausea	2
Diarrhea	1
Pretibial edema	1
Neuropathic pain	2
Alopecia	1
Increased pigmentation	1
Arthralgia	1
Myalgia	2
Pruritus	2
Erithromelalgia	2
Transient ischemic stroke (TIS)	3
Deep vein thrombosis	4
Sudden cardiac death	1

Conclusions: In the current study in which 249 subjects for whom different therapeutic options were applied such as steroids, anti-D, splenectomy, IVIG, azathiopyrine, cyclophosphamide, danasol, vincristin, rituximab before using Eltrombag but no response was achieved were evaluated

retrospectively, despite the outcomes being promising the patients should be followed closely for rapidly developing thrombocytemia and thromboembolic events.

C0358
PLATELET HEAT SHOCK PROTEIN 70 (HSP70) IS A REGULATOR OF PLATELET INTEGRIN ACTIVATION, GRANULE SECRETION AND AGGREGATION

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Background: Molecular chaperones that regulate protein quality control, such as the ubiquitously expressed heat shock protein 70 (Hsp70), participate in diverse aspects of cellular and physiological function. Recent studies have reported roles for specific chaperones in blood platelets in maintaining hemostasis; however, the functions of Hsp70 in platelet physiology remain uninvestigated.
Methods: Here we characterize roles for Hsp70 in platelet activation and function. *In vitro* biochemical, microscopy, flow cytometry and aggregometry assays of platelet function as well as *ex vivo* analyses of platelet aggregate formation in whole blood under shear were carried out under Hsp70-inhibited conditions.
Results: Inhibition of platelet Hsp70 blocked platelet aggregation and granule secretion in response to collagen-related peptide (CRP), which engages the ITAM-bearing collagen receptor GPVI/FcRγ complex. Hsp70 inhibition also reduced platelet $\alpha_{IIb}\beta_3$ activation downstream of GPVI, as Hsp70-inhibited platelets showed reduced PAC-1 and fibrinogen binding. *Ex vivo*, pharmacological inhibition of Hsp70 in whole human blood prevented the formation of platelet aggregates on collagen under arterial shear. Biochemical studies further supported a role for Hsp70 in maintaining the assembly of the LAT signalosome, which couples GPVI-initiated signaling to integrin activation, secretion and platelet function.
Conclusions: Together, our results suggest that Hsp70 regulates platelet activation and function by supporting LAT-associated signaling events downstream of platelet GPVI activation, suggesting a role for Hsp70 in the intracellular organization of signaling systems that mediate platelet secretion, "inside-out" activation of platelet integrin $\alpha_{IIb}\beta_3$, platelet-platelet aggregation, and ultimately hemostatic plug and thrombus formation.

Pregnancy and thrombosis

C0168
THE INVESTIGATION OF MOLECULAR THROMBOPHILIA CAUSES IN IRANIAN WOMEN WITH RECURRENT PREGNANCY LOSS

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Background: Recurrent pregnancy loss (RPL) is a common health issue among Iranian pregnant women that has been strongly associated with specific inherited thrombophilic gene polymorphisms. Various studies have indicated that common thrombophilic gene mutations increase the likelihood of developing a thrombosis in uteroplacental blood flow, thus improving obstetric outcome in pregnant women. Since there are various ethnic groups living in Iran, investigation of genetic thrombophilic risk factors can be helpful in designating a diagnostic template for each pregnant women with unexplained fetal loss.
Methods: In this cross sectional study, we have investigated all the women with RPL that referred to Noor genetic diagnostic laboratory in Ahvaz, Iran during Sep. 2011- Nov. 2015. Patients aged 19 to 39 years with history of at least two RPL were included in our study. Genomic DNA was extracted from peripheral blood, and polymorphism genotyping was conducted using PCR-RFLP and DNA sequencing for diagnosis of factor V Leiden G1691A, prothrombin G20210A, MTHFR C677T and A1298C, PAI-1 -675 4G/5G and -844 A/G mutation.
Results: Of the 70 adverse pregnancy outcomes, 55 women were found to have one the inherited thrombophilic gene mutations. The ethnic origins of the studied cases included: Arab 26 (47.2%), Lor 16 (29%), Fars 9 (16.3%) and other ethnicities individuals 4 (7.2%). The mean age of patients was 30.11 (±5.36) years. Mutations of the MTHFR at locus 1298 and 677 along with PAI at positions -675 and -844 were 54.54% (30/55), 30.9% (17/55), 20% (11/55), 10.9% (6/55), respectively. One case had homozygous mutation of factor V Leiden G1691A, while there was no detected mutation of prothrombin G20210A in our population.
Conclusions: We determined a significant high frequency of MTHFR polymorphisms in our population that may necessitate detection of such mutations in Iranian women with the risk of RPL. More comprehensive thrombotic risk factor studies need to be done among pregnant women with different ethnic origins.

C0336
PREGNANCY IN HIGH RISK ANTITHROMBIN DEFICIENCY: PREVENTION OF VENOUS THROMBOEMBOLISM WITH THE LMW HEPARIN PROPHYLAXIS REGIMENS USED IN NORDIC COUNTRIES

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Background: The risk of venous thromboembolism (VTE) during pregnancy in heterozygous antithrombin (AT) deficiency is high in type I (quantitative deficiency), high in type II reactive site defect, but low in the type II with subtype heparin binding site (HBS) defect. Type II HBS defect is rare in Nordic countries but frequent in many countries. The recommended intensity of low molecular heparin (LMWH) in these pregnancies is controversial. In Denmark and in Sweden a uniform LMWH dosage was used. In Norway different LMWH dosages were used.
Methods: This retrospective study included only high risk women, mostly type I. Diagnosis of VTE was by objective methods. The LMWH blood level was measured by anti-FXa assay. The AT mutation was determined.

Results: The Danish cohort included 29 women with 40 term pregnancies. The Swedish cohort included 15 women with 31 term pregnancies. A standard dose of 5000 IU/12h and infusion of AT concentrate at delivery was administered to all. At low LMWH levels the dose was increased. VTE occurred in one women of the Danish cohort and in one woman of the Swedish cohort. The combined occurrence was 3.0%. The Norwegian cohort consisted of 27 women with 46 term pregnancies; all resulted in healthy newborns. Pregnancy losses had occurred in 20 of these women. LMWH doses ranged 2500 IU-16500 IU/24h. VTE occurred during 7 term pregnancies (15%), and in 20% of the total material including losses. The mean LMWH dose administered to the 7 women with VTE (6785 IU/24h) was significantly lower than the mean dose (9508 IU/24 h) in term pregnancies without VTE (P<0.01). The risk of VTE was increased by an additional thrombophilia, and by a previous VTE. The mean dose increased after our reported pilot study in 2003 had recommended higher doses. AT concentrate had been administered at 40 of the 46 deliveries. 3 VTEs occurred post partum, in 2 of the 3 cases, AT concentrate was not given. The risk of VTE was significantly higher with presence of additional thrombophilia, in those with a previous VTE, and in women with delivery prior to 2003. Bleeding was restricted to cases with obstetric pathology.
Conclusions: The risk of VTE was increased by presence of an additional thrombophilia, by a previous VTE, and by a LMWH dosage below 10 000 U/24h. Monitoring the LMWH blood level appears useful, particularly with additional risk factors. The results suggest that infusing AT concentrate at delivery may reduce the risk of post partum VTE.

Proteomics and epigenetics

C0136
EXOSOMAL MICRORNA SIGNATURE PREDICTS FUTURE ISCHEMIC EVENTS IN HIGH CARDIOVASCULAR RISK PATIENTS

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Background: High LDL-cholesterol plasma levels constitute an independent risk factor for atherothrombotic cardiovascular disease. We aimed to study whether microRNAs (miRNAs), non-coding RNAs involved in post-transcriptional regulation of gene expression, in circulating exosomes are prognostic markers of future cardiovascular events. We aimed to study this prognostic signature in high cardiovascular risk (HCVR)-patients with familial hypercholesterolemia that have a very high-risk for premature ischemic events.
Methods: Exosomes were isolated from platelet-free plasma obtained from HCVR-patients (Framingham Risk Score [FRS] =17) without clinical manifestation of disease at entry but that were to suffer an atherothrombotic event within 3.1±0.4 years post-sampling (N=42) and from age/treatment-matched low cardiovascular risk (LCVR)-patients (FRS=3; N=30) that did not have an event within the same time-period. Fully clinically characterized patients were from the SAFEHEART cohort. miRNA from exosomes was obtained with the Exo-MiR extraction kit. miRNA profiling (n=6/group) was performed using Megaplex-pool A microRNA arrays. Differentially expressed miRNAs were validated by RT-qPCR with Taqman miR-Custom Array Cards in the entire population.
Results: miRNA profiling revealed that 21 exosomal miRNAs were differentially expressed in HCVR-patients compared to LCVR-patients. RT-qPCR validation confirmed that ten of these differentially expressed miRNAs, including miR-130b, miR-133a, miR-142-3p, miR-200c, miR-324-5p, miR-339-3p, miR-660, and miR-744, were significantly increased, and miR-122 was decreased in exosomes of HCVR-patients. A ROC curve analysis of a five-miRNA signature (including the best five discriminators) was calculated and an AUC of 0.795±0.069 [95%CI:0.660-0.930] (P<0.001) for ischemic event presentation was obtained.
Conclusions: Thirty-six months before the acute event miRNAs could predict the presentation of an ischemic event. Ten miRNAs were found modified in HCVR-patients. For the first time, an exosomal miRNA signature (miR-130b, miR-142-3p, miR-200c, miR-660, and miR-744) is described as a potential prognostic marker of atherothrombotic events in high cardiovascular risk patients before symptom presentation.

Surgery: Hemostasis and Thrombosis

C0132
LOW PREVALENCE OF SYMPTOMATIC VENOUS THROMBOEMBOLISM FOLLOWING RENAL TRANSPLANTATION

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Background: Venous thromboembolism (VTE) is a major health issue that may result in complications such as post-thrombotic syndrome, pulmonary hypertension and even death. Risk factors for thromboembolic events following surgery and preventive measures have been widely documented in the literature. However, the appropriate thromboprophylaxis in individuals undergoing kidney transplantation remains unclear. The aim of the study was to determine the prevalence of symptomatic VTE within the first 90 days following renal transplantation (RT). A secondary aim was to document the prevalence of major bleeding evaluated during the same period.
Methods: A retrospective study was conducted on consecutive patients undergoing RT, at the Hospital Privado Universitario Centro Médico de Córdoba, Argentina, from January 1, 2006 to December 31, 2013. Exclusion criteria were age less than 18 years and patients undergoing combined organ transplantation. Patients did not receive pharmacological or mechanical thromboprophylaxis routinely. Medical records were reviewed from the day of transplantation until the following 90 days. Symptomatic lower extremity deep venous thrombosis and pulmonary thromboembolism confirmed by objective methods were recorded. Risk factors for the development of VTE and hemorrhagic complications were documented.
Results: A total of 511 renal transplant procedures were performed; 62 patients (12%) were excluded on the account of being recipients of combined organ transplantation and 8 patients (1.5%) were lost of follow-up. Follow-up was completed on 441 patients; 4 patients (0.9%) developed deep venous thrombosis, and 14 patients (3%) died, none of them had evidence of VTE. The most frequent causes of death were septic shock and severe hemorrhage. Factors associated with the development of VTE were duration of surgery greater than 4 hours (P= 0.006), and a history of VTE (P< 0.001). A total of 23 patients (5.2%) had major bleeding. Two patients (0.4%) died from bleeding complications, and 17 (3.85%) required a reoperation to control the hemorrhage.
Conclusions: This study shows a low prevalence of symptomatic VTE in patients undergoing renal transplantation despite not having used thromboprophylaxis routinely. The rate of major bleeding was significant, and despite the high risk of VTE assigned by scores such as the Caprini Score, which suggest pharmacological prophylaxis, our data raise questions about the appropriate prophylaxis for these patients.

POSTERS

Animal, cellular and molecular research in thrombosis

C0052
DIFFERENTIATION OF ANTAGONISTS OF PROTEINASE ACTIVATED RECEPTOR 1 AND 4 IN NONHUMAN PRIMATE MODELS OF HEMOSTASIS AND ANTI-THROMBOSIS

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Background: Platelet activation is a crucial step in the maintenance of hemostasis and in the development of thrombosis. Thrombin is the most potent stimulus of platelet activation. Thrombin-led platelet activation is mediated by activation of the proteinase activated receptors (PAR), a group of GPCR activated by tethered ligands. Platelet activation by thrombin differs across species. Only NHP platelet activation is known to be mediated by PAR1 and 4 similar to humans, which limits the translational value of in vivo studies to NHPs. Earlier studies have demonstrated a range of distinct in vitro activities of PAR1 and 4 in platelet activation. A primary goal of this study is to investigate and compare the roles of PAR1 vs PAR4 in hemostasis and thrombus development.
Methods: Nonhuman primate (NHP) models for pharmacokinetic (PK), ex vivo platelet aggregation (pharmacodynamics, PD) responses, the FeCI3 injury-mediated arterial thrombosis (efficacy) and template bleeding (bleeding risk) were developed in Cynomolgus Macaques. Selective small molecule antagonists with low nanomolar potency of PAR1 and PAR4 were synthesized, characterized in a range of vitro screen and counter-screen assays, and studied head-to-head in those NHP models.
Results: Treatment of animals with antagonists of PAR1 or PAR4 both resulted in strong inhibition of ex vivo platelet aggregation (PD). At doses that led to similar level of inhibitory activity toward PD effect, animals treated with a PAR4 antagonist showed similar levels of anti-thrombosis efficacy, but longer time of bleeding in comparing to animals treated with a PAR1 antagonist.
Conclusions: These findings indicated that antagonism of PAR1 will likely lead to a superior therapeutic index (efficacy vs bleeding risk) profile over antagonism of PAR4.

C0079
INFLUENCE OF THYROLIBERIN AND ITS SYNTHETIC ANALOG DIGIPRAMIN ON ERYTHROCYTE AND PLATELET INTERACTION

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Background: It is known that the condition of the microcirculation system depends on the status of the rheological properties of the blood. Because red blood cells make up 98% of the total blood volume, they have a key role in the rheological parameters. It was shown that only upon activation of platelets by various inducers ascertained interaction formed elements during thrombus formation. It was found that some peptides - nootropics can have a significant impact on blood cells, changing their function. A special place in modern research is the study of the influence of thyroliberin - nootropic drug on hemostasis system and the structural features of red blood cells. The state of erythrocyte membranes depends on their resistance to various harmful agents. The aim of this study was to examine changes in ADP - induced platelet aggregation in the presence of red blood cells under the influence of thyroliberin and its synthetic analogue digipramin.
Methods: Work performed on white rats. Blood was collected from the jugular vein with sodium citrate. Peptides (thyroliberin and digipramin) at a concentration of 10-4M were added to platelet-rich plasma (PRP) or a mixture of erythrocytes and PRP. As a control, used an equal volume of 0.85% NaCl. The precipitate erythrocytes were washed three times with saline and diluted 1: 1000 and added to PRP. Platelet aggregation was measured in by the inductor - ADP - 10 uM. on aggregometer.
Results: In experiments in vitro studies the interaction of red blood cells with activated platelets under the influence of regulatory peptides. It has been shown that both thyroliberin and digipramin reinforce platelet aggregation PRP ($p<0.01$). Aggregation adding thyroliberin amplified by 95%, adding digipramina - 55%. When added to the suspension of erythrocytes and PRP is amplified platelet aggregation 45-50%. While adding to PRP peptides and erythrocyte a decrease aggregation compared to adding only peptide or only erythrocytes.
Conclusions: It is found that the peptides reduced the interaction of activated platelets with the red cells, thereby reducing the risk of thrombotic complications in their use in clinical practice.

C0101
ANTITHROMBOTIC AGENTS, RIVAROXABAN AND CILOSAZOL, PREVENT LUNG AND RENAL INJURY FOLLOWING ABDOMINAL AORTA ISCHEMIA/REPERFUSION IN A RAT MODEL

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Background: Ischemia/reperfusion (I/R) during abdominal aorta surgeries leads to remote organ damage and the major part of this damage occurs upon reperfusion via oxygen free radicals. A novel direct factor Xa inhibitor, Rivaroxaban and an antiplatelet agent, Cilostazol are analyzed in this study for their protective effects on lung and renal tissues following abdominal aota ischemia/reperfusion model in rats.
Methods: Thirty-two male Spraque-Dawley rats were randomized as sham group (I/R, n=8), control group (n=8), and I/R+ Rivaroxaban (n=8, 20mg/kg orally administered before ischemia) and I/R+Cilostazol (n=8, 100mg/kg orally administered before ischemia) groups. Ischemia and reperfusion was induced by clamping the infrarenal aorta for 2 hours and declamping for reperfusion for 4 hours. Lung and renal tissue assays were performed for lipid peroxidation product malondealdehyde (MDA) and Glutathione Reductase (GR) and Glutathione Peroxidase (GPx) levels were also studied. Lung and renal tissues were also examined histopathologically under light microscopy.
Results: Both Rivaroxaban and Cilostazol attenuated lung and renal cell damages occurred by downregulating the level of MDA and upregulating the levels of GPX and GR. These results are confirmed also with the histopathological results.
Conclusions: These results suggested that one dose oral administration of both Rivaroxaban and Cilostazol effectively ameliorates the ischemia/reperfusion induced oxidative damage of lung and renal tissues by virtue of their antioxidant and anti-inflammatory potentials.

C0103
AN ANTIPLATELET AGENT, CILOSTAZOL, ATTENUTATES MYOCARDIAL DAMAGE INDUCED BY ABDOMINAL AORTA ISCHEMIA/REPERFUSION IN A RAT MODEL

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Background: Perioperative myocardial infarction is a devastating complication of surgical procedures of abdominal aorta. Ischemia/ reperfusion via clamping and declamping of the aorta leads to remote organ damage and the major part of this damage occurs upon reperfusion via oxygen free radicals. An antiplatelet agent, Cilostazol is analyzed in this study for its cardio protective effect following abdominal aota ischemia/reperfusion model in rats.
Methods: Twenty-eight male Spraque-Dawley rats were randomized as sham group (I/R, n=8), control group (n=8), and I/R+Cilostazol (n=8, 100mg/kg orally administered before ischemia) groups. Ischemia and reperfusion was induced by clamping the infrarenal aorta for 2 hours and declamping for reperfusion for 4 hours. Myocardial tissue assays were performed for lipid peroxidation product malondealdehyde (MDA) and Glutathione Reductase (GR) and Glutathione Peroxidase (GPx) levels were also studied. Myocardial tissues were also examined histopathologically under light microscopy.
Results: Cilostazol attenuated myocardial cell damage occurred by downregulating the level of MDA and upregulating the levels of GPX and GR. These results are confirmed also with the histopathological results.
Conclusions: These results suggested that one dose oral administration of Cilostazol effectively ameliorates the ischemia/reperfusion induced oxidative damage of myocardial tissue via its antioxidant and anti-inflammatory potential.

C0134
REACTION OF HAEMOSTASIS AND FIBRINOLYSIS, PROVOKED BY WEAK STATE MAGNETIC FIELD DURING LEARNING PROCESS IN RATS

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Background: It is well known that informational overloads can provoke different physiological and mental disorders, causing cardiovascular, nervous and internal diseases. As a rule cognitive activity of modern humans is realized in condition of increased level of magnetic field (MF), produced by different electronic constructions (computers, TV, laboratory and life technics, etc.). One of component of complex MF environment is static magnetic field (SMF), with little value of MF induction. The aim of this work is to show, that even small SMF influences can cause significant biochemical, physiological and behavioral changes in in organism of experimental rats, if these influences are coinced with moderate cognitive and informational load.
Methods: Wistar rats were learning to solve cognitive foodseaching task during some repeating procedures (N 30) Learning were observed in two situations: on the background of natural MF with 32±2 μT (microtesla) induction (1-st group) and on the background of static MF - SMF-, formed by three magnets, placed under the maze (2-nd group). Control group was represented by rats with free behaviour in conditions of living room. The parameters of haemostasis and fibrinolysis were determined in blood, taken from v.jugularis before and after learning process.
Results: Unlike control and 1-st group the explorative activity in all SMF induced rats was suppressed and required external stimulation for success. The formed habits in these animals were very unstable and was accompanied by active stress and neurotic reactions. The learning process, taking place without SMF load, led to weak activation of anticoagulant activity (AT-111) and some parameters of haemostasis (fibrinogen level rising), supported by light activation of fibrinolysis (euglobulin clot lysis time - ECLT- decreased on 25%, t-PA activity raised on 20% ($p<0.02$)) The learning process alone is natural factor of rats living and did not cause significant modulation of haemostasis and fibrinolysis. But SMF adding led to sharp changes of biochemical parameters. AT-111 activity fell to 36-72% in 84% of rats, APTT decreased twice in 86% of rats, PAI-1 activity fell till 100%, t- PA-activity increased in 2.5 times. This is regulatory reaction in normal rats
Conclusions: Learning process in normal rats in condition of SMF activated coagulation and regulatory defence fibrinolysis. But real living situation (age, stress, trauma, etc.) can break regulatory mechanism and provoke prethrombosis and thrombosis

C0203
SPECIAL FEATURES OF THROMBOLYSIS PRODUCED BY THROMBOLYTIC PREPARATION LONGOLYTIN

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Background: Longolytin is the proteases's complexes, isolated from cultivate fluid during cultivation of suprophyte low fungi Arthrobotrys longa. It is a new thrombolytic substance, studied in vitro and in vivo experiments as in intravenous introduction to v.jugularis to rats, and in external thrombolysis by application to thrombi, formed in surface ear marginal rabbit's vein. The aim of this work is to present the peculiarity of thrombolytic action of longolytin on thrombi in ear marginal rabbit's vein.
Methods: Thrombi were formed in surface ear marginal rabbit's vein by thrombin injection to clumping segment of vein. After thromb was stabilized clumps were taken off, and longolytin gel (0.3-3% concentration in glycerol) was applying every hour during 7-8 hours. There were determined changes of thrombus size by visual control (as product of two perpendicular diameters of thrombus in mm^2) and was calculated the velocity (V.) of thrombus dissolution (the ratio of thrombus size to time mm^2/min)
Results: There were revealed the next peculiarities of thrombolysis by longolytin. 1) Big thrombi dissolved with more great velocity (V.) than small ones. If thrombi size was 20-40mm^2, V. of thrombolysis was 0.04-0.12 mm^2/min, if thrombi size was 3-10 mm^2, V. was 0.02-0.04 mm^2/min. 2) Fresh thrombi dissolved faster, than old ones. V. thrombolysis in first 3 hours was 1.5 times greater, than in next 7 hours. 3) There were not observed dependence of V. of thrombolytic process on longolytin doses in interval 0.3-3%. 03% longolytin (10 cases), 1% (12 cases) and 3% (15 cases) dissolved with V. 0.08-0.10 mm^2/min. It was could be as result of polycomposition of longolitin, possible presentation of fibrinolysis inhibitors or other substances in its compound. 4) Thrombolytic action of longolytin varied in dependence on different reasons: individual peculiarity of every rabbit (individual variations of different parameters were significant), season, cosmic influences (V. thrombolysis in summer was greater than in winter). In individual rabbit V. thrombolysis was greater in right ear, than in left ear.
Conclusions: Longolytin is not toxic, its production is simple and not expensive. It revealed good thrombolytic properties on external rabbits thrombi. It is perspective preparation for treatment of surface thrombi.

C0231
INFLUENCE OF NEUROHYPOPHYSAL PEPTIDES AND THEIR NEW SYNTHETIC ANALOGUES ON THE PLATELET AGGREGATION

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Background: The neurohypophysal peptides vasopressin (AVP) and oxytocin (OT) have variety action on the haemostasis system. It is known that OT and AVP caused blood coagulation due to the increased secretion of tissue thromboplastin and factor VIII: C into the blood stream, and these peptides are the weak platelet inductors.
Methods: Influence of AVP, OT and its new synthetic analogue on the platelet aggregation induced by addition thrombin or adenosine diphosphate (ADP) was studied in experiments in vitro with rat's washed platelets. The new analogue of OT-carbetocin or depotocin (DT) disintegrates much more slowly in the organism owing to its considerable metabolic resistance, which reflects in its prolonged action. 0,05ml of peptides were added to 0.2 ml of the platelet suspension before the aggregation agent was added (0,05ml of ADP or 0,5U of thrombin).
Results: The results of this study demonstrate, that AVP leads to increase of thrombin-induced aggregation (TLA) - stimulation index (SI) - 83 % but doesn't influence aggregation (ADP-IA). OT increases TIA (SI - 26%) and ADP-IA (SI - 18%). DT depresses ADP-IA (inhibition index -InI - 26%) and TIA (InI - 81%). Additional experiments show that DT has very high antithrombin activity (thrombin time was prolonged twice and fibrinogen clotting activity of thrombin is only 1.55 NIH U/ml).
Conclusions: Consequently, neurohypophysal hormones and their synthetic analogues have different effects on platelet aggregation under the action as ADP or thrombin. The most significant reduction occurred under the influence of analogue of oxytocin - depototocin, due to its high antithrombin activity.

C0259
WITH UPDATE ON KARYOTYPES ANOMALIES EVALUATION AS RETROSPECTIVE OBSERVED IN POLYCYTHEMIA VERA DIAGNOSIS AND PREDIAGNOSIS CASES

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Background: Polycythemia vera (PV) is a hematologic neoplastic disorder which is included in the chronic myeloproliferative neoplasia (CMPN).
Methods: In this study we retrospectively evaluated 87 PV patients who were referred to our department for cytogenetic analysis between 1999 and 2015. There were 26 female (30%) and 61 male (70%) patients with a mean age of ~52. Bone marrow aspirate materials were cultured for 24 and 48 hours by uninduced culture technique, with application of GTL banding method, and evaluated according to ISCN in cytogenetic perspective
Results: In 76 (87.4%) of the 87 samples cytogenetic results were obtained. Karyotype was normal in 47 (~62%) patients, whereas in 29 (~38%) cases cytogenetic anomaly was observed. Most frequently observed cytogenetic anomalies were structural and quantitative abnormalities of chromosomes 20 (34.5%), 18 (20.7%), and Y chromosome (20.7%). Less common abnormalities include trisomy 9, structural and quantitative abnormalities of chromosomes 6 and 11 (13.8%) and structural abnormalities of chromosome 13 (10.3%).
Conclusions: According to the current literature cytogenetic anomalies are observed in ~13-35% of PV patients. Most frequent observed cytogenetic anomalies are; 20q and 13q deletion, 8 and 9 trisomies. Cytogenetic anomalies and their evolution is of utmost clinical importance since they have been associated with transformation of PV into other myeloid malignancies like AML, MDS or IMF. Different from the literature in our study we observed low frequency of trisomy 8 (~7%), and high rates of marker chromosomes (20.7%) and loss of Y chromosome (17.2%). Our other findings are in line with the literature. Cytogenetic abnormalities guide clinicians to monitor the disease with regard to prognosis and treatment.

C0285
ENDOMETRIAL MRNA EXPRESSIONS OF CYTOKINES IN WOMEN WITH IN VITRO FERTILIZATION FAILURE

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Background: Implantation is a complex process involving crosstalk between endometrium and embryo. Cytokines play a role on endometrial receptivity in the implantation period. This study was aimed to evaluate endometrial mRNA expression levels of several cytokines in women with previous in vitro fertilization (IVF) failure and control subjects in the implantation period.
Methods: Women with previous IVF failure (n:14) and control subjects (n:17) between the ages of 20 and 35 were recruited for this study. Endometrial sampling was taken between 21-24th days of menstrual cycle from each subject. Samples were preserved in a tube containing RNA later solution which stabilizes RNA in the tissue. After one day storage of samples at +4 C, RNA later solution around the tissue was suspended using pipette. All endometrial samples were stored until the date of RNA purification at -80 C. Total RNA isolation was performed from samples stored at -80 C using commercial RNA isolation kit. cDNA synthesis was done from isolated RNA by reverse transcriptase enzyme and stored -20 C. mRNA expressions of cytokines (IL-17A, IL-10, IL-12A, TGF, IL-20, IL-8, and TNF) were evaluated quantitatively by q-PCR.
Results: When comparing cytokine levels of control and IVF groups, there is an increase 63% in IL-17A, 42% in IL-10, 51% in IL-12A, 41% in TGF, 16% in IL-20, 219% in IL-8, and 22% in TNF in IVF group versus control subjects.
Conclusions: Increased mRNA expressions of IL-17a and IL-8 seem to have a negative impact on endometrial receptivity in women with previous IVF failure.
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C0361
THE EFFECT OF *MYRTUS COMMUNIS* EXTRACT ON RENAL INJURY IN RATS WITH BILE DUCT LIGATION

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Background: Progressive renal failure occurs in patients with chronic liver disease and advanced hepatic failure. Bile duct ligation (BDL) model is used to allow the study of renal function alterations in a short period of time and mimics clinical conditions characterized by obstructive jaundice, such as biliary atresia and choledocal cysts. Myrtus communis (MC) is a very popular plant and has many positive effects on tissues.
Aim: To evaluate the effect of MC extract on kidney tissue factor (TF) activity of rats with BDL
Methods: A total of 32 female, three months old, Sprague-Dawley rats were used. Control group (n=8), control+MC extract group (n=8), BDL group (n=8) BDL+MC extract (n=8, oral). BDL groups were subjected to bile duct ligation. Control+MC and BDL+MC groups received a daily dose of MC extract (50mg/kg dissolved 1 ml in saline) by orogastric tube for 28 days after BDL. Control and BDL groups received 1 ml saline. At the end of experiment

period, the animals were sacrificed under anesthesia, kidneys were taken and homogenized in saline. Tissue factor activity was determined in tissue homogenates.
Results: TF activity was increased significantly in BDL group when compared to control group. MC extract caused a decrease in TF activity when compared to BDL group.
Conclusions: MC extract decreased renal damage induced by bile duct ligation in rats. The beneficial effects of MC extract on renal tissue can be due to improved liver function or due to direct action on the kidney. Further studies are needed to be done.

Anticoagulant drugs

C0049
MONITORING THE EFFECTIVENESS OF THERAPY WITH NEW ORAL ANTICOAGULANTS IN PATIENTS OBSERVED IN LABORATORY HEMOSTASIS AND ATHEROTHROMBOSIS CLINIC ARCHANGELSK

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Background: Anticoagulants are among the most frequently used medicinal drugs in various fields of clinical medicine. Anticoagulants are among the most frequently used medicinal drugs in various fields of clinical medicine. Anticoagulants of older generation is very effective in preventing thromboembolic events, but they have a narrow therapeutic range and considerable individual sensitivity.
All this dictates the need for regular monitoring of anticoagulants, which complicates their use in areas where such monitoring is not organized, or poorly, or the patient does not want/ is not able to closely monitor the effect of the drug. This was the basis to search for new anticoagulants taken orally. On the basis of the laboratory of hemostasis and atherothrombosis 1GKB them. Volosevicth E. E. is a database of patients receiving New Oral AntiCoagulants (NOAC). The generation is very effective in preventing thromboembolic events, but they have a narrow therapeutic range and considerable individual sensitivity. All this dictates the need for regular monitoring of anticoagulants, which complicates their use in areas where such monitoring is not organized, or poorly. This was the basis to search for new anticoagulants taken orally.
Methods: On the basis of the laboratory of hemostasis and atherothrombosis clinic is a database of patients receiving NOAC.
Results: All observed 117 patients, of whom 45 men and 72 women. The average age is 63.9 years.
Patients with atrial fibrillation: low risk bleeding= 20.4%, average= 72.7%, high= 6.9%, the CHADS2-VASC score: 1 point is 4.3%, 2 points and more – 95.7%. CC (creatinine clearance) >60= 61.5%, QC 45-59= 23%, 30-44= 7.8%, <30- 7.7%.
Patients with pulmonary embolism: low bleeding risk= 64%, medium risk= 30%, high - 6%. CHADS2-VASC score: 1 point - 15%, 2 points or more - 85%. CC >60= 89.5%, 45-60 CC= 10.5%.
Patients with DVT/PTFS: low bleeding risk= 63.6%, average= 26.3%, high= 10.1%, CHADS2-vasc score: 1 point to 21%, 2 points and more 79%. CC >60= 89.5%, 45-60 CC= 10.5%.
Patients with AMI/PICS/Stroke/Arterial thrombosis: low bleeding risk= 21.4%, average= 64%, high= 14.6%, CHADS2-vasc score: 1 point to 22%, 2 points or more - 78 %. CC >60= 35%, 45-60 CC= 65%.
Conclusions: It is planned to conduct a study aimed at assessing the quality of life of patients, identify the level of anxiety, evaluation of compliance to treatment by measuring anti-XA activity and anti-IIA

C0087
META-ANALYSIS OF THE EFFECTIVENESS AND SAFETY OF NEW ORAL ANTICOAGULANTS IN THE TREATMENT OF VENOUS THROMBOEMBOLISM.

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Background: The meta-analysis of effectiveness and safety of new oral anticoagulants compared to the standard VTE therapy.
Material and methods: A systematic review was carried out in correspondence with the "PRISMA" statement. In the search systems of PubMed, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), a search was carried out by the following key words: Rivaroxaban, Dabigatran, Apixaban, Deep Vein Thrombosis, new oral anticoagulants (NOAs). Researches included into the meta-analysis had to satisfy the following criteria: RCT evaluating NOAs with VTE patients in comparison with traditional therapy. The ultimate point of effectiveness appeared to be the combination "DVT + fatal or non-fatal PE, and safety was estimated according to the number of major bleeding (MB).
Results: In correspondence with the criteria of inclusion for carrying out the meta-analysis 5 RCTs were included: EINSTEIN-DVT; EINSTEIN-PE; RE-COVER; RE-COVER II; AMPLIFY. Data analysis has shown that the effectiveness of the standard therapy and NOAs is comparable (RR=0.93; 95% CI (0.77-1.12)), p=0.44. The effectiveness is also comparable at the estimation of frequency of repeated thrombosis development (RR=0.82; 95% CI (0.63-1.08)), p=0.16 and the combination of DVT ± fatal or non-fatal PE (RR=1.09; 95% CI (0.84-1.41)), p=0.50. The principal ultimate point of safety of all RCTs was the composite of MB and clinically relevant nonmajor bleeding (CRNMB). The result for the composite of MB and CRNMB on the background of NOAs usage is positively lower (RR=0.70; 95% CI (0.51-0.95)), p=0.02.
Conclusions: At treatment of VTE NOAs possess comparable effectiveness, being, at the same time, safer than the standard therapy.

C0100
THE TREATMENT OF VENOUS THROMBOEMBOLISM

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Background: Today factors IIA inhibitors - dabigatran begun introducing in clinical practice. The aim of our research was to study of the dabigatran etexilate efficacy and safety in the treatment of patients with venous thromboembolism.
Methods: We analyzed medical cards of 27 patients with venous thromboembolism who were treated in the surgical department of Karaganda #1 city hospital during 2009-2014. Men were 18 (66%) women - 9 (34%). The patients' age ranged from 25 to 80 years old and in an average was 54.3 ± 2. The disease mean duration, before admission, was 6.4 ± 2.5 days. Patients were investigated on routine clinical and biochemical blood and urine tests. Patients received dabigatran etexilate in dosage 150 mg 2 times daily within the 6 months.
Results: The probability of pulmonary embolism was in 3 (12%) patients and had the spread character of thrombotic processes according to the ultrasound angioscanning. Floating thrombus was in the femoral vein. The free part length of the blood clot does not exceed 4 cm in all cases. The top of a blood clot was fixed to the vein wall during the first 3 days after the start of anticoagulation therapy which was confirmed by ultrasound. The thrombus growth was not fixed at the patient on the dynamic ultrasound investigation in the course of treatment. The pulmonary embolism was diagnosed in 3 (12%) patients on the lungs computed tomography in the day of admission. Disease relapse detected in 1 (4%) patient. Various

complications of the anticoagulant therapy reported in 4 (16%) patients. Internal bleedings (uterine, urinary and rectal) were developed in 3 (12%) patients. In all cases, they were not clinically significant (not require hospitalization and coagulation therapy) and resolved by a twice reduction of anticoagulant dose. The stable increase, more than the 3 times, of the ALT and AST was discovered in 1 (4%) patient during treatment and therefore the anticoagulant therapy was discontinued at that patient. The thrombosed veins complete recanalization was found in 7 (28%) patients, partial recanalization - in 10 (40%) and occlusion - in 8 (32%) on the ultrasound angioscanning after the 6 months treatment.

Conclusions: The dabigatran etexilate in a dose of 150 mg twice of day within the 6 moths effectively prevents thrombus growth, disease recurrence and the recanalization process of thrombosed veins in the patients with venous thromboembolism.

C0114
APPLICATION OF BASIC AND SPECIAL COAGULATION TESTS FOR MEASURING RIVAROXABAN ACTIVITY

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Background: Rivaroxaban (Xarelto®) is an oral anticoagulant, direct and selective factor Xa inhibitor, which has a predictable pharmacokinetic. It is administered at fixed doses, with maximum anticoagulant effect at 2h-4h after intake. Coagulation studies will be needed in cases of hemorrhagic or thrombotic complication, urgent or planned surgery, and certain specific situations (extreme weight, renal insuficiecia, drug interactions).

Methods: Multicenter study included 51 adult patients with VTE and AF treated with rivaroxaban followed in the University Hospital Fundación Jimenez, UH Gregorio Maranon and UH Clínico San Carlos. Exclusion criteria: patients taking rivaroxaban as primary prophylaxis in orthopedic surgery. The following data were collected: age, sex, weight, indication of rivaroxaban, thrombotic and hemorrhagic history, creatinine, glomerular filtration rate, concomitant diseases, concomitant medication, bleeding risk factors. Coagulation study includes: prothrombin time, cephalin time, fibrinogen. Levels of anti-Xa activity were determined using HemosIL Liquid Heparin kit (Instrumentation Laboratory). The concentration of rivaroxaban was tested by a chromogenic assay using specific calibrators TECHNOVIEW Rivaroxaban High Set Cal. All determinations were performed at 2 and 24 hours after ingestion of the drug.

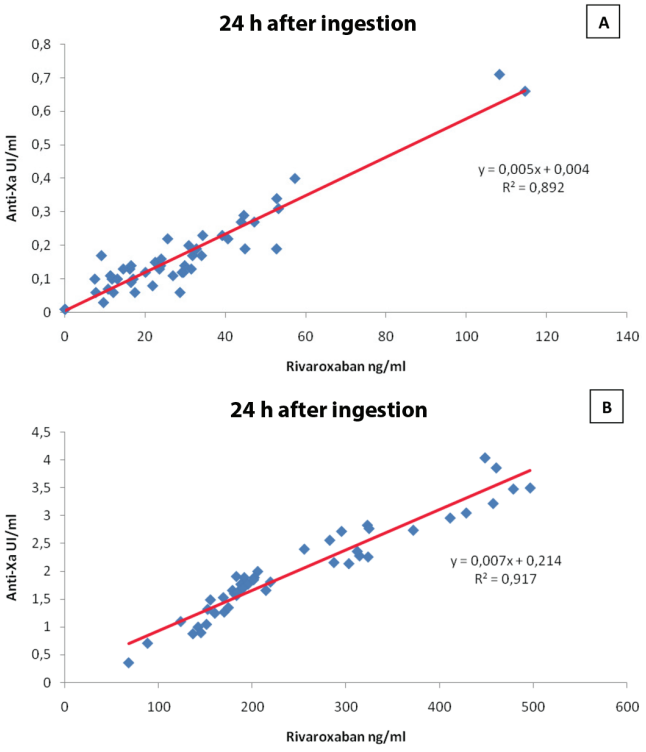

Fig. 1. A) Correlation levels of anti-Xa activity and rivaroxaban after 24 hours. B) Correlation levels and anti-Xa activity after 2 hours rivaroxaban.

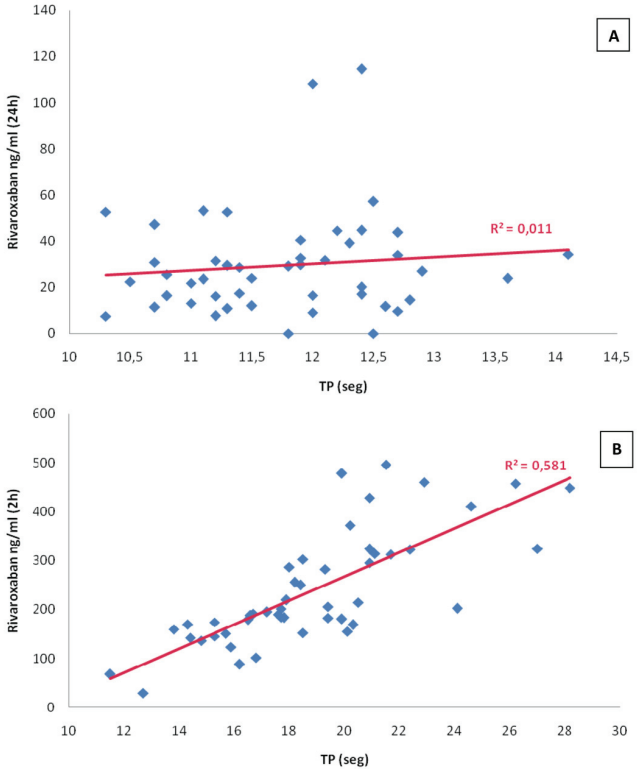

Fig. 2. A) Correlation between TP and rivaroxaban after 24 hours. B) Correlation between TP and rivaroxaban after 2 hours.

Results: The mean age was 65.37±16.37 years (28-89), 45% (n=23) of patients were female and 55% (n=28) were men. 18% received a dose of 15 mg/24h, while the remaining 82% received 20 mg/24h. The average weight was 73.0±11.7 kg. Figures 1 and 2 show the correlation between levels of rivaroxaban and anti-Xa activity and PT. Mean concentration was 239.70 and 29.2 ng/ml at 2 and 24 hours after dosing. There is an interindividual variability in the concentration of rivaroxaban in patients older (289.5 ng /ml) and under 80 (225 ng/ml); which coincides with lower glomerular filtration rate (59.9 vs 78/1 ml/min).

Conclusions: Determination of the rivaroxaban plasma concentration is useful in some clinical circumstances. The anti Xa chromogenic assay with calibrators for rivaroxaban is a quantitative method, easy to perform, allowing us to determine its plasma level. Applying a correction factor rivaroxaban plasma concentration (ng/ml) can be estimated from determination of the anti-Xa activity with a calibrated for heparin (IU/ml) test.

C0139
INFLUENCE OF ANTICOAGULANT THERAPY TYPE ON THE QUALITY OF LIFE IN PATIENTS WITH DEEP VENOUS THROMBOSIS

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Background: Studies have shown efficacy and safety of both classic and new oral anticoagulants (NOACs) in treatment of patients with deep venous

thrombosis (DVT). Quality of life (QoL) in patients receiving different types of anticoagulant therapy remains a subject of interest and research.
Methods: The study included 170 patients with DVT: 103 male (60.58%) and 67 female (39.42%) patients, mean age 57.83 (± 13.3) years. All patients received conservative therapy and were divided into 3 groups: 1 – rivaroxaban 15mg BID for 3 weeks with following 20mg QD (48 patients), 2 – enoxaparin with warfarin therapy (73 patients), 3 – enoxaparin for 8-10 days with following switch to rivaroxaban 15mg BID for 3 weeks with following 20mg QD (49 patients). The Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ) was used to evaluate QoL at admission, 10 days, 1, 3, and 6 months after the onset of treatment: higher scores show poorer QoL.
Results: At admission all patients had a poor QoL (66.5±19.6 points). At 10 days of treatment patients in group 1 had a better QoL (44.7±20.5) as compared to those in group 3 (56.8±19.7) (p=0.043334). Patients in groups 2 and 3 had similar scores at 10 days. Patients in group 1 had a better QoL during all follow-up period reaching 38.2±14.1 points at 6 months. QoL in patients who received warfarin improved by the 1st month (46.9±17.9) and later worsened due to the development of complications (50.6±20.9). QoL in patients in group 3 improved by the 6th month (48.3±17.4), however it was lower as compared to patients in group 1 (38.2±14.1). Thrombus recanalization rates were analyzed in order to understand better the differences in QoL among the patients. At 1 month recanalization rates were considered satisfactory in patients in groups 1 and 3, scoring 58.3% and 63.3%, respectively. Patients in group 2 had lower rates of recanalization (20.5%). At 6 months of anticoagulant therapy recanalization was better in groups 1 and 3 as compared to group 2 (87.5%, 87. 7% vs 54.8%, respectively), which may be attributed to a low treatment compliance in warfarin group (Rosendaal index 54%).
Conclusions: QoL in patients who received rivaroxaban was higher as compared to those who received warfarin. QoL depends on the recanalization rates, affecting the physical score of CIVIQ. A fixed dosage of anticoagulant drug leads to a better treatment compliance and better results according to psychological score.

C0216
EXPLORING POTENTIAL ANTICOAGULANT DRUG FORMULATIONS USING THROMBIN GENERATION TEST

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Background: Many anticoagulant drugs inhibiting proteins of the coagulation cascade have been developed. The main targets of anticoagulant drugs are thrombin and factor Xa; inhibiting these factors delays thrombus growth, thus preventing thrombosis while increasing bleeding risk. A balance between thrombosis and bleeding is ensured in the 'therapeutic window' of the anticoagulant drug concentration range. Novel anticoagulant drugs and combinations thereof are being developed. We rank coagulation factors as potential anticoagulant drug targets in combination with thrombin inhibitors, aptamer HD1 and bivalirudin, providing a background for several promising dual target treatment strategies.
Methods: The thrombin generation test was used to assess the whole coagulation cascade in normal and factor deficient human blood plasma with particular factor content varied in the range of 0-100%. The same plasma with thrombin inhibitors, bivalirudin and HD1, were studied to simulate dual anticoagulant treatment.
Results: Potential therapeutic windows were estimated for coagulation factors, ranking them as targets for anticoagulant drugs. Thrombin and factor Xa have been revealed as the most promising targets, which fully agrees with the current drug development strategy. Inhibitors of factors Va and VIIa are expected to have narrow therapeutic windows. Inhibitors of factors VIIIa and IXa are expected to have a moderate anticoagulant effect. Factors XI and XII are poor targets for anticoagulant drugs. Compared with plasma that is deficient in factor II, the thrombin inhibitors bivalirudin and aptamer HD1 had increased activity. Both inhibitors were tested in deficient plasma providing a model of potential drug combination. The most promising combinations were anti-thrombin with anti-V/Va and also anti-thrombin with anti-IX/IXa. Each combination had an incremental dose-effect dependence that is promising from the standpoint of the therapeutic window.
Conclusions: Although anticoagulant drugs function in various ways, some anticoagulant drug combinations could be evaluated. Pronounced synergetic effects are expected in the case of partial inhibition of factor V with a wide therapeutic window. Factor IX is especially interesting because its restricted effect on thrombin generation could be accentuated with thrombin inhibitors. This combination could substantially decrease thrombin generation without the risk of preventing it completely. This feature could be extremely relevant for therapeutic applications.

C0237
DOES TOPICAL APPLICATION OF TRANEXAMIC ACID DURING CARDIAC ELECTRONIC DEVICE IMPLANTATION AFFECT COAGULATION PROFILE?

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Background: The perioperative use of antithrombotic therapy is associated with increased bleeding risk after cardiac implantable electronic device (CIED) implantation. Topical application of tranexamic acid (TXA) is effective in reducing bleeding complications after various surgical operations. However, there is no information regarding local TXA application during CIED procedures. The aim of this study was to evaluate bleeding time and coagulations tests before and after CIED procedure with topical TXA application in patients receiving uninterrupted dabigatran or rivaroxaban.
Methods: Fifteen consecutive patients receiving uninterrupted dabigatran (n=9) or rivaroxaban (n=6) were included in the study. Concomitant antiplatelet treatment was present in half of the study population. Blood sample were collected 2 hours before and 8 hours after the procedure. Coagulation profile was examined (bleeding time, platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT) and fibrinogen. Fibrinolysis was evaluated by measurement of concentrations of D-dimer. TXA was given topically (by a special technique) in the pocket after pocket formation.
Results: Postoperative values of bleeding time, platelet count, PT, aPTT, TT, fibrinogen and D-Dimer did not change significantly compared to preoperative values. No bleeding and thromboembolic complications occurred in the study group preoperatively. Also, device related problems did not record during 6 months follow-up.
Conclusions: This study demonstrated for the first time that topical TXA application during CIED implantation did not affect coagulation profile.

C0239
THROMBOPROPHYLAXIS WITH RIVAROXABAN AFTER TOTAL HIP AND KNEE ARTHROPLASTY - OUR THREE YEARS EXPERIENCE

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Background: Venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism, is an important complication in a major orthopedic surgery and is associated with significant morbidity and mortality. Therefore, current recommendations suggest that in these patients thromboprophylaxis must be routinely used. The main goal of our study was to track the effectiveness and possible side effects with the drug rivaroxaban used as thromboprophylaxis in patients after total hip and knee arthroplasty.
Methods: Our study is retrospective analysis of the occurrence of thromboembolic and hemorrhagic complications in 232 orthopedic patients (130 patients with total hip arthroplasty and 102 patients with total knee arthroplasty) where drug rivaroxaban (Xarelto) was used as postoperative thromboprophylaxis. According to current recommendations for thromboprophylaxis in orthopedic surgery, the initial dose of rivaroxaban is

10 mg and patients received the drug 6-10 hours postoperatively (depending on postoperative hemorrhage) and then continued with the same dose once every 24 hours. In total knee arthroplasty thromboprophylaxis with rivaroxaban lasted a minimum of 12 days and after total hip arthroplasty at least 35 days.
Results: There were two cases of deep vein thrombosis of the popliteal vein in patients after total knee arthroplasty, proven by ultrasonographic examination and a case of pulmonary thromboembolism (non-fatal) in patients after total hip arthroplasty, diagnosed by angiography of the pulmonary vessels. There was not registered any case of serious or fatal hemorrhage (bleeding that would trigger the use of packed red cells).
Conclusions: Used as thromboprophylaxis after total hip and knee arthroplasty, rivaroxaban is effective and safe anticoagulant drug. The oral administration of the drug is more acceptable to patients and gives an advantage over parenteral administration of low molecular weight heparins. In contrast to vitamin - K antagonists as an oral anticoagulant drug, rivaroxaban has minimal interaction with drugs and food and fixed dose regimen, with no need for regular laboratory monitoring for dose adjustment, which is very important for patients who are less mobile after orthopedic operations. Negative properties of the drug is that even though there is an antidote, it is still not used in routine clinical practice and high cost (in Macedonia this drug is not on the list of medicines covered by the Health Insurance Fund).

C0241
VITAMIN K DEFICIENCY DUE TO STRICT LOW VITAMIN K DIET IN PATIENTS WHO ARE ON LONG-TERM WARFARIN ANTICOAGULATION

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Background: Response to the vitamin K antagonist, warfarin, is affected by several factors that may inhibit or exaggerate its effect, including genetic factors (CYP2C9), dietary intake, medications and comorbidities. The aim of this study was to explore the acquired vitamin K deficiency in patients who are on long term warfarin anticoagulation.
Methods: We investigated 205 patients who are on long-term warfarin anticoagulation for atrial fibrillation. They were 85 men and 12 women, aged 72 ± 13.2, (range 51-107) years, who are on long-term warfarin anticoagulation for atrial fibrillation and presented with International Normalization Ratio (INR) above the therapeutic level of 2-3. Medications and comorbidities that may exaggerate warfarin effects were excluded.
Results: INR was 4.2 ± 0.7 (range 4.1-7.7). Two male patients presented with intracranial bleeding, 7 patients presented with gum bleed (3 men and 2 women), 35 with bruises (14 men and 21 women) and 164 were asymptomatic. There was no correlation between INR level and severity of bleeding.
Conclusions: Strictly low vitamin K diet may potentiate warfarin effect and lead to serious bleeding due to vitamin K deficiency.
Recommendation: Patients on long-term warfarin need to be continuously assed for factors that may inhibit or potentiate warfarin effect, particularly, diet and medications including herbal medicine.

C0301
RELEVANCE OF THE CYP2C19 POLYMORPHISM FOR LOADING AND MAINTENANCE DOSE OF PRASUGREL AND CLOPIDOGREL TREATMENT EFFECT IN CORONARY ARTERY DISEASE PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION: THE PRAISE-GENE STUDY

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Background: CYP2C19 polymorphism has been reported to be associated with altered antiplatelet activity of clopidogrel. On the other hand, prasugrel exerts greater and more consistent platelet inhibition with rapid onset when compared to clopidogrel in both healthy subjects and stable coronary artery disease patients. We sought to compare the effect of prasugrel and clopidogrel on CYP2C19*2 or *3 loss of function (LOF) alleles in patients undergoing percutaneous coronary intervention (PCI).
Methods: In this prospective, two-center, randomized, open-label study, patients with LOF who had undergone PCI were enrolled. Eighteen patients out of forty five gene screening by the Spartan RX CYP2C19 system (Spartan Bioscience Inc, Ottawa, Canada) were randomized to either clopidogrel (600 mg LD, followed by 75 mg MD daily) or prasugrel (30 mg LD, followed by 5 mg MD daily). The primary endpoint was HPR at 24 hours after PCI, as determined by the VerifyNow assay.
Results: Higher inhibition of platelet aggregation was observed in the prasugrel group than the clopidogrel group (Pre-PCI: 236.7±70.6 vs 267.7±60.9, p=0.352; Post-PCI: 79.7±104.7 vs 221.6±45.7, p=0.002; 30 days: 206.4±60.2 vs 132.6 ±60.4, p=0.028).
Conclusions: Compared to clopidogrel, prasugrel led to a greater reduction platelet reactivity in CYP2C19*2 or *3 loss of function (LOF) alleles patients who underwent PCI. Periprocedural myocardial necrosis and clinical follow up will be presented.

C0330
STRATEGY OF ANTICOAGULATION THERAPY IN CANCER PATIENTS

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Background: Thrombophilia is a serious risk factor for cancer patients.
Aims: To determine the optimal mode of appointment of antithrombotic prophylaxis in perioperative period in cancer patients.
Methods: The study involved 889 patients with gynecological cancer in the perioperative period.
Group I - LMWH for 10 days before surgery 0.3 ml, cessation of therapy 24 hours before surgery, then 0.3 ml for 10 days postoperatively - 213 patients.
Group II - LMWH 24 hours before surgery, then 0.3 ml for 10 days in postoperative period - 212
Group III - LMWH 0.3 ml for 10 days postoperatively - 216
Group IV - unfractionated heparin 5000 IU 3 times a day for 10 days in the postoperative period - 248
Results: Before surgery rate of subcompensated DIC was 18.5-50%. After surgery rate of subcompensated DIC has increased significantly to 52-75%.
In group I, normal levels of DIC markers (TAT, PF4, F1+2) has been observed in 1-3 days.
In group II normalization of DIC markers has been observed in 3-5 days.
In group III DIC markers tended to normalize in 5-7 days.
In group IV normalization of DIC markers has been detected only on the 7th day. D-dimer in some patients remained heightened for up to 10 days. In addition, 28 patients (13.7%) formed extensive bruising in the painful injection.
Conclusions: The proposed scheme prophylaxis: LMWH 10 days before surgery and cancel 24 hours prior to surgery, then 0.3 ml for 10 days in the postoperative period - virtually eliminates the risk of thrombosis and contributes normalization of DIC markers in 3 days. This scheme could be recommended for all cancer patients as a minimum program.

C0337
A CASE OF PROLONGED COAGULOPATHY CAUSED BY SUPERWARFARIN POISONING IN A WORKER

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Background: Superwarfarins are long-acting coumarin derivatives. Poisoning should be suspected when an acquired bleeding disorder due to

persistent deficiency of vitamin K dependent clotting factors and a lack of sustained response to treatment with conventional doses of vitamin K are present.

Methods: Herein, we describe a case of superwarfarin poisoning.

Results: A 40-years-old man was referred to outpatient clinics with a month history of recurring epistaxis and hemarthoses. Administration of fresh frozen plasma (FFP) temporarily corrected the markedly abnormal international normalized ratio (INR), prothrombin time (PT) and activated partial thromboplastin time (aPTT). A sustained deficiency of vitamin K-dependent clotting factors II, VII, IX, X was noticed; Factor II: 26.9%, Factor VII: 0.1%, Factor IX: 13.3%, Factor X: 23.5%, factor V: 82%, factor VIII: 131%, INR: 4.04, PT: 48.5 sec, aPTT: 48.3 sec, d-dimer: 21 ng/mL, fibrinogen: 5.01 g/L. INR and PT normalized in the dilution assay excluding any acquired inhibitors. A hypochromic microcytic anemiain accordance with chronic blood loss was present. Platelet count was 164 x 10^9/L. Peripheral blood smear showed no fragmentation.

Liver function tests, hepatobiliary ultrasound and endoscopic examinations of the gastrointestinal tract were normal. Intoxication with an anticoagulant superwarfarin remained a possible diagnosis of exclusion. Blood and urine levels of warfarin were studied at biochemistry laboratory of Forensic Medicine Institute in Ankara and revealed a high blood level of warfarin, 32 ng/dL, and a positive urine test. Thereafter, the patient admitted that he has been working as a car washer and using various chemicals against rats in the working environment. Despite treatment with both oral and intravenous vitamin K, he continued to bleed. FFP and when required factor concentrates were given during the bleeding episodes. Continuous use of oral vitamin K in long term normalized his coagulation tests and bleeding episodes disappeared.

Conclusions: This classical clinical picture can easily be undiagnosed if not evaluated properly. Awareness is important for health care providers to enable early and proper diagnosis. Community education to prevent toxic exposure is also important in prevention. Long-term vitamin K supplementation is the recommended treatment. In order to predict the treatment period with vitamin K, half-life of the superwarfarin can be estimated by repeated measurements of toxic molecule blood levels.

C0340
EFFICIENCY OF DIRECT ORAL ANTICOAGULANTS ON ANTIPHOSPHOLIPID ANTIBODY SYNDROME: A CASE REPORT

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Background: The antiphospholipid-antibody syndrome (APS) is an acquired autoimmune disorder characterized by arterial and/or venous thromboembolism associated with persistent antiphospholipid antibodies (aPL). Thrombotic events (TE) may occur under anticoagulant therapy (AC) and selection of AC is challenging. We present a case with recurrent TE under warfarin and low molecular weight heparin (LMWH) and results with rivaroxaban and dabigatran for the prevention of TE.

Case: 38year old male presenting to emergency department with dyspnea and chest pain. Thrombosis was detected in right pulmonary artery by thorax CT-angiography. He did not state previous or family history of thrombosis and he was free of temporary thrombosis risk factors and low extremity venous doppler imaging was normal. IgG type anticardiolipin antibody was 47 U/ml. Though lupus anticoagulant and anti- β2 antibodies were negative. LMWH and warfarin treatments were given consequently. LMWH was replaced with acetil salisilic acid (ACA). Warfarin plus ACA treatment was continued for 6 months and 6 days after the cessation of treatment left non-massive pulmonary embolism was developed. LMWH and warfarin treatment was given. On the 18th month of warfarin treatment, bilateral femoral artery occlusion was observed. Treatment was replaced with clopidogrel 75 mg, ACA 300 mg and rivaroxaban 30 mg and 20 mg for maintenance. At the 30th month of this treatment progression was observed in the pulmonary artery occlusions and rivaroxaban was replaced with enoxaparine 6000U twice daily. He was clinically diagnosed as heparin induced thrombocytopenia while on LMWH and fondaparinux 7.5mg/day was started. After the normalization of platelet counts, treatment was reorganized as dabigatran 150 twice daily, clopidogrel 75 mg and ACA 300 mg. On the second month of this treatment left renal artery occlusion was observed and after the thrombolytic treatment, he is now followed up on 5 mg fondaparinux.

Conclusions: The superiority of DOACs in patients with APS is still unclear. In this case the antithrombotic effects of factor Xa inhibitors (fondaparinux and rivaroxaban) were observed to last longer than a direct thrombin inhibitor, dabigatran. Further studies are needed to evaluate the effects of factor Xa inhibitors in patients with severe thrombotic potential.

C0350
ASSESSEMENT OF QUALITY OF ANTICOAGULATION WITH VKA IN PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

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Background: Antiphospholipid syndrome (APS) is an autoimmune thrombophilia that can affect both the venous and arterial circulations, with recurrence often occurring in the same vascular bed of the original thrombotic episode.

Antithrombotic drugs, including oral vitamin K antagonists (VKA), are the therapeutic cornerstone for patients with antiphospholipid syndrome (APS) and thrombosis. Although VKA are highly efficacious in the prevention and treatment of thromboembolic disease, optimal use of these agents in clinical practice is challenged by their narrow therapeutic window.

The proportion of time spent in the International Normalized Ratio (INR) range of 2.0-3.0 (TTR) is important for the safety and effectiveness of AVK anticoagulation, and TTR below 60% indicates that AVK therapy is inefficient. The aim of this study was to analyse the TTR in a population affected by APS on treatment with VKAs, in comparison to AF patients.

Methods: We performed a retrospective observational study including 30 APS and 30 Atrial Fibrillation (AF) patients, admitted to outpatient clinics between August 2014 and January 2016, all treated with Warfarin (INR target 2.5).

TTR values of patients were calculated by using Rosendaal method and TTR of APS patients vs. AF patients were compared using Student unpaired t test. Multivariable linear regression analysis was performed including factors potentially affecting TTR including: age, gender, presence of APS (vs. AF), weight and height. (SPSS-23.0, SPSS Inc.).

Results: Among the 60 patients included in this analysis, there were 897 INR measurements over a median of 13 months of follow-up. The median number of INR draws per patient was 13.

The mean age was 45 ± 14.6 years for APS patients and 71 ± 10.35 years for AF patients.

Mean TTR of APS patients was 60.1% vs. 78.0% of AF patients ($p = 0.001$). A multivariable linear regression analysis confirmed that the presence of APS (vs. AF) was independently associated with a worse TTR (r^2=18.7%, p=0.001). Analysis of the time outside the therapeutic range revealed that, for both groups of patients, the time above therapeutic range, exceeded that below therapeutic range ($p<0.001$).

Conclusions: In our study, we found that APS patients had lower TTR values than AF patients, although patients with AF were significantly older. As APS patients disclose a lower quality of anticoagulation with AVK, we believe the efficacy of non-vitamin K oral anticoagulants in this high-risk patients should be tested.

C0372

PRE-EXISTENCE OF PROTHROMBOTIC STATE IN PATIENTS WITH ATRIAL FIBRILLATION DESPITE THERAPY WITH NEW AND TRADITIONAL ANTI-COAGULANT DRUGS

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Background: Oral anticoagulants such as warfarin (W) have been conventionally used for the management of atrial fibrillation (AF). Despite the effectiveness of W, its use in AF patients requiring anticoagulation is suboptimal with an even greater underuse seen in elderly patients who are at higher risk of stroke. New oral anticoagulants such as rivaroxaban (R) and apixaban (A) have been approved to manage thrombotic and cardiovascular disorders including AF.
Objective: To profile the baseline level of circulating thrombogenic biomarkers von Willebrand Factor (vWF), prothrombin fragment 1.2 (F1+2), microparticle bound tissue factor (MP-TF) and plasminogen activator inhibitor (PAI-1) in patients with AF. Additionally, the effect of both newer (R and A) and traditional (W) anticoagulants on the levels of thrombogenic biomarkers in patients with AF will be assessed.
Methods: Citrated blood was drawn from thirty AF patients prior to ablation surgery and spun at 3000 rpm to obtain platelet poor plasma. Normal plasma samples from healthy controls were purchased from a commercial source (George King Biomedical, Overland Park, KS). The plasma samples were analyzed using a biochip array (Randox, London, UK) for metabolic syndrome biomarkers including PAI-1 and ELISA kits for vWF, MP-TF (Hyphen BioMed, Nueville-Sur-Oise, France) and prothrombin F1+2 (Siemens, Newark, DE).
Results: Circulating levels of vWF, MP-TF and PAI-1 were statistically increased in patients with AF compared to normal ($P<0.0001$, $P<0.0001$, and $P=0.0014$, respectively). Circulating levels of prothrombin F1+2 showed no difference between the AF and normal group ($P=0.2696$). AF patients (n=30) were divided into two groups based on their usage (Group 1, n=21) and non-usage (Group 2, n=9) of any anticoagulant. Furthermore, those on anticoagulants were divided based on their use of newer (R and A, Group 3, n=16) or traditional (W, Group 4, n=4) anticoagulants. A statistical increase in vWF ($P<0.0001$), MP-TF ($P<0.0001$) and PAI-1 ($P=0.011$) remained in Group 1 compared to normal while a statistical increase in prothrombin F1+2 ($P=0.0343$) and PAI-1 ($P=0.0040$) were noted in Group 2 compared to normal. vWF ($P=0.0036$) and MP-TF ($P=0.0059$) were elevated in Group 1 compared to Group 2 while prothrombin F1+2 ($P=0.0697$) and PAI-1 ($P=0.4548$) showed no difference between the two groups. Furthermore, there was no statistical difference in the level of any thrombogenic biomarker in AF patients between Group 3 (R and A) and Group 4 (W).
Conclusions: Elevated levels of vWF, MP-TF and PAI-1 seen in AF patients compared to normal provide insight into an additional risk of thrombogenesis associated with AF which is not targeted by current anticoagulant medications. Of the 30 patients examined in this study, 8/9 (89%) patients who were not on anticoagulants had a stroke risk stratification score of 0 while 20/21(95%) patients who were on anticoagulants had a score of >1. This data suggests that although very effective in lowering prothrombin F1+2 levels in AF, the newer anticoagulants, R and A, and the traditional anticoagulant, W, still leave additional prothrombotic biomarkers unaffected. Thus additional pharmacological interventions may be needed to optimize the management of thrombotic stroke in atrial fibrillation.

C0375

OVINE AND PORCINE HEPARINS EXHIBIT BIOSIMILARITIES IN CONTRAST TO BOVINE COUNTERPARTS

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Background: The currently used unfractionated heparin (UFH) and low molecular weight heparins (LMWH) are mostly derived from Porcine mucosal tissue. Since the technology to manufacture heparin has advanced and the quality assurance practices are in place, improved products with high potency and purity are now available. Considering these factors the resourcing of heparins utilizing bovine (cow) and ovine (sheep) tissues is discussed at regulatory and pharmaceutical levels. The purpose of this study is to compare 5 individual batches of UFH obtained from Bovine, Ovine, and Porcine origin and their depolymerized product obtained by benzylation followed by alkaline hydrolysis representing enoxaparins.
Methods: The molecular profile of the heparins and enoxaparins from various sources were determined using the size exclusion method. The anticoagulant potency was measured use clot based methods such as aPTT and Thrombin Time. Chromogenic substrate based methods were used to determine the USP potency in terms of anti-Xa and anti-IIa activities (Hyphen Biomedical, Ohio, USA). The interaction between AT and heparins and enoxaparin were investigated in a purified biochemical system, using AT supplemented buffered assay.Thrombin Generation inhibition studies were carried out using a flourometric method (Technoclone, Vienna, Austria).The relative interaction of the heparins and enoxaparins with heparin induced thrombocytopenia (HIT) antibody induced aggregation of platelets were investigated using serum pool obtained from clinically confirmed HIT cases using aggregometry.
Results: The molecular profile of the Bovine, ovine, and porcine heparins and enoxaparin were almost identical. The global anticoagulant and amidolytic protease assays for the bovine heparin were consistently lower than porcine and ovine samples. In the purified system the Porcine and Ovine preparations consistently showed lower IC50 values for both the thrombin and Xa inhibition in contrast to the bovine heparin. Similar trends were observed in the anti IIa assays. The USP potency of the Porcine and Ovine heparins ranged from 180 to 190u/mg, whereas the Bovine was found to be 130-140 u/mg.The anti-Xa – IIa ratio for the heparin were comparable. The ovine and porcine enoxaparin exhibited comparable potencies which ranged 94-110 u/mg whereas bovine enoxaparin was slightly lower 80-87 u/mg. However the antiXa and anti-IIa ratios were comparable. The AT mediated inhibition of factor Xa and anti-IIa was stronger with heparins in comparison to the enoxaparins. Similarly heparins produced stronger inhibition of thrombin generation in comparison to the enoxaparin. In the HIT screening there was no difference between the HIT responses in the heparins from different species. Similar results were obtained with enoxaparins.
Conclusions: These studies show that while bovine, ovine and porcine heparins and enoxaparins exhibit comparable molecular profiles however in some of the functional assays bovine heparin and enoxaparin exhibited somewhat lesser potencies especially in the pharmacopeial assays. No differences were noted in the HIT antibody interactions among heparins and enoxaparins from different species. These studies demonstrate that ovine and porcine heparins are biosimilar and can be developed as such for clinical purposes. Potency adjustment for in vivo usage may be required to obtain comparable anticoagulant responses for the bovine heparin and enoxaparin.

Antithrombotic drugs

C0175

PROTEOLYSIS AND ISOPEPTIDOLYSIS DURING THROMBOLYSIS

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Background: All worldwide publications dedicated to thrombolysis optimization are based on the ideas of thrombus degradation as the stabilized fibrin-polymer proteolysis. Isopeptide bonds undegradable by proteases remain within D-D dimers as stabilized thrombi terminal degradation products. By discovering enzyme Destabilase endo-ε-(γ-Glu)-Lys isopeptidase and designing the means for producing recombinant

protein, it became possible to assess a state of developing thrombi depending on degree of their stabilization. Owing to this, it started to elaborate the conception of the mechanisms underlying fibrinolysis and thrombolysis.
Methods: The study was conducted with male Sprague Dawley rats (weight 450-550 g, age 5 months, total 46 rats). All animals were surged to provoke $FeCl_3$-induced thrombosis (10% $FeCl_3$): arterial – in carotid artery (23 rats) or venous – in jugular vein (23 rats). In each model of thrombosis there were 3 groups. 24h after the onset animals of Group 1 were intravenously injected with saline, Group 2 –Streptokinase, Group 3 – Destabilase. After that, 48h after the onset thrombi were removed, weighed, dissolved in 2% acetic acid and evaluated to measure thrombi stabilization degree.
Results: Destabilase administration decreased weight of venous thrombi vs. saline- and streptokinase-treated rats by 47.5% ($p<0.01$) and 40.3% ($p<0.05$), respectively. After administering Streptokinase and Destabilase, weight of arterial thrombi was reduced by 36% ($p<0.01$) and 74% ($p<0.01$), respectively. The thrombus stabilization degree during venous thrombosis showed no differences between groups. However, administration of Destabilase decreased arterial thrombus stabilization degree by 200% ($p<0.01$) and 227% ($p<0.01$) compared to saline- and streptokinase-treated rats, respectively. Arterial thrombus stabilization degree was similar in saline- and streptokinase- treated rats ($p=1$).
Conclusions: Intravenous administration of recombinant Destabilase is followed by thrombi slow (> 24h) dissolution. Degree of thrombolysis stimulated by Destabilase was higher than by Streptokinase, clinical thrombolytic agent. In similar setting, degree of lysis was higher for arterial vs. venous thrombi. Degradation of isopeptide bonds by Destabilase was a crucial parameter for stabilized fibrin lysis. It results in slow spontaneous transition of the old thrombi from solid to soluble state. Thus, Destabilase is able to perform thrombolysis independent of proteolysis.

C0228
ANTITHROMBOTIC ACTIVITY OF HEPARIN COMPLEXES WITH PEPTIDES

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Background: Natural heparin and its complexes are the main anticoagulants of the organism (Walenga J., 2012). Previously it is established that the complexes of heparin with the peptides and some amino acids have anticoagulant, fibrinolytic and antiplatelet activity in vitro and in vivo. The interaction of heparin with these compounds is due to its structural properties. Short proline-containing peptides Pro-Gly and Pro-Gly-Pro also have antithrombotic effects (Ashmarin et al., 2008).
Aim: The aim of this study was to investigate the possibility of a combination of arginine, Pro-Gly and Arg-Pro-Gly with heparin to participate as inhibiting agents in the conversion of fibrinogen to fibrin.
Methods: Peptides (Institute of molecular genetics Russian Academy of Sciences) and heparin with high molecular weight (Hep) ("Serva") were used in this investigation. The formation of heparin complexes with arginine (R), peptide Arg-Pro-Gly (RPG) and Pro-Gly (PG) was proved by biochemical methods. The rat model of pretrombosis (the generation of thrombin in the bloodstream) and standard methods registration of platelet aggregation, anticoagulant activity (APTT-test), fibrinolytic activity of blood plasma were used in experiments.
Results: 10 minutes after intravenous injection of complexes Hep-RPG, Hep-PG and Hep-R high degree of fibrinolytic, anticoagulant and antiplatelet activity was observed in rat blood. On rat models of prethrombosis it was showed that preliminary intranasal introduction (before thrombus formation) of heparin-peptides complexes (1 mg/kg body weight) prevented the formation of fibrin clots and the formation of blood clots accordingly. The received results can be presented by degree of reduction effects of thrombus formation prevention in the following way: Hep-RPG (85-90%) > Hep-PG (78 - 82%), Hep-R (50-57%).
Conclusions: The complexes of heparin high molecular weight with amino acid arginine, peptides Pro-Gly and Arg-Pro-Gly prevented development of thrombus formation. Thus, peptides and their heparin complexes can be used as the long-term antithrombotic agents.

C0238
MAJOR BLEEDING COMPLICATIONS DURING CARDIAC ELECTRONIC DEVICE IMPLANTATION IN PATIENTS RECEIVING ANTITHROMBOTIC THERAPY: DO LOCAL TRANEXAMIC ACID HAVE ANY PREVENTIVE ROLE?

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Background: The perioperative use of antithrombotic therapy is associated with increased bleeding risk after cardiac implantable electronic device (CIED) implantation. Topical application of tranexamic acid (TXA) is effective in reducing bleeding complications after various surgical operations. However, there is no information regarding local TXA application during CIED procedures. The purpose of our study was to evaluate major bleeding complication rates during CIED implantation with and without topical TXA use in patients receiving antithrombotic treatment.
Methods: Consecutive patients undergoing CIED implantation while receiving warfarin or dual antiplatelet (DAPT) or warfarin plus DAPT treatment were included in the study. Study population was divided in two groups according to presence or absence of topical TXA use during CIED implantation. Major bleeding complications (MBC) defined as any bleeding leading to transfusion, surgical intervention for pocket evacuation or revision, pericardial effusion, hemothorax, or life-threatening bleed. Thromboembolic events were defined as transient ischemic attack, stroke, myocardial infarction, deep vein thrombosis, and pulmonary embolism within 90 days of procedure.
Results: A total of 135 consecutive patients were identified and included in the analysis. The mean age was 60 years old. Topical TXA application during implantation was reported in 52 patients (TXA group). The remaining 83 patients were assigned to the control group. The major bleeding complication rate was lower in TXA group compared to control group (5.8% vs 20.5%, P= 0.024). Univariate logistic regression analysis identified history of recent stent implantation, perioperative warfarin use, perioperative warfarin plus DAPT use and topical TXA application during CIED procedure as predicting factors of MBC. Multivariate analysis of factors with $P<0.1$ in univariate analysis showed that perioperative warfarin plus DAPT use (OR = 8.144, 95% CI: 2.589-25.618, $P < 0.001$) and topical TXA application during CIED procedure (OR = 0.170, 95% CI: 0.042-0.690, P = 0.013) were independent predictors of MBC. No thromboembolic complications was recorded in the study group.
Conclusions: The present study demonstrated for the first time that the topical TXA application during CIED implantation is associated with reduced MBC in patients with high bleeding risk.

C0254
EXPLORING THE SPECIFICITY AND OPTIMAL CONDITIONS FOR EXPRESSING THE MAXIMUM ACTIVITY OF THE NOVEL ANTIPLATELET AGENT VORAPAXAR, IN VITRO

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Background: Protease-activated receptors (PARs) 1 and 4 are expressed on human platelets and mediate thrombin induced activation, thus playing a crucial role in atherothrombosis. Vorapaxar is a reversible oral PAR-1 antagonist, which has recently been approved for the secondary prevention of atherothrombotic events in patients with a history of myocardial infarction or peripheral arterial disease. The aim of the present study was to further shed light into the specificity and optimal experimental conditions for the expression of maximum antiplatelet activity by vorapaxar, *in vitro*.

Methods: Platelets in platelet-rich plasma (PRP) prepared from whole blood of healthy volunteers were incubated with vorapaxar at various concentrations ranging from 0 to 5μM for several time intervals up to 60 min at 37°C. Platelets were activated by various agonists, TRAP-6, ADP, arachidonic acid, collagen or the specific PAR-4 activating peptide (AYPGKF-NH_2). Platelet activation was monitored by light transmittance aggregometry (LTA) and flow cytometry (FC) determining the membrane expression of P-selectin (CD62P-PE) and the activation of the integrin-receptor αIIb/β3 (PAC-1-FITC binding).
Results: Vorapaxar at any concentration and at any time interval studied, did not influence platelet activation (platelet aggregation, P-selectin expression and PAC-1 binding) induced by ADP, arachidonic acid, collagen or AYPGKF-NH_2. As expected vorapaxar inhibited platelet activation induced by the PAR-1 agonist, TRAP-6, in a dose-dependent manner. However, its potency was highly influenced by the incubation time, the time required to express its maximum anti-aggregatory activity being 60min (IC_{50} value: 0.09μM), whereas the time required for the maximum inhibition of PAC-1 binding and P-selectin expression was 30min (IC_{50} values: 0.91μM and 1.00μM, respectively).
Conclusions: Vorapaxar is a highly specific towards PAR-1 antiplatelet drug, however at concentrations similar to those administered in patients in the two phase 3 clinical trials, it may not immediately influence the platelet functionality but rather it is a slow-acting antiplatelet agent. This phenomenon may explain, at least partially, the results of the TRACER clinical trial in which vorapaxar was administered in patients with acute coronary syndromes.

C0272
IDENTIFICATION OF NEW BIOMARKERS FOR HIGH ON-TREATMENT PLATELET REACTIVITY TO ASPIRIN AND CLOPIDOGREL

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Background: Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is one of the cornerstone therapies for the secondary prevention of an atherothrombotic event in patients with an acute coronary syndrome (ACS). However, a considerable number of patients continue to experience recurrent ischemic events due to individual variability in response to aspirin or clopidogrel or both drugs. The aim of this study was to investigate new platelet activation parameters that could be associated with high on-treatment platelet reactivity (HTPR) to aspirin or clopidogrel in ACS patients undergoing percutaneous coronary intervention (PCI).
Methods: Citrated blood was collected from 118 ACS patients at 5-days after the administration of DAPT with aspirin (100mg/day) and clopidogrel (600mg loading dose, 75mg/day). HTPR to aspirin was determined using platelet aggregation to arachidonic acid (AA) by Light Transmittance Aggregometry (LTA) (% aggregation to AA>20) whereas HTPR to clopidogrel was assessed by VASP analysis (PRI values; platelet reactivity index >50%). We determined TRAP-14-induced platelet aggregation by LTA, the membrane expression of P-selectin and integrin-receptor $\alpha_{IIb}\beta_3$ by flow cytometry in resting and activated with ADP platelets as well the levels of secreted RANTES, GM-CSF, VEGF, IL-1β and IL-8 in plasma using Bioplex system. The levels of plasma thromboxane B_2 and urine 11-dehydro TxB_2 were also determined by ELISA.
Results: The 21% of patients (AA-Aggregation=38.5±18%) exhibited HTPR to aspirin and the 33% of them (PRI=66.5±13%) showed HTPR to clopidogrel. Among all studied platelet parameters, those correlated with HTPR to aspirin were the platelet aggregation to TRAP-14 (r=0.319, P=0.004) and the expression of integrin $\alpha_{IIb}\beta_3$ in resting platelets (r=0.293, P=0.032). Furthermore, the platelet parameters correlated with HTPR to clopidogrel were the platelet aggregation to TRAP-14 (r=0.307, P=0.04), the membrane expression of $\alpha_{IIb}\beta_3$ in resting platelets (r=0.445, P=0.014) as well as the membrane expression of P-selectin either in resting (r=0.489, P=0.04) or in ADP-activated platelets (r=0.525, P=0.002).
Conclusions: We identified a series of platelet parameters that are correlated with HTPR to aspirin or clopidogrel. Importantly, most of these parameters are correlated with HTPR to both drugs suggesting that there may be common pathways underlying the HTPR to aspirin and clopidogrel in ACS patients underwent PCI.

C0316
EVALUATION OF RESISTANCE TO STANDARD ANTIPLATELET THERAPY IN PATIENTS UNDERGOING UNSTABLE ANGINA

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Background: The aim of the study was to evaluate the resistance to standard antiplatelet therapy and its effect on clinical outcomes in patients with unstable angina.
Methods: The study included 102 patients with unstable angina. Laboratory studies included: General blood analysis, biochemical blood analysis with determination of lipid profile, the level of thrombin; coagulation hemostasis (level of fibrinogen (FG), antithrombin III (AT III), D–dimer, factor XA). Aggregatogram impedance on the MULTIPLATE device with the determination of ASPItest, ADPtest, TRAPtest (inductor - thrombin) and COLtest (inductor - collagen).
Results: Over 18 months of follow-up of 55 patients showed a favorable course of the disease and 47 persons - with the development of recurrent coronary events (in 2 of 102 patients developed Q-myocardial infarction, 9 patients underwent CABG, in 27 cases performed stenting of coronary arteries).Rhythm disturbances (short paroxysms unstable ventricular tachycardia) was observed in 5 patients. Three patients with unstable angina died suddenly from acute coronary insufficiency, one had developed recurrent polymorphic ventricular tachycardia, followed by asystolia. Mortality was 3.9%.
The patients with cardiovascular complications during the period 1-18 months of follow up had a significantly higher level of endogenous thrombin potential (p=0.002), peak concentration of thrombin (p=0.001), time of peak concentration (p=0.04) and indicating activation of coagulation blood potential in this subgroup and the inefficiency of the ongoing antiplatelet therapy. According impedance agregatogrammy revealed that among those included in the study, 18 (17.64%) of the patients recorded decreased sensitivity to aspirin in the standard dose of 75 mg in 24 patients (23.5%) to clopidogrel 75 mg and 9 persons (8.8%) -to aspirin and clopidogrel, i.e. at 32.3% of the people included in the study revealed a high residual platelet reactivity in patients receiving standard doses of antiplatelet agents.
Conclusions: Over 18 months of follow-up resistance to ASA and clopidogrel more than 2.5 [CI, 1.9; 2.8] increases the likelihood of the recurrent ischemic complications despite ongoing standard antithrombotic therapy. Suggested screening predictive model of the development of adverse outcomes in patients with unstable angina, which includes the following indicators: ASPI- test (AUC)> 56U, ADP- test (AUC)> 62U, MPV ≥ 9,6fl, under which increases the risk of recurrent coronary events 12 times.

C0318
THE EFFECTS OF THROMBOLYTIC THERAPY ON THE CYTOKINE PROFILE OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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Background: To study the cytokine profile (TNF-α, IL-1β, IL-6 and IL-10) in the patients with acute myocardial infarction (AMI) with ST segment elevation, who received thrombolytic therapy (TLT).

Methods: The study included 88 patients with AMI with ST-segment elevation admitted to the emergency cardiologic department. The average age of the patients was 52.4 ± 8.4 years. The control group consisted of 100 healthy participants of similar age. The cytokine profile (TNF-α, IL-1β, IL-6, IL-10) of all the patients was studied after the admission. Sets of reagents for human cytokines for ELISA ("Vector - Best", Russia) were used to determine the cytokine profile. The patients were divided into two groups: 1st group – patients who received Actilyse as TLT (n=67), and the 2nd group – patients who did not received TLT (n=21). Also, no TLT was administered on late hospitalization (more than 12 hours after the onset of AMI) and existence of contraindications. The data were processed using a statistical analysis software package Microsoft Excel 2007 and SPSS version 20.0 software (Licensed to Semey State Medical University, Kazakhstan).
Results: In the group 2 (no TLT) AMI patients, the levels of pro-inflammatory cytokines IL-6, TNF-α were 2.2 times lower than in the group 1 ($p < 0.005$). The levels of IL-10 in patients of the 1st group was 1.8 times higher than in the 2nd group ($p < 0.005$). No prognostic significance was found in the IL-1β levels. Thus, it appears that the mechanism by which the TLT has also anti-inflammatory effects in the AMI patients is directly related to the correlation of inflammatory process and thrombus formation. In the present study, the proinflammatory cytokine profile decreased in the patients of the group 1 who received TLT, compared to the patients of the group 2. Conceivably, the above can explain the rapid decrease in the inflammatory component.
Conclusions: 1) In the AMI patients a systemic inflammation was detected. It was reflected in the increased levels of inflammatory cytokines TNF-α, IL-6, which are proinflammatory markers. 2) The decease of concentrations of TNF-α, IL-6 in the patients, who received TLT, indicates the effectiveness of TLT, which suppresses systemic inflammation.

C0345
EVALUATION OF TIME IN THERAPEUTIC RANGE IN ANTICOAGULATED PATIENTS WITH VENOUS THROMBOEMBOLISM: A SINGLE-CENTER, RETROSPECTIVE, OBSERVATIONAL STUDY

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Background: Patients with venous thromboembolism (VTE) frequently require vitamin K antagonists (VKAs) to prevent recurrent events, but their use increases hemorrhage risk. We performed a study to assess the quality of international normalized ratio (INR) control, using time in therapeutical range (TTR) and to identify predictors of poor control and to examine the relationship between INR control and adverse outcomes in VTE patients.
Methods: We performed an observational, retrospective study, including all patients hospitalized for VTE who attended the internal medicine department of a Moroccan hospital (2010–2013), whose target INR was 2.0-3.0. The primary outcome under investigation was the TTR calculated according to F.R. Rosendaal's algorithm.
Results: 171 VKA-treated patients were evaluated; 53.2% men. The average age of our patients at diagnosis was 49.8 ± 16.6 years [17-92].The most common location of VTE was the lower limbs with 91.8% cases; proximal in 83.6%. Five etiological groups have been distinguished: thrombophilia (5.8%), Behcet disease (9.4%), neoplasia (14.6%), with transient risk factor (34.5%) and idiopathic (35.7%). Patients were followed for a mean period of 178 days. The mean TTR was 41.2% (SD 32.9%) and 74.3% the patients had a mean TTR < 65%. The rates of major bleeds and thromboembolic events were 0.5% and 2.2%, respectively. In the statistical analysis, having a cancer and a non idiopathic VTE were negatively associated with a lower TTR ($P < 0.05$).
Conclusions: Anticoagulation control needs to be improved in our unit. These results are informative and may help to identify patients who will require closer monitoring or innovative strategies to optimize the outcomes of oral anticoagulant therapy.

Arterial thrombosis and atherosclerosis

C0091
SERUM URIC ACID AND ALBUMIN LEVELS ARE ASSOCIATED WITH DEEP VENOUS THROMBOSIS

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Background: Deep venous thrombosis (DVT) and venous thromboembolism are associated with inflammatory process. Inflammation gives rise to a hypercoagulable state and endothelial damage. Serum uric acid (SUA) is suggested to be involved in oxidative stress and inflammatory response. It is also reported to play important role in endothelial function and vascular remodeling. Serum albumin is one of the main proteins in plasma and is responsible from 70-80% of the plasma oncotic pressure. Besides the effect of albumin on intravascular volume, it has antioxidant, anticoagulant, anti-inflammatory and antiapoptotic effects. This retrospective study investigates the association of SUA and serum albumin levels with DVT.
Methods: This retrospective study was conducted from October 2014 to November 2014 on 146 patients with DVT and 150 healthy individuals as control group. The diagnosis of DVT was confirmed by venous duplex scan. The relationship between SUA and serum albumin levels and predisposition to DVT was analysed by using logistic regression analysis.
Results: Our results revealed that higher SUA (OR: 1.607, 95% CI: 1.012-2.552, p= 0.044) and lower serum albumin levels (OR: 2.071, 95% CI: 1.185-3.618, p= 0.011) were significantly associated with DVT.
Conclusions: Serum uric acid and albumin levels may be used as a predictor for venous thromboembolism.

C0096
CLINICAL CHARACTERISTICS AND ETIOLOGIES OF ARTERIAL THROMBOSIS: A SERIES OF 45 PATIENTS

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Background: The aim of this study was to describe epidemiological and clinical features of patients with arterial thrombosis (AT) and to determine their etiologies.
Methods: We conducted a retrospective study of patients admitted in an internal medicine department from 2000 to 2015, who presented with arterial thrombosis.
Results: Forty five patients were included. The sex-ratio M/F was 0.73. Mean age at the AT diagnosis was 50.2 years [range 23 and 80 years]. Among patients, 28.8% had at least one personal history of venous thrombosis, 13.3% of patients had diabetes and 26.6% had hypertension. Fifteen patients had hypercholesterolemia and eighteen patients were smoker. The mean delay to etiological diagnosis was of 107.5 days. AT was concomitant to venous thrombosis in 26.6% of cases. Intermittent claudicating was noted in 33.3% of cases. The AT was located in lower limbs in 37.8% of cases and in upper limbs in 22.2% of cases. Thrombosis was bilateral in five cases. Digestive arteries were involved in 4 cases (Superior mesenteric artery thrombosis in all cases). Cerebral arteries thrombosis (patients having stroke) and central retinal artery thrombosis was found in 11 and 5 patients respectively. Coronaries thromboses were noted in three patients and renal artery thrombosis was found in one case. Anemia was noted in 35.5% of cases.

AT was associated to Atherosclerosis in 10 cases and to cardiac embolism in one case. Five patients had Behçet's disease and 3 had another systemic vasculitis. Six patients had an antiphospholipid syndrome (2 with systemic lupus erythematosus). Systemic lupus erythematosus was evident in three cases. Buerger's disease was diagnosed in one patient. AT was associated to a cancer in 2 cases. Protein S and protein C deficiency were noted each one, in a case. *Homocysteine level was high in 13.3% of patients (mean rate was 32.44* μmol/L). Treatment was based on heparin (n=30), vitamin K antagonists (n= 28) and/or antiplatelet agents (n=26). Eleven patients underwent surgery, nine patients had a thrombectomy, four patients had an artery bypass graft and three other had a coronary stent placement. AT complication were observed in 24.4% of cases: amputation (n=7), necrosis (n=10), ulcerations (n=6) and infection in 5 cases. Three patients died.
Conclusions: AT were associated to different causes, in our series systemic diseases like vasculitis and antiphospholipid syndrome were the most frequent.

C0099
LIPID METABOLISM AND COAGULATION FACTORS IN PATIENTS WITH CORONARY ARTERY DISEASE AFTER STENTING

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Background: Treatment of coronary artery disease is one of the most complex areas of modern medicine. A breakthrough in the treatment of coronary heart disease is associated with the development of Interventional cardiology. Taking into account of the high coronary heart disease prevalence, the number of surgical interventions for this disease is growing every year.
The aim of our research was to analyze the lipid levels and coagulation parameters in patients with surgical interventions on the heart.
Methods: We analyzed medical cards of the 80 patients' with the coronary artery diseases, myocardial infarction, after stenting on two or three coronary arteries. After stenting, all patients had treated in the cardiology department of Karaganda #1 city hospital.
Results: According to the research results, the number of males predominated over the females and consisted 59 (74%) and 21 (26%) respectively. In the course of laboratory test analysis, it was found the increase of activated partial thromboplastin time in thirty eight (75%) patients, fibrinogen level in twenty two (27.5%) and thrombin time in three (3.75%) patients. The prothrombin index decreased in eights (10%) from the total number of examined patients. Retraction of the blood clot had been reduced in sixty two (77.5%) patients. The positive soluble fibrin monomer complexes were observed in nine (11.25%) patients.
The lipid metabolism analysis showed cholesterol level increasing in fifteen (18.7%), triglycerides in nineteen (23.75%) patients, and high density lipid level increased in twenty one (26. 25%) patients. Increased low density lipoprotein level was observed in only ninths (11.25%), very low density lipoproteins was at five (6. 25%) patients.
Conclusions: Thus, the changes of the lipid metabolism and coagulogramm indexes as fibrinogen, activated partial thromboplastin time can create conditions for the early development of atherosclerosis.

C0133
RETROSPECTIVE EVALUATION OF PATIENTS WITH ACUTE MESENTERIC ISCHEMIA

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Background: Acute mesenteric ischemia is a cause of acute abdomen and bad prognosis. In spite of the recent advances in diagnostic techniques, mortality rate of acute mesenteric ischemia is still 50-70%. Patient's age and comorbidities effects these high mortality rates.
Methods: Patients who were admitted to Istanbul University Istanbul Medical Faculty Emergency Surgery Department between January 2010 and July 2015, were retrospectively reviewed. Age, sex, WBC, CRP, lactate, radiological findings, treatment, mortality, morbidity and hospital stay were recorded.
Results: The study group included 59 patients. 31 (53%) were male, 27 (47%) female. Mean age was 62 (28-94). Mean WBC was 18500, crp 209, INR 1.54, lactate 4.3. 43 (73%) of 59 operated due to physical examination, laboratory values and BT findings. 16 (27%) patients were conservative treatment by antithrombotic injection. (Catheter, fibrinolytic therapy) 5 (8%) patients went into diagnostic laparoscopy. The patients who underwent surgery was performed intestinal resection (32, 54%) and colonic resection (16, 27%). 6 (10%) went into embolectomy. 16 patients performed second look and 7 (43%) of them went into resection because of necrosis. 30 (51%) patients died and mean hospital stay was 17.8 (1-133) days.
Conclusions: Treatment of mesenteric ischemia is best done with a confirmed CT angiogram. Main treatment of mesenteric ischemia is surgical embolectomy and thrombolytic therapy. Evaluation of intestinal ischemia must be done by laparoscopy during a second look procedure after treatment.

C0147
THROMBIN GENERATION IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE WITH INDICATIONS TO ANGIOGRAPHY

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Background: Coronary artery disease (CAD) may be treated by invasive procedures like percutaneous interventions and coronary artery bypass grafting (CABG). In any case preliminary visualisation by coronary angiography is required. The reason for early or delayed complications such as stent/graft thrombosis or restenosis is activation of coagulation cascade with different level of thrombin generation in heart of it.
Methods: 96 patients, suffered from CAD (age 61 (43-79, 75 male, 21 female) and 23 healthy persons without symptoms of atherosclerosis, non smokers of with the same age group and with the same gender distribution were included. According the severity of CAD and angiography results patients were divided into 3 groups: with progressive atherosclerosis and indications for PCI (I group, n=65), stable CAD and indication for CABG (II group, n=16) and those who had no indications to invasive treatment (III group, n=15). Thrombin generation were measured by Thrombinoscope (Netherlands) in duplicate before procedures. Results are presented as Lag Time (min), Endogen Thrombin Potential (ETP, nmol/min), Peak thr. (nmol) and ttPeak (min).
Results: There were obtained prolongation of Lag Time in all patients with CAD. In I group it was significant compared with donors – 3.0 (2.7-3.3) min vs 2.5 (2.4-2.8) min in healthy persons, $p<0.05$. In other groups the bias was statistically non significant: 2.8 (2.6-3.3) min in II group and 2.9 (2.4-3.2) min in the III one ($p>0.05$). We revealed also the tendency to ETP increasing in patients with indications to coronary revascularization (in I and II groups): 1717.4 (1550.4-1967.5) nmol/min and 1766.1 (1557.7-1897.6) nmol/

min, respectively, vs 1644.3 (1486.8-1770.7) nmol/min and 1674.2 (1584.3-774.9) nmol/min in donors and III group of patients. Other results had no significant differences between compared groups.
Conclusions: The retardation of thrombin generation in vitro (Lag time prolongation) was noted by other authors (Smid, M., et al) and may depend on TFPI activation according to endothelial dysfunction and inflammation in patients with progressive atherosclerosis. Further studies are needed to increase patient groups and getting additional results.

C0273
ARE AGE AND JAK2V617F MUTATION RELATED TO THROMBOSIS IN CHRONIC MYELOPROLIFERATIVE DISEASES?

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Background: Since the discovery of the JAK2V617F mutation in the pathogenesis of MPN in 2005, many studies have been conducted to evaluate the clinico-hematological importance of this mutation. High-risk patients are defined as those who are older age and have had a thrombotic attack. In this study, our aim was to identify the effects of age, JAK2V617F mutation status, hematological parameters on risk of trombosis.
Methods: We retrospectively evaluated 155 patients total who had been diagnosed based on the WHO MPN diagnosis criteria, between 2007 and 2015 in the Department of Hematology at Ankara University. The frequencies of the JAK2V617F mutation, thrombosis, hemorrhage, treatment side effects, fibrosis and leukemic transformation between the groups were evaluated by the Pearson chi-square test.
Results: Patient characteristics were shown in table. No significant difference was detected between the groups due to treatment side effects ($P > 0.05$). In both groups, the most frequent second line treatments used in both PV and ET were thromboreductin and ASA, while the PMF patients in the young adult group also underwent allogeneic stem cell transplantation. The thrombosis frequency during follow-up was similar between groups (24% vs 18%, P=0.522), even in JAK2V617F mutation-positive patients (23% vs 27%, $P > 0.05$). Thrombosis in the central nervous system was most commonly detected in the geriatric group (34%), while intra-abdominal thrombosis was most common in young adults (43%). There was no significant relationship between leukocyte, hemoglobin and platelet counts and the frequency of thrombosis in the geriatric and non-geriatric group ($P > 0.05$). Ten geriatric patients (20%) and 9 young adult patients (9%) had severe hemorrhage, and this difference was not statistically significant between the groups ($P > 0.05$).

Table 1

Characteristics	Geriatric Group (n=51)	Non-Geriatric Group (n=104)
Diagnosis		
Polycthemia Vera (PV)	22 (43%)	35 (34%)
Essential Thrombocytemia (ET)	25 (49%)	42 (40%)
Primary Myelofibrosis (PMF)	4 (8%)	27 (26%)
Female/Male	32/19	37/67
JAK2V617F mutation +	35 (69%)	41 (39%)
1st line treatment for PV	Hydoxyurea (HU) Acetysalicylic acid (ASA) (60%)	Phlebotomy ASA (57%)
1st line treatment for ET	HU ASA (54%)	HU ASA (48%)
1st line treatment for PMF	No treatment (38%)	Allogeneic Stem Cell Transplantation Steroid (37%)

Conclusions: In this study, no significant relations were detected in between thrombosis risk with age, JAK2V617F mutation status and hematological parameters in MPN.

C0280
SUDDEN ONSET VISION LOSS AS AN INITIAL MANIFESTATION OF ELEVATED SERUM LIPOPROTEIN(A) LEVELS: REPORT OF TWO CASES

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Background: Isolated cilioretinal artery occlusion (CLRAO) or cilioretinal venous occlusion (CRVO) may cause sudden loss of vision. In such cases, prothrombotic risk factors should be investigated. Lipoprotein(a) [Lp(a)] is an atherogenic lipoprotein particle which displays adjunctive thrombotic properties by inhibition of the fibrinolytic pathway. Elevated levels of Lp(a) is rarely associated with CLRAO or CRVO. In this study, we reported two cases, one with isolated CLRAO and another with combined CLRAO and CRVO as initial manifestations of elevated serum Lp(a) levels.
Methods: Case 1 concerns a 13-year-old female with a complaint of sudden vision loss in the right eye. After complete ophthalmologic evaluation, she was diagnosed of having right CLRAO. Thrombophilia work-up was normal except the high plasma Lp(a) level of 373.3 mg/dl. In order to reduce Lp(a) levels, cascade filtration procedure was performed and the patient was started on oral niacin treatment. On the eighth day the visual acuity had fully recovered. Cascade filtration was applied once every two week. We aimed to keep the Lp(a) levels below 100mg/dl. She is ongoing in good condition with reduced levels of Lp(a).
Results: Case 2 concerns a 17-year-old female with a complaint of sudden vision loss in the right eye. Ophthalmologic examination revealed that she was having combined CRVO and CLRAO. Laboratory parameters were remarkable for an elevated level of Lp(a) of 94.8 mg/dl. Thrombophilia work-up was normal. Treatment with anticoagulants and oral niacin were initiated. The patient's visual acuity gradually improved but she developed optic atrophy. Cascade filtration was not applied because spontaneous recanalization was developed. Oral niacin treatment was started.
Conclusions: Elevated plasma Lp(a) levels might be related with retinal vascular occlusions and should be checked in such cases both to determine the etiology of the vascular occlusion and to detect other family members with increased Lp(a) level and thromboembolism risk. Oral niacin treatment and cascade filtration may be benefit for these patients. There is no definitive cut off level of Lp(a) for cascade filtration. Further studies are needed to optimize to perform cascade filtration for children.

C0288
SUBOCCLUSIO ARTERIAE SUBCLAVIAE IN A 50-YEAR-OLD WOMEN: CASE REPORT

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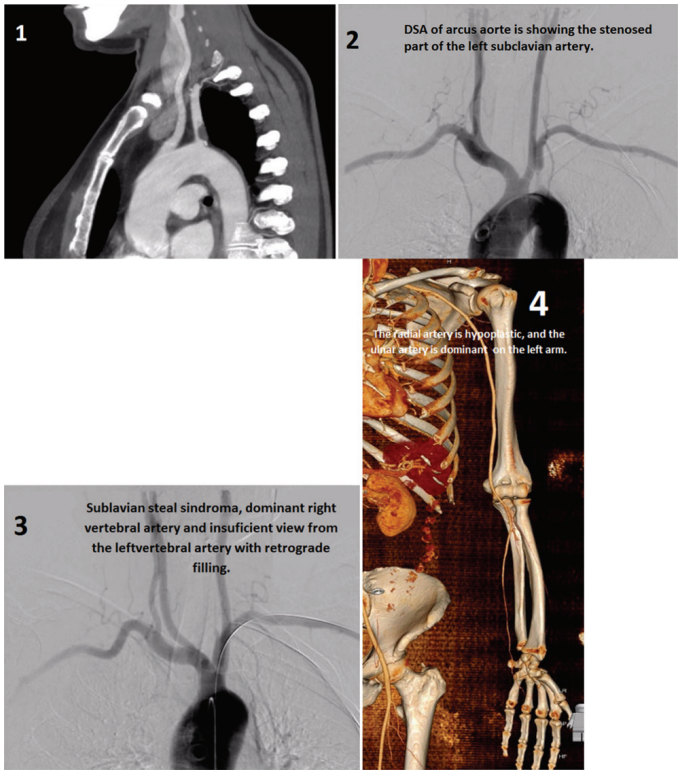
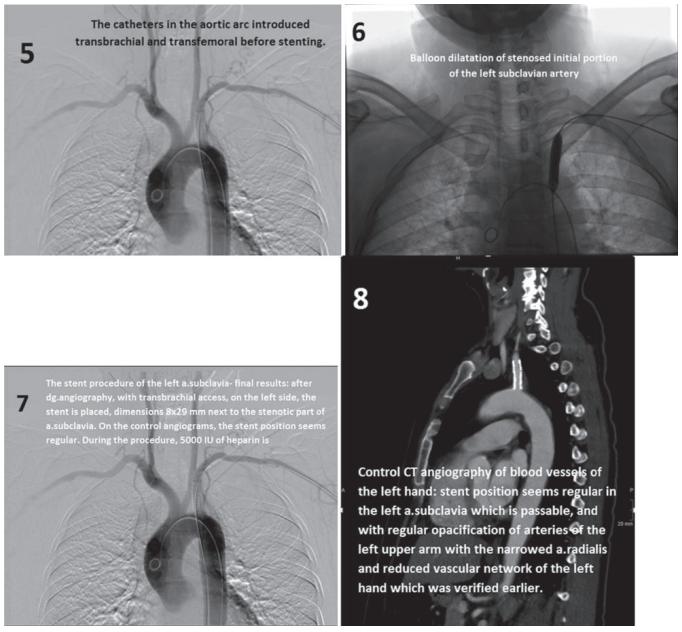
Background: Reception of the patient at the Department of Emergency Medicine because of the severe pain in her left arm caused four hours before the reception, followed by numbness and lividity in fingers of the left hand, especially I-III fingers. After the perpetration of an ultrasound examination, vascular surgeon does not indicate additional diagnostics or surgical reconstructive treatment, and the patients is welcomed to our department. Three weeks earlier, the patient had been treated in the hospital at the secondary level because of the similar problems understood as microembolisations of the left hand. After four days, with improved clinical symptoms, with no pain, with the loss of finger lividity of her left hand, the patient was released from hospital at her own request due to family situation. As fair as the diagnosis is concerned, the patient underwent an ultrasound of the blood vessels only, and was released on low molecular weight heparin in the next 15 days (1x60 mg Enoxaparin s.c.) with vasodilators. Six days after the discontinuation of heparin, the symptoms reappeared.
Methods: CT angiography of blood vessels of the left hand: stenosis of the output part of the left a. subclavia 2 cm long with the narrowest lumen. The most of the lumen is occupied by thrombotic deposits, calcificates are

not seen. The rest of a.subclavia, a. brachialis and a. ulnaris are with regular angiographic characteristics. Radial artery with its whole flow is fragile and the vascularisation of the left hand is supported through the dominant a.ulnaris. It is indicated that endovascular treatment of the left a. subclavia should be done. The stent procedure of the left a.subclavia- final results: after dg.angiography, with transbrachial access, on the left side, the stent is placed, dimensions 8x29 mm next to the stenotic part of a.subclavia. On the control angiograms, the stent position seems regular. During the procedure, 5000 IU of heparin is administrated. Control treatment if necessary

Results:



Conclusions: Control CT angiography of blood vessels of the left hand: stent position seems regular in the left a.subclavia which is passable, and with regular opacification of arteries of the left upper arm with the narrowed a.radialis and reduced vascular network of the left hand which was verified earlier.



C0326
RISK FACTORS, TREATMENT AND PROGNOSIS OF THROMBOSIS IN CHILDREN, A SINGLE CENTER EXPERIENCE

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Background: Advances in tertiary care in pediatrics resulted in increased thrombosis, increased use of anticoagulation and thrombolytic treatment. We aimed to study the risk factors, treatment and prognosis of patients with acute thrombosis admitted to a tertiary care center.

Methods: The charts of the patients who were diagnosed with acute thrombosis between January 2006 and March 2013 at Ankara University Children's Hospital were evaluated retrospectively. Seventy four patients were diagnosed with acute thrombosis and 44 of them were evaluable for the underlying disease, localization of thrombosis, genetic risk factors, treatment and prognosis which constituted our cohort.

Results: Median age was 59.5 months (11 days-18 years). Twenty eight male and 16 female. Twenty one (47.7%) patients were under 2 years of age. Median follow up period was 34.2 months (range: 2-60 months). Twenty patients (45.5%) had arterial, 24 (54.5%) had venous thrombosis. Twenty one (47.7%) patients had congenital heart disease. Acquired risk factors were thought to be the reason for thrombosis in 24 (54.5%) patients. MTHFR, FV leiden and Prothrombin 20210G-A mutations were found in 26 (59.1%), 15 (34.1%) and 2 (4.5%) patients, respectively. Twelve patients (27.2%) did not have any genetic risk factors while 10 patients (22.7%) had more than one. Eleven (25%) patients had central nervous system thrombosis and 9 (81.2%) of them had MTHFR mutation. Of the 20 patients with arterial thrombosis 3 (15.0%) had MTHFR homozigot, 6 (30.0%) had MTHFR heterozigot and 6 (30.0%) had FV leiden mutations. Cardiac catheterization was performed in 17 (85.0%) of 20 patients with arterial thrombosis. Medical treatment was given to 39 (88.6%) of 44 patients. Unfractioned heparin was the most commonly used anticoagulant [n=19 (48.7%)]. Tissue plasminogen activator was used in 12 patients (30.8%). Resolution of thrombosis was complete in 21 (47.7%) and partial in 21 (47.7%) patients. No resolution was detected in 2 (4.6%) of 44 patients.

Conclusions: Cardiac catheterization was determined as the most important risk factor for thrombosis in our tertiary care hospital. With the advanced invasive diagnostic and treatment options, the risk for thrombosis has increased. Determining the acquired and genetic risk factors might help to guide the duration of treatment and prophylxis as well as the measures for prevention.

C0349
THE ROLE OF BIOCHEMICAL MARKERS IN ATHEROTHROMBOSIS WITH PLATELET ACTIVATION-RELATED; AN IN VIVO PROSPECTIVE STUDY

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Background: It has reported that *in vivo* platelet activation plays role on occurance of atherothrombosis pathogenesis and serious diseases such as stroke, peripheral artery occlusion, acute mycardial infarctus (AMI). The aim of the study is to examine the relationship between several biochemical markers, myocardial markers and platelet activation on patients diagnosed atherothrombosis and get necessery progression.

Methods: Prospectively, pre-operative (Group I) and post-operative (Group II) 50 mature (age between 33 and 77) patients who diagnosed with atherothrombosis, had choosen from the Cardiovascular Surgery Department of Marmara Pendik Training and Research Hospital (Commencement date: 2015 September). All patients have treatments with antiplatelet agent (minimum 10 days). Whole blood samples collected in 3.2% sodium citrate tubes before platelet agrregation was measured to examine the rate of platelets activation, using optical aggregometry (5

μM agonist ADP). Patients demographic data (age, sex etc.), biochemical markers and myocardial markers have corralated with platelet aggregation test results.
Results: In this research we compared results of all biomarkers depend on sex and between pre and post-operative group. After controlling for demographic and all biochemical and myocardial markerlevels, sex affect wasassociated with elevated levels of C-reactive protein (CRP) and Troponin I in subjects. LDL-cholesterol, total cholesterol and triglyceride concentration levels were detected in patients and compared. They levels were not significantly associated with myocardial markers in patients with atherothrombosis. Mean aggregation results were higher in women than men, however levels of aggregation were not significantly higher in both group (Group I and Group II).
Conclusions: For understanding of the pathophysiology of atherothrombosis we have matched these biomarkers to make a correlation between them and atherothrombosis.

Atrial fibrillation

C0041
STUDY OF SAFETY AND EFFECTIVENESS OF DABIGATRAN TO PREVENT THROMBOEMBOLIC EVENTS IN PATIENTS WITH ATRIAL FIBRILLATION

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Background: Since approval dabigatran use in prevention of thromboembolic events for patients with atrial fibrillation in 2010, the manage of this drug has increased given the excellent safety profile has presented in clinical trials [1]. However the problem is to know the results in daily real hematology services. The objective of this study was analyze the efficacy and safety of patients with dabigatran from 2010-2014 in the hematology unit of our hospital.
Methods: A retrospective study was conducted of patients who they were treated with dabigatran in our unit from 2010-2014. Patients were followed until discontinuation drug or to the last follow. The dose of dabigatran and indications was chosen to clinical judgment. The main variables investigated were the percentage of patients discontinued the drug, the number of major bleeding and number of events thromboembolic leading to drug withdrawal. Major bleeding was defined according to the criteria of the ISTH 2005 .Statistical analyzes were performed using SPSS 21.0 (SPSS Inc., Chicago, IL).
Results: A total of 54 patients were finally included. Median of CHADVASC2 and HAS-BLED was 3 and 2 points respectively. Most patients, 50 (92%), used dose 110mg. Median follow-up was 760 days RI (375-1300) 34 patients (63%) continue with the drug nowadays. Patients who discontinued the drug 20 (37%), only 8 (14%) left the drug by a direct side effect, 4 (7%), for heartburn and another 4 (7%) for major bleeding. The other 12 patients, 7 (8%) did it due to medical indication, 4 (7%) by renal failure, 1 (2%) due to death unrelated patient. There were no thrombotic events that would have required removal drug.
Conclusions: Data from our study are similar to those published in the RE-LY (1) supporting results safety and effectiveness.
Reference:
[1] Eur Heart J. 2009 Nov;30(21):2554-5

C0353
THE PREVENTION OF TROMBOEMBOLIC COMPLICATIONS IN NON-VALVULAR ATRIAL FIBRILLATION

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Background: In recent years it is approved that along with antagonists of vitamin K, new oral anticoagulants have clinical advantages and can be used safely. One of such preparations is Rivaroxaban under a trade name of Xarelto. This drug is a high-selective direct inhibitor of Xa factor. Activation of an X factor with formation of Xa factor (FXa) plays the central role in the coagulation cascade. The goal of our research is definition of safety of Xarelto in routine clinical practice in patients with non-valvular AF.
Methods: During 6 months we studied 45 patients with non-valvular AF. They were evaluated according to the approved AF-protocol. This study included patients aged 52-68 years. There were 22 men and 23 women, mean age of 59 years, the average height were 172.2±2.1 cm, and weight were 68.1±1.3 kg. The patient selection was carried out using a scale CHA_2DS_2 Vas_c (to assess the risk of stroke and thromboembolism in patients with atrial fibrillation). We used HAS-BLED to assess the risk of major bleeding within 1 year. According to the scale $CHA_2DS_2Vas_c$ average ratio was 3.2 points, indicating the average risk of thromboembolic complications, and indicates a need for anticoagulation. On a scale HAS-BLED- average ratio was 1 point, indicating a low risk of bleeding and the possibility of anticoagulant. The drug "Xarelto" used at a dose of 20 mg per day in admission of the patients in hospital. The laboratory tests carried out at the first contact with the physician, and every 3 months we monitored the laboratory tests of cell blood counts (hemoglobin, red blood cells, platelets), prothrombin time and INR, and other biochemical blood tests (ALT, AST, Bilirubin, creatinine).
Results: The risk of bleeding of the patients who used Xarelto, was minimal. The drug is also well tolerated in patients with renal failure (1 and 2). We saw increasing of partial prothrombin time (PTT), about 1.0 times. Mean levels of INR ranged from 2.0 to 2.32. And other indicators of laboratory investigation were normal.
Conclusions: Xarelto (Rivaroxaban) 20 mg per day is safe in routine clinical practice, and within 1 year observation, there was significantly reduction in risk of thrombosis in patients with non-valvular atrial fibrillation.

Bleeding management of patients under antithrombotic therapy

C0305
THE VERIFYNOW IS THE MOST PREDICTABLE METHOD TO DEFINE LOW PLATELET REACTIVITY FOR BLEEDING EVENTS IN KOREAN PATIENTS ON P2Y12 INHIBITOR MAINTENANCE THERAPY

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Background: Although low platelet reactivity (LPR) during aspirin and $P2Y_{12}$-inhibitors is associated with bleeding, standardized and clinically validated thresholds for accurate risk stratification in Korean are lacking. We sought to determine the optimal predictive value of LPR using three different platelet functions measurement assays.
Methods: We enrolled 800 patients receiving aspirin and $P2Y_{12}$-inhibitors at maintenance dose after PCI, and 699 (87%) were treated with clopidogrel, 101 (13%) with new $P2Y_{12}$ inhibitors. Accepted bleeding scales included BARC type ≥ 2. Platelet reactivity was measured by the light transmittance aggregometry (LTA), VerifyNow $P2Y_{12}$ assays and multiple electrode platelet aggregometry (MEA).
Results: There were total 18 (2.3%) bleeding events within 1 year after DAPT therapy. LPR for bleeding were defined as ≤ 15% for LTA (AUC: 0.796, P<0.0001), ≤ 139 PRU (AUC: 0.867, P<0.0001) and ≤ 25 U for MEA (AUC: 0.747, p= 0.0001). For univariate analysis, the independent predictor of bleeding is LTA (HR; 5.003, 95 % CI: 1.793 – 13.96, p= 0.0022), VerifyNow (HR; 21.26, 95 % CI: 6.194 – 72.99, P<0.0001) and MEA (HR: 7.425, 95 % CI: 2.163 – 25.49, p= 0.0015). However, multivariate analysis revealed that only VerifyNow (HR: 11.49, 95 % CI: 2.891 – 45.67, p= 0.0004) was an independent predictor of 1 year bleeding events.
Conclusions: The predictive cut off value for bleeding is higher in Korean compared with Western. The VerifyNow is the most predictable method on bleeding compared with LTA and MEA.

C0309
TWO CASES OF ACQUIRED HEMOPHILIA A

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Background: Acquired hemophilia A (AHA) is an autoimmune disorder that usually represents with spontaneous hemorrhages caused by inhibitory effects of autoantibodies against factor VIII. AHA may be related with pregnancy, autoimmune diseases, malignancy, infections, or medications. Over 50% of cases are idiopathic. Herein, we will report two cases of AHA one of which is related with a solid malignancy while the other one is idiopathic.
Methods: CASE1 : A 46-year old woman wasadmitted with severe ecchymosis in extremities. On history ischemic cerebrovascular event, adrenocortical carcinoma and thrombosis in vena cava inferior were recorded and she was taking warfarin, antiepileptic drugs. Laboratory investigations revealed that aPTT: 107 sec (ref range: 22-34), PT: 25 sec (ref range: 8.8-14), INR: 2.5 (ref range: 0.8-1.2) and platelet count was normal. APTT was not normalized with 2 hours mixing test and FVIII activity was 3% while FVIII inhibitor level was >350 BU/mL (ref range: <0.6). Prednisolone 1 mg/kg/day iv and cyclophosphamide 500 mg/day iv weekly was started. One month later she was admitted to the intensive care unit with sepsis caused by intrabdominal abscess. She was expired on 4th day.
CASE2: 63 years old obese lady was presented with large ecchymosis. Laboratory investigations showed that hb: 7.4g/dl, wbc: 12.8 $x10^9$/L and platelet count: 420 $x10^9$/L. Her coagulation work up showed that PT: 11.7 sec and INR: 1.0 while her APTT was 74 sec and was not corrected in 2 hours mixing test. FVIII was <1% and FVIII inhibitor level was >32 BU/mL. Recombinant FVIIa (90 IU/kg every 12 h; three days), prednisolone 1 mg/kg/day iv, cyclophosphamide 500 mg/day iv in three weeks was started. Etiological evaluations for collagen vascular disease, viral hepatitis, solid or hematologic malignancy were unremarkable. She was discharged with oral prednisolone 112 mg/day. Five weeks later she was admitted to the hematology department with thrombosis in right main femoral vein. FVIII and inhibitor levels were in normal ranges. Fraxiparine was started. On 12th day of hospitalization she had septic shock, cardiopulmonary arrest and was expired.
Conclusions: Different than congenital hemophilia, AHA presents mostly with muco-cutaneous or soft tissue bleedings in elderly, in both gender. Underlying malignancy is present approximately in 10% of cases. Over 50% of AHA cases are called idiopathic but it's unclear if they will develop malignancy on prolonged follow up. Clinicians should be suspicious of AHA in patients presented with unusual bleedings and prolonged a PTT. Mixing studies will be useful to rule out etiological causes such as heparin therapy, antiphospholipid antibodies or FXII deficiency. Etiological evaluations should be including malignancy, autoimmune diseases and connective tissue diseases.

Coagulation and Tissue factor

C0308
DETERMINATION OF FACTOR II CODONS GENOTYPE IN SOUTH EAST IRANIAN PATIENTS WITH HEREDITARY DEFICIENCY OF FACTOR II

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Background: Congenital Prothrombin deficiency is a rare bleeding disorder that is inherited autosomal recessive pattern, the prevalence of this disorder is about 1 in every 2 million, but in areas with a high rate of consanguinity is more common. Some of these areas include the south-east of Iran's. Prothrombin deficiency have two types: 1) Hypo-prothrombinemia (Type I) with lower levels of activity and antigen is known. 2) Dys- prothrombinemia (Type 2) with normal or near normal dysfunction protein synthesis known. Factor II deficiency leads to a range of the most common symptoms of umbilical cord bleeding, epistaxis, menorrhagia and delayed wound healing, while Heterozygous patients usually are asymptomatic or mild symptoms of bleeding overexpressed. To date there is no report on the absence of Prothrombin, absence of prothrombin is incompatible with life.
Methods: This study on 12 patients with an inherited deficiency of prothrombin is done. Early diagnosis based on clinical symptoms, laboratory evaluation and family history has been done. Then measure the function levels of prothrombin and thus confirmed the initial diagnosis of the disease, the patient was evaluated by PCR on DNA. Then factor II gene sequencing and genotyping finally occurred, identified and examined.
Results: Molecular studies indicate a Point mutation in exon 7 as were in 3 patients and a Frame shift mutation in exon 14 due to the addition of a base Thymine at position 1760-1761 was observed in one patient, both of which have been reported for the first time. Statistical analysis showed no association between mutation and clinical symptoms. As well as, there was no significant relationship between severity of bleeding and activity level of factor II in the study (P value = 0.5). In clinical symptoms, there was a significant relationship, only between the level of activity factor II and post partum hemorrhagia (P value= 0.018), menorrhagia (P value= 0.018).
Conclusions: Clinical symptoms observed in this study compared with world was different. Molecular detection revealed a missense (p.282 asp>asn) mutation and frameshift mutation (c.1760-1761 ins T).

C0310
DETERMINATION OF FACTOR X CODONS GENOTYPE IN PATIENTS WITH HEREDITARY DEFICIENCY OF FACTOR X IN SOUTH EAST IRANIAN POPULATION

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Background: Congenital factor X deficiency is a rare bleeding disorder which is estimated worldwide prevalence of 1 per ~ 1 million. The disease is also a severe disease with autosomal recessive inheritance. The factor X deficiency has a high frequency in areas with the high rate of consanguineous marriage and however these type of marriage has been seen in the population of Southeastern Iran very much. Due to higher prevalence of factor X deficiency and absence of a molecular and clinical study in this region, we assessed the clinical manifestations as well as demographic and genetic features in patients with FXD in southeastern Iran.
Methods: 15 Iranian patients from Sistan and Baluchestan (S&B) Province were selected. Their diagnosis was based on the assessment of clinical features, familial history, and laboratory data such as increased PT and APTT as well as their FX coagulant activity (FX: C). DNA was extracted from peripheral blood samples. All exons (the coding regions), intron/exon boundaries as well as 5' and 3' untranslated regions (flanking regions) of the FX were amplified by polymerase chain Reaction (PCR). Sequencing was implemented on PCR products, and the results were analyzed using codon code aligner software.
Results: Molecular detections revealed a missense (p: pro422Leu) mutation in two patients from one family, one mutation in splice site (IVS2-1G>A) in two patients for the first time and a synonymous (c.268T>C) mutation in two patients for the first time. Congenital factor X deficiency FXD involves 4.5% of RBDs in S&B Province, which is lower than national and international incidence. The clinical symptoms were different from previous studies in Iran.
Conclusions: Statistical analysis didn't revealed satisfying correlation between the types of mutations and clinical manifestations unless post-circumcision bleeding. There was significant correlation between severity of bleeding features and the level of factor X activity (P value= 0.001). There were a significant correlation between the level of factor X activity and epistaxis (P value=0.004) and gum bleeding (P value=0.004).

C0312
EVALUATION OF PATIENTS WITH HEMOPHILIA; ULUDAG UNIVERSITY EXPERIENCE

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Background: Hemophilia is an X-linked congenital bleeding disorder that is complex to diagnose and to manage. The primary aim care is to prevent and treat bleeding with disease specific factor concentrate. Treatment of patients especially those with severe forms of disease must be done by a multidisciplinary team of healthcare professionals. In this review, in order to create our hemophilia center, we present our hemophilia cases retrospectively.
Methods: Patients with hemophilia identified by a retrospective review of records of the Uludag University Hospital, Hematology Department. Proportions of hemophilia A and B were 77% and 23% respectively. According to factor activities, 26 (46%) patients were considered to have severe hemophilia A, 14 (25%) patients were considered to have moderate hemophilia A and 16 (29%) patients were considered to have mild hemophilia A (Table 1).
We diagnosed most cases of hemophilia A at infant ages and patients with hemophilia B at adolescent ages. Hemophilic arthropathy of the knee was common among patients with hemophilia A and bleeding of knee-joint was higher in this group (Table2).
We evaluated that 4 patients (7%) had an elective major surgery and mostly we needed to us additional replacement treatment for dental extractions. Just 35 patients (62%) receive prophylaxis in hemophilia A group, most of them tertiary. Use of plasma-derived clotting factors rate were 50%, recombinant factors rate were 12%.

Table 1

	Numbers of patients (n=73)	Clotting factor activity <1%	Clotting factor activity 1-5%	Clotting factor activity >5%
Hemophilia A	56 (76%)	26	14	16
Hemophilia B	17 (24%)	-	10	7

Table 2

	Hemophilia A	Hemophilia B
Knee	25	2
Elbow	20	-
Ankle	13	-
Shoulder	1	-
Wrist	2	-
Hip	3	-
Others	1	-

Results: Hemophilia is an X-linked congenital bleeding disorder caused by a deficiency of coagulation factor VIII or factor IX. Clotting factor level affects the bleeding severity. Hemophilia A is more common than hemophilia B, representing 80-85% of the total hemophilia population. We have the same rates in our hemophiliac population. In our patients, most bleeding occurred internally into the joints (especially knee-joint) and muscles that was consistent with the literature. Inhibitor positivity was found in 2 (3%) of these patients and this rate was lower than literature knowledge.
Conclusions: Follow-up and treatment of hemophilia patients should be conducted in center experienced in this area. Key elements of the plan are a multidisciplinary approach, early planning, patient education and appropriate follow-up.

C0360
EFFECT OF EXERCISES AND CALORIC RESTRICTION ON SOME BIOCHEMICAL PARAMETERS OF BRAIN TISSUES IN METABOLIC SYNDROME MODEL

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Background: The aim of this study is to examine the effects of exercise and/or caloric restriction on rat brain tissue in metabolic syndrome model induced by high fructose diet.
Methods: Sprague-Dawley male rats were divided into five groups: control (C), metabolic syndrome (M), metabolic syndrome with exercise (M-E), metabolic syndrome with caloric restriction (M-CR) and metabolic syndrome with exercise and calorie restriction (M-E-CR). To induce metabolic syndrome 10% fructose solution was given to rats in drinking water for 3 months. Exercise and caloric restriction were applied to the related groups for 6 weeks after the induction of metabolic syndrome. Lipid peroxidation (LPO), sialic acid (SA), glutathione (GSH) levels, sodium dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST) and tissue factor (TF) activities were measured in rat brain tissue homogenates.
Results: In brain LPO, SA values increased in M group compared to C group, decreased in M-E-CR group compared to M group. GSH levels, SOD, CAT and GST activities decreased in M group compared to C group, increased in M-CR and M-E-CR groups compared to M group. TF activity increased in M, M-E, M-CR and M-E-CR groups compared to C group, however the increase was significant only in ME group.
Conclusions: Brain damage and impaired antioxidant levels were improved by combined exercise and caloric restriction treatment. This study was supported by Marmara University Scientific Research Projects Commission (Project No. SAG-C-YLP-041213-0449).

Coronary, cerebrovascular and peripheral vascular disease

C0053
VERTEBROBASILAR DOLICHOECTASIA AND STROKE RISK FACTORS

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Background: Vertebrobasilar dolichoectasia (VBD) is a dilatative arteriopathy associated with a decreased blood flow and thrombus formation. The prevalence of VBD in the tertiary neurology centers is about 0.3-4.4%. The most important clinical presentations of dilatative arteriopathy include cerebral ischemia, compression of cranial nerves and parenchymal or subarachnoid hemorrhage. Recurrent stroke in patients initially presenting with stroke is around 40%.
Methods: We investigated the risk factors and the rate of stroke recurrence in 35 patients detected dolichoectasia in the vertebrobasilar system among 2611 ischemic stroke patients, who had been followed in a comprehensive stroke unit from 1996 through 2011.
Results: All patients with VBD referred to us with ischemic stroke. The ratio of VBD in our stroke population was 1.34%. Ages of the patients with VBD were between 38-85; mean age on presentation was 63.5 and 60% of the patients were male. Comorbidity of hypertension was 80%, while diabetes mellitus 20%, hyperlipidemia 28.5%, smoking 37.1%, alcohol consumption 8.57% and cardiac disorder 31.4%. All patients with VBD underwent antiaggregating drug therapy. All patients with hypertension were put on the antihypertensive treatment, mostly dual or triple drugs. Almost all of the hyperlipidemic patients were given lipid lowering agent. The rate of the stroke recurrence was 8.5% in our patients with VBD.

Conclusions: Although vertebrobasilar dolichoectasias are usually accepted as benign entities; they must be followed carefully for the high risk of recurrent strokes. All risk factors, especially hypertension, diabetes and smoking, should be controlled with optimum medical treatment.

C0062
HYPERTRIGLYCERIDEMIA AND ISCHEMIC STROKE

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Background: The role of hypertriglyceridemia as an independent risk factor for ischemic stroke (IS) is controversial. Clinical investigations have primarily focused on the association between elevated levels of low-density lipoprotein cholesterol and low levels of high-density lipoprotein cholesterol as stroke risk factors. Hypertriglyceridemia may lead to pathophysiological processes such as endothelial dysfunction, atherosclerosis and the production of a prothrombotic state, which could contribute to IS risk.
Methods: Case Report: We presented a rare case with familial hyertriglyceridemia and iatrogenic mechanisms of stroke.
Results: One year ago, a 29-year-old female, a genetic engineer, was admitted to the university hospital for the evaluation of chronic nausea. She had hypercholesterolemia (total cholesterol >600mg%) and hypertriglyceridemia (>9000mg%). Later on, similar but less intensive findings were detected in her asymptomatic mother and sister. She was diagnosed with familial hypertriglyceridemia and it was decided to treat her via apheresis. This led to infective endocarditis with formation of vegetations on tricuspid valve and left atrium. She had to be operated at the cardiovascular surgery clinic, where a bioprosthetic valve was inserted in her. She was left hemiparetic after the operation. Diffusion weighted cranial MRI showed diffuse hemodynamic ischemia at the territory of the middle cerebral artery. Carotid Doppler and CT anjiography were completely normal. The etiology of stroke was considered as cardioembolic, but hyperviscosity due to hypertriglyceridemia probably contributed to the cerebral ischemia. Her triglyceride level was reduced to 1000-1500mg%. She is still on antilipemic and antiaggregating drugs and having made a full recovery, is back at work now.
Conclusions: Accumulating evidence has shown that promotion of thrombogenicity, elevated plasma fibrinogen levels, lowered fibrinolytic activity, elevated levels of clotting factors compared to normolipidemic controls may contribute to ischemic stroke in patients with hypertriglyceridemia. On the other hand, as in our case, elevated plasma viscosity plus iatrogenic factors may be the leading cause for developing stroke.

C0064
ANTIPHOSPHOLIPID ANTIBODIES AND STROKE RECURRENCE IN WOMEN

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Background: Antiphospholipid syndrome (APS) is an autoimmune disorder mainly presenting with thrombosis of the arterial and venous system in the presence of persistent antiphospholipid antibodies. Systemic lupus erythematosus (SLE) is a systemic autoimmune disease affecting many organs in the body. APS can either occur as a primary disease or secondary to SLE. Sneddon's syndrome (SS) is an arteriopathy, manifesting with stroke or transient neurological symptoms and a skin rash, livedo reticularis. About 40-60% of patients with SS are also positive for antiphospholipid antibodies. A limited number of studies examined the effect of antiphospholipid antibodies on the risk for recurrent stroke and the results are still controversial.
Methods: We investigated the vascular risk factors and the rate of stroke recurrence in patients diagnosed with APS, SLE and SS among 2611 patients with ischemic stroke who had been followed in a comprehensive stroke unit from 1996 to 2011. None of the patients with SLE and SS were positive for antiphospholipid antibodies. Since all three diseases affect women more commonly than men, we excluded the male patients.
Results: Among female (1190 of 2611) stroke patients, 38 patients were diagnosed as APS (n=19), SLE (n=11) or SS (n=8) according to latest criteria. All were referred to us with arterial ischemic stroke. Mean age was 44.08 ±11.81 (25-71). Main comorbidities were hypertension (36.8%), hyperlipidemia (15.8%), cardiac disorders (13.2%) and diabetes (5.3%). 39.5% of the patients were smokers and none of them consumed alcohol. The rates of risk factors among groups were not different significantly. All patients have undergone antiaggregant or anticoagulant therapy and SLE patients also received immunosuppressive agents. The stroke recurrence rate was 36.8% for APS, 27.3% for SLE and 25% for SS. Recurrent attacks were mostly transient ischemia or minor stroke. Although recurrent stroke rates appeared higher for APS, the results were not statistically significant (p= 0.78 for all groups, APS vs. SLE p=0.59, APS vs. SS p=0.55).
Conclusions: According to these findings, the recurrent stroke risk for female APS, SLE and SS patients presenting with arterial stroke is similar. However, the small number of the cases might have failed to show an otherwise statistical significance; therefore larger studies are necessitated for more definitive results.

C0115
PLASMA FACTOR VIIA–ANTITHROMBIN COMPLEXES LEVELS IN ACUTE ISCHEMIC STROKE ARE NOT ASSOCIATED WITH C–REACTIVE PROTEIN AND STROKE SEVERITY

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Background: Few studies have investigated the role of factor VIIa–antithrombin complexes (FVIIa–AT) in blood coagulation, however no data are available regarding levels of FVIIa–AT in acute ischemic stroke. The goals of the current study were: (1) to determine the plasma FVIIa–AT levels in patients diagnosed with acute ischemic stroke and healthy subjects and (2) to clarify the relationship between FVIIa–AT levels, C–reactive protein (CRP) and stroke severity.
Methods: We evaluated 27 patients with acute ischemic stroke (median age 70 years) and 18 healthy age– and gender–matched controls (median aged 68 years). Admission FVIIa–AT levels were measured in plasma samples by ELISA and serum levels of CRP at admission were measured with an immune turbidimetric assay. The patients were divided into two groups: 1) with CRP < 3mg/L (n=11), and 2) with elevated CRP (≥ 3 mg/L, n=16). Stroke severity at admission was assessed using the National Institutes of Health Stroke Scale (NIHSS) and patients were further divided into two groups: 1) with NIHSS score of ≤7 (n=14) and 2) with NIHSS score of >7 (n=13).
Results: Compared with control subjects, acute ischemic stroke victims had significantly lower FVIIa–AT levels at admission (Me=106.5 pM vs 154.94 pM, p<0.001). Levels of FVIIa–AT did not differ between the CRP groups. Moreover, patients with higher NIHSS score had similar FVIIa–AT levels than the ones with lower NIHSS scores. In relation to these negative results we did not find statistically significant correlations between FVIIa–AT levels, CRP levels and NIHSS score.
Conclusions: Decreased plasma factor VIIa–antithrombin complexes levels in acute ischemic stroke patients at admission are not associated with C–reactive protein levels and stroke severity.

C0122
CLINICO-LABORATORY PREDICTORS OF CORONARY RESTENOSIS IN MAN OF KAZAKH NATIONALITY

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Background: The most common complication of coronary stenting it is restenosis of coronary arteries, which is developed during the first 6 months after percutaneous coronary angioplasty in 20-40% in patients with uncomplicated myocardial infarction and in 60% in patients with complicated myocardial infarction. The aim of the research: the estimation of clinico-laboratory predictors on the risk elevation of restenosis in Kazakh population.
Methods: 95 males of Kazakh nationality were examined. Questionnaire of the patients was made paying attention to finding of arterial hypertension and hereditary factors of cardiovascular pathology. Biochemical findings of lipid specter, coagulogramm, changing of throbocyte level and association of genetic variation in candidate genes were estimated. All the patients were divided in two groups: the 1st group consisted of 45 patients with restenosis of coronary arteries determined by coronarography during 1 year after stenting, the 2nd group - 49 patients without the signs of restenosis. The mighty of association of analyzed signs were determined with the help of the quantity of Odds Ratio (OR).
Results: Special attention was paid to the fact that the arterial hypertension was more often in the 1st group (53.33%) in comparison with the 2nd group (18.37%) (p-value – 0.00003; OR – 5). The signs of hypercoagulation were seen in 15% in the 1st group, in the 2nd group there were only 11% of cases (p-value – 0.001). Moderate level of thrombocytosis was seen in each 2nd patient of the 1st group and in each 4th patient of the 2nd group. The marked disturbances of lipid metabolism were determined in the 1st group in comparison with the 2nd group (p-value - 0,004). Statistically significant association with the risk of restenosis was found with thrombomodulin (THBD) gene polymorphism rs1042579 (OR-1.7, p-value – 0.01) and fibrinogen beta-chain gene polymorphism rs1800790 (OR-2.1, p-value – 0.009).
Conclusions: 1) Availability of coronary heart disease and hypertension in the first line of kinship relatives increases the risk of coronary artery restenosis after stenting to 6.4 and 5 times, respectively. 2) Laboratory biochemical predictors of restenosis may be hypercholesterolemia (OR-1.5 p-0.0001), hypertriglyceridaemia (OR-8.8, p-0.004), hyperlipidemia (OR-4, 8, p-0.0001). 3) Reveling of thrombomodulin (THBD) gene polymorphism rs1042579 and fibrinogen beta-chain gene polymorphism rs1800790 may be used as predispose factors of coronary restenosis.

C0158
VENOUS THROMBOSIS IN UNUSUAL SITES: THROMBOPHILIA MARKERS

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Background: Venous thrombosis in uncommon sites usually includes venous thrombosis of the upper extremities, abdominal, cerebral and retinal venous thrombosis. Such venous thromboembolisms require specific etiologic and therapeutic approach. The purpose of this study is to establish the profile of thrombophilia markers in patients with uncommon site venous thromboembolism (VTE).
Methods: patients with unusual site VTE were recorded between January 2013 and October 2014. Demographic data, personal risk factors and results of thrombophilia investigation were analyzed. Screening for inherited thrombophilia included tests for antithrombin activity (AT): stachrom AT, protein C (PC) and protein S (PS) activities (respectively, Staclot PC and Staclot PS) and the activated PC resistance test (Staclot aPCR).
Results: Ninety-nine patients were enrolled. The mean age was 37.6 year-old [4 months-75 year-old]. The sex ratio was 0.55. The VTE sites were: upper limbs (n=7), cerebral (n=43), abdominal (n=36) and retinal (n=5) veins. Jugular veins, right heart and vena cava represented 8% (n=8) of total sites. Combined unusual site VTE was observed in 9 cases. An underlying disease or triggering event was reported in 28 patients: pregnancy (n=4), post-partum (n=3), haemopathy (n=5), chronic liver disease (n=7), systemic disease (n=3), inflammatory bowel disease (n=3), infection (n=2), contraceptive pills (n=1). In the abdominal sites, combined thrombophilia markers were observed in 11 patients and mainly related to liver failure. Concerning cerebral vein thromboses, there were a PS deficiency in one patient, PC deficiency in one patient and activated PC resistance in one patient. Among thromboses in upper limbs, PC deficiency was noted in one patient and an activated protein C resistance in one patient. Furthermore, the tests were normal in all patients with retinal vein thrombosis.
Conclusions: Unusual site thromboses represent uncommon and heterogeneous manifestations of VTE. The literature focused on risk factors of developing such thromboses. Combined deficiencies in abdominal thrombosis are difficult to interpret especially in liver failure. Both local and systemic risk factors have been involved in Retinal Vein Occlusion but only hyperhomocysteinaemia and anticardiolipin antibodies seemed significantly and independently associated with such thromboses.

C0161
CEREBRAL AMYLOID ANGIOPATHY AND MRI-VISIBLE PERIVASCULAR SPACES

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Background: Perivascular spaces (PVS) surrounding cerebral perforating arterioles and venules are an important drainage conduit for cerebral interstitial fluid. The data about enlarged PVS, their etiology and specificity to cerebrovascular disease or ageing is unclear.
Methods: We presented four cases with MRI-visible enlarged perivascular spaces and cerebral paranchimal hemorrhage. All patients fulfil the modified Boston criteria for probable cerebral amyloid angiopathy.
Results: Case-1: A 66-year-old man gave the history of an acute intracerebellar hemorrhage 3 months ago and progressive cognitive decline since then. He had diabetes mellitus and hypertension for 10 years. His MRI showed enlarged PVS and resorbed cerebellar hemorrhage and cerebral micro bleeding on susceptibility weighted imaging of MRI sequences.
Case-2: A 63-year-old man, displaying progressive walking difficulty, cognitive impairment, coordination disorder for 6 months had hypertension for 12 years. His MRI showed bilateral hemispheric white matter ischemic lesions, pontin infarction and diffuse microbleeding on the gradient echo sequences in addition to the enlarged PVS on basal ganglia and centrum semiovale.
Case-3: A 81-year-old man, having indifference and forgetfulness during the last year had acute left hemiperesis, no history of diabetes and hypertension. His MRI displayed two intracerebral hematomas located in the left temporal lobe and deep basal ganglia and leukoaraiosis as well as visible perivascular spaces.
Case-4: A 65-year-old woman had the anamnesis of left hemiparesis and hypertension for 4 months. Her MRI showed a resorbed thalamic hemorrhage and diffuse small vessel disease on the centrum semiovale, corona radiata and subcortical white matter and marked PVS.
Conclusions: Dilatation of PVS in the cerebral white matter in cerebral amyloid angiopathy may relate to impaired interstitial fluid drainage due to amyloid deposition in perforating arterioles. Further investigations of MRI-visible PVS in stroke are required to determine their pathophysiological role in cerebral amiloid angiopathy.

C0196
THE DIAGNOSTIC VALUE OF SPECAM-1 AND VESSEL WALL DISORDERS IN ARTERIAL HYPERTENSION ASSOCIATED WITH DIABETES MELLITUS OF TYPE 2

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Background: PECAM-1 is type-I transmembrane glycoprotein expressed on the surfaces of platelets, leukocytes and endothelial cells, which can appear its biological function mainly via signal transduction rather than adhesion. It works as bidirectional regulator of platelet reactivity and thrombosis serving as suppressor of thrombus formation. Some studies proved that PECAM-1 plays a role as a part of mechanosensory responsible complex in the arterial walls. It was set that PECAM - 1 assisted to develop the atherosclerotic injury of vessels by strengthening of migration of leucocytes.
Methods: Our aim was to set the level of the expression of soluble PECAM (sPECAM-1), taking into consideration the state of endothelial vasodilatation, and mechanical features of arteries in patients with arterial hypertension and diabetes mellitus of type 2, using enzyme immunoassay method. For this purpose 146 patients with arterial hypertension and among them were 101 patients diabetes comorbidity were examined.
Results: It was set the reliable correlation between the sPECAM-1 expression and insulin resistance index level (HOMA-IR) ($p<0.05$). The decline of tensility, elasticity, local inflexibility and increase of one point pulse wave velocity were accompanied by forced expression of adhesion molecule ($p<0.05$). Positive correlation was verified between sPECAM-1 concentration and shear stress ($p=0.058$) in endothelium dependent vasodilation, and, also, negative correlation between sPECAM-1 increasing and endothelium sensitivity in vasodilatation test ($p=0.08$). Taking into account these associations the optimal diagnostic value of this molecule was calculated for endothelial dysfunction state. The diagnostic value by the AUC of sPECAM concentration was set at 77.3±6.18% (65.2% - 89.5%), $p<0.001$. Diagnostic OR was 13.0 for cutpoint of 52.25 ng/ml of sPECAM-1, likelihood ratio for true positive results at this level was 1.11 (0.45 – 2.78).
Conclusions: The overexpressed level of sPECAM-1 can be use as the additional predictor of mechanical damage of big vessels in patients with arterial hypertension.

C0199
THE BASAL ACTIVITY OF VON WILLEBRAND FACTOR AFTER PREVIOUS THROMBOTIC COMPLICATIONS IN PATIENTS WITH ARTERIAL HYPERTENSION ASSOCIATED WITH DIABETES MELLITUS OF TYPE 2

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Background: The number of clinical studies has shown the critical role of von Willebrand Factor (VWF) in haemostasis from the point of view of its relationship with thrombotic complications in cardiologic patients. Increased levels of VWF are associated with different atherothrombotic complications, which are not limited to myocardial infarctions (MI), but also include stroke. Some study proved the potential role of VWF in various non-hemostatic processes, like intimal thickening, tumor cell apoptosis and inflammatory processes. From the other hand, the vessel injuries such as macroangiopathy and microangyopathy are typical clinical complications of the diabetes mellitus type 2. We supposed that von Willebrand Factor may play more recent role in the state of the vessel injury in patients with concomitant arterial hypertension and diabetes mellitus even after the episodes of outcomes such as MI or stroke.
Methods: For this purpose we have learnt the activity of VWF in blood plasma of 157 patients with arterial hypertension, among them 101 patients suffered from diabetes mellitus of type 2, using specific standardized VWF-reagent ("RENAM", Russia). 23 persons of the study group had previous 6 month myocardial infarction and 19 patients previously had transient ischemic attack (TIA) last 6 month too. 11 people had both types of these outcomes.
Results: We have set a reliable increase of VWF activity in group of patients with concomitant diabetes mellitus of type 2 ($p<0.01$) on the contrast of arterial hypertension only. Also in the subgroup with the previous myocardial infarction the level of basal activity stayed higher than in other subgroups ($p=0.06$). In subgroup with TIA we also noted the tendency of the non-reliable increase of the VWF activity ($p=0.19$). But the activity of VWF in the groups of both outcomes was the highest, increasingly differs both from group with MI ($p=0.018$) and of group of TIA ($p=0.031$).
Conclusions: Our data proves the hypothesis that the level of basal activity of VWF stays increased after the acute thrombotic episode, mostly specific in previous MI and especially in association of MI and TIA and may be as a prognostic factor of newer recurrent episode of thrombotic complication, but due to this we need to realize more specific clinical investigation.

C0271
A COMPARISON OF CILOSTAZOL AND PENTOXIFYLLINE FOR TREATING INTERMITTENT CLAUDICATION: SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: Intermittent claudication (IC) is a common compliant in patients with peripheral vascular disease and may increase the risk of cardiovascular mortality. Antiplatelet treatment showed a reduction of vascular events among IC patients. The aim of this study is to compare the safety and efficacy of cilostazol versus pentoxifylline for the management of IC from published randomized controlled trials (RCTs).
Methods: A computer literature search of PubMed, Scopus, Web of Science, and Cochrane Central was conducted using relevant keywords. We included RCTs comparing cilostazol and pentoxifylline for the management of IC. Records were screened for eligible studies and data were extracted and synthesized using Review Manager version 5.3 for windows. Change in claudication distance and ankle brachial index were pooled as mean difference (MD between cilostazol and pentoxifylline group) in a fixed effect model using inverse variance (IV) method. All-cause mortality and complications were pooled as odd ratio (OR) in a fixed effect model using Mantel Haenzel (M-H) method. Heterogeneity was assessed by visual inspection of the forest plots and measured by I-square and Chi-square tests. P value below 0.05 was considered significant.
Results: Four RCTs were included in this study (N=1260 patients, cilostazol group n=628, and pentoxifylline group n=632). The overall effect estimate did not favor cilostazol in terms of initial claudication distance (MD f 20.00, 95% CI [-1.50 to 41.50], p=0.07), absolute claudication distance (MD 13.41, 95%CI [-43.52, 70.34], p=0.64), ankle brachial index (MD -0.01, 95% CI [-0.12, 0.10], p=0.85) and all-cause mortality (OR 0.58, 95% CI [0.17, 1.98], p=0.38). For complications, the pooled effects were: headache (OR 2.20, 95% CI [1.16, 4.17], p=0.016), diarrhoea (OR 1.80, 95% CI [0.79, 4.12], p=0.16) and abnormal stool (OR 3.12, 95% CI [1.57, 6.21], p=0.001).
Conclusions: Evidence is insufficient to confirm the superiority of cilostazol over pentoxifylline. Moreover, cilostazol shows an increase in risk of headache and abnormal stool.

C0347
INTERMITTENT LDL LOWERING THERAPY: RESET THE VASCULAR AGING CLOCK

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Background: Atherosclerotic cardiovascular disease is the leading cause of death worldwide. Adolescents and young adults have an increasing cardiovascular risk related to high rate of obesity, due to higher rates of type 2 diabetes, increasing blood pressure and dyslipidemia. A number of trials have shown that in adolescence and young adulthood risk factors are stronger determinants of atherosclerosis 15 to 20 years later than risk factors estimation at the time of the atherosclerotic screening imaging study.
Methods: It is well known that atherosclerosis begins at a very young age and the earliest lesions of atherosclerosis are present in late adolescence. Advanced lesions develop in the third and fourth decades of life, particularly in men with established cardiovascular risk factors. Evidence based medicine suggests that atherosclerosis regression and normalization of vessels is possible when LDL-cholesterol lowering occurs early in the course of atherosclerosis. A new paradigm was proposed and focused on curing atherosclerosis early in the course of the disease.
Results: Concept of this approach is to reset the vascular aging clock and it consists of: (i) initial short-term aggressive regression therapy i.e. an early moderate-intensity statin LDL-C–lowering strategy in children and adolescents, (ii) and an early, very aggressive LDL-C–lowering strategy in young adults, including the use of statins and possibly other lipid-lowering agents, (iii) followed by periodic retreatment to suppress atherosclerosis development. The final aim is to prevent subsequent cardiovascular events.
Conclusions: This new approach and new paradigm has been proposed propose which in essence is an aggressive pharmacological intervention i.e. "curing" atherosclerosis in the very beginning and therefore prevention of later development of clinically significant atherosclerotic disease.

C0348
WHAT IS DE FACTO SUBCLINICAL ATHEROSCLEROSIS: BIOMARKER, CONDITION OR DISEASE?

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Background: The aim of this article is to discuss a question - what is de facto subclinical atherosclerosis? At the moment it is worldwide accepted term for clinical entity which is practically undefined. What is subclinical atherosclerosis? Is it, (i) biomarker of cardiovascular risk, (ii) biomarker of subsequent cardiovascular events, (iv) or, preclinical atherosclerosis, (iii) or, incipient atherosclerosis, and finally, is it biomarker, condition or disease?
Methods: At the moment we have a number of observational studies indicated that increased values of atherosclerosis biomarkers as carotid IMT and/or coronary calcium score has predictive value of upcoming cardiovascular events. It means that we spoke about atherosclerotic markers and not subclinical condition. New ACC/AHA 2013 guideline introduce term of atherosclerotic vascular disease (ASCVD) which is actually appropriate term.
Results: Atherosclerotic disease is, irrespective of hemodynamically significance, long life threaten and thus deserve our full attention, rigorous controls, risk factor reduction and appropriate treatment. Difference of asymptomatic or symptomatic atherosclerosis should be based due to hemodynamically conditions i.e. grade of stenosis and plaque characteristics and not on subclinical or clinical atherosclerosis. Hemodynamically non-significant atherosclerotic disease should be grade as: (i) very early stage asymptomatic disease, (ii) moderate, borderline, asymptomatic disease with stable atherplaques. Hemodynamically significant atherosclerotic disease should be grade as: (i) borderline, stenotic disease, with stable atheroplaques, (ii) borderline, stenotic disease with unstable atheroplaques, (iii) severe, critical stenotic disease irrespective of plaque characteristics.
Conclusions: So, where is the place of subclinical atherosclerosis? If we found just single atherosclerotic plaque on any vascular bed, no matter of protrusion in the vessel lumen, it is no more subclinical atherosclerosis, it is atherosclerotic vascular disease. Aim should be to prevent further development of significant cardiovascular events, i.e. myocardial infarction, cerebrovascular insults, and arterial occlusive disease. Finally, we state that term, subclinical atherosclerosis is insufficient and that in real clinical work, should not be used.

C0355
SERUM VITAMIN B12 AND FOLIC ACID LEVELS IN ACUTE CEREBRAL ATHEROTHROMBOTIC INFARCTION

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Background: Hyperhomocysteinemia is an independent risk factor for atherothrombotic cerebral stroke. Vitamin B12 and folic acid are important determinants of homocysteine metabolism.
Methods: We evaluate the relation between vitamin B12 and folic acid levels and acute cerebral stroke in this study.
Results: Blood aliquots drawn within 24-48 hours after the stroke from hospitalized patients (n=60) with the diagnosis of acute ischemic cerebrovascular episode and also blood samples from 60 healthy controls without any vascular risk factor were analyzed. With a competitive chemo luminescence assay, serum levels of vitamin B12 and folic acid were measured in blood samples taken within 48 hours after the stroke. The differences and correlations were tested using frequency test, student-t test and multivariate analysis. Mean serum vitamin B12 levels were significantly lower in the patients than in the control subjects, 249.40 (S.D.: 170.3) and 271.8 (S.D.: 149.05.0) pg/ml respectively (p=0.01). This difference was independent from other risk factors. Likewise, mean serum folic acid levels were not lower in the patients than in the control subjects, 11.31 (S.D.: 6.17) and 13.61 (S.D.: 6.19) ng/ml, respectively (p=0.5).
Conclusions: We conclude that low vitamin B12 and folic acid concentrations are associated with an increased risk of stroke. For understanding the effects of B12 and folate in stroke patients, more detailed follow-up studies with long period are needed.

Deep vein thrombosis and PE

C0045
FORGOTTEN ENEMY. HEMORHEOLOGIC DISTURBANCES CAN LEAD TO THROMBOSIS IN SOME MYELOPROLIFERATIVE NEOPLASMS

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Background: Hemorheologic disturbances are the part of Virchow's triad. When this fact is forgotten antithrombotic prevention have low efficiency. The aim was to study the blood rheological behavior in patients with some myeloproliferative neoplasms.
Methods: Whole blood viscosity (WBV) was assayed in 16 adults with polycythemia vera (PV), in 42 young with acute lymphoblastic leukemia

(ALL), and in 67 healthy volunteers as the control group. Of patients 38% had thrombosis. Hematocrit, erythrocytes count and erythrocyte indices (MCV, MCH, MCHC), leukocyte count, fibrinogen and B-type natriuretic peptide (BNP) were analyzed simultaneously. In calculations parameters had for erythrocytes aggregability, erythrocytes deformability and shear flow.
Results: Increased WBV revealed totally in PV patients but not for all conditions in ALL patients. WBV was dependent on leukocytes count, MCH and on MCV. In all patients blood flow properties different from normal. Both myeloproliferative neoplasms increased totally erythrocyte aggregation but did not violate deformability of red blood cells, and lead to abnormal clot properties. Of patients 40% had elevated BNP assuming subclinical cardiac dysfunction. The latter explains discoordinated changes in shear stress values (Tau 9.84 mPa in PV, 16.7 mPa in ALL vs 12.2 mPa in donors) required for fully reversible erythrocyte aggregation. As a result, the residual units like "erythrocyte-erythrocyte" and/or "erythrocyte-leukocyte" interferes with the laminar flow due to forming of stagnation zones and violates mechanically the blood flow in small vessels.
Conclusions: We found that patients with some myeloproliferative neoplasms have abnormal blood flow properties creating non-hemocoagulation conditions for clot forming. We identified elevated WBV, impaired reversibility of erythrocyte aggregation due to increased hydrodynamic resistance of aggregates formed from different blood cells. From a pathophysiological point of view, the revealed hemorheologic disturbances could be as a trigger to start of VTE or to growth of blood clot in the area of permanent venous catheter. Therefore targeted hemorheologic therapy looks attractive in addition to usual VTE prevention. However the choice of methods requires that this study shall be continued.

C0061
MESENTERIC ISCHEMIA: THE TIP OF THE ICEBERG

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Background: Acute mesenteric ischemia refers to a sudden hypoperfusion of the bowel, one possible cause being mesenteric vein thrombosis (MVT). This is a rare entity present only in 1 of 15,000 individuals, but has an overall reported mortality of up to 50%. Early diagnosis is complex and of upmost importance before bowel ischemia is instored.
Methods: A 67 year old woman admitted in our center presenting abdominal pain of 48 hours evolution. She had a history of diabetes, hypertension, severe pulmonary hypertension, moderate tricuspid valve insufficiency with dilation of right heart cavities and two miscarriages at 4 months pregnancy. Two weeks before she had been admitted in the Internal Medicine Department for acute renal failure due to excessive use of diuretics and anemia. Physical examination showed pain and tenderness in right hemi-abdomen and defense. Rutinary bloodwork showed 22,580 leucocytes (85.2% of neutrophils) and reactive C protein 230 mg/L. Abdominal CT showed filling defect starting in the portal vein up to splenic and superior mesenteric vein and its branches, as well as bowel wall engorgement (positive Rigler sign). The patient underwent emergency surgery and required bowel resection due to irreversible ischemia of the ileum. After surgery, treatment with intravenous unfractioned heparin was instored and an evaluating protocol for patients with established tromboembolism for acquired and inherited risk factors was indicated.
Results: On the fifth day of the postoperative period the patient started treatment with low molecular weight heparin as a bridge to definitive anticoagulation with acenocumarol. More specific blood tests showed an unexplained prolongation of activated partial thromboplastin time which strongly suggested the presence of lupic anticoagulant, and a VIII factor of 319%. Once confirmed the diagnosis of a thrombofilic disorder the patient received discharge after an uneventful postoperative period and indefinite oral anticoagulation.
Conclusions: The most common presentations of venous thromboembolism are deep vein thrombosis of the lower extremities and pulmonary embolism. Since up to 75% of cases of MVT associate underlying factors (either acquired or hereditary), careful background checks and thorough examinations in search for clues of the fundamental causes of this pathology are essential to avoid its progression and recurrence. Therefore, the first step in treating MVT is recognizing underlying factors.

C0074
SYMPTOM OF "IRONED OUT GLUTEAL SULCUS" – A RELIABLE DIFFERENTIAL DIAGNOSTIC "TOOL" FOR THE DIAGNOSIS AND CLINICAL MONITORING OF THE DEEP VENOUS THROMBOSIS (DVT) OF ILIAC VEINS

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Background: Topalov (1981) substantially expands and complements the pattern of Shumacker (1952) for the six typical correlations between the oedema location and the level of the venous thrombosis with five new correlations, one from which is the symptom of "ironed out gluteal sulcus".
Methods: Topalov (1976) establish DVT of the common and external iliac veins in 8.65% from studied 2236 patients with venous thrombosis. The nature of the symptom of "ironed out gluteal sulcus" in these patients is discussed.
Results: The presence of oedema is important clinical symptom for DVT. On the extent to which the oedema reaches the different parts of the body the physician can draw conclusions for the upper level of the thrombosis in the affected vein. Topalov (1981) showed the symptom of "ironed out gluteal sulcus" as important clinical diagnostic "tool" for the iliac veins thrombotic status. The symptom is positive in the cases with the DVT in the common iliac veins and is negative in the cases in which the DVT in the common iliac veins is absent. The positive symptom of "ironed out gluteal sulcus" in the cases with the DVT of common iliac veins is due to the facts, that the venous drainage from the basin of the internal iliac veins is partially or totally interrupted. As results in the regions drained through the parietal influent branches of the internal iliac veins venous stasis occur, the oedema is developed in the soft tissues of the gluteal region and the gluteal sulcus is "ironed out". However, for the exact clinical diagnosis, the patient must be examined in a stand position, without clothes which cover the gluteal regions and the lower limbs. In addition, in the cases with DVT of the common iliac veins the venous stasis is developed in the rectum, urinary bladder, prostatic gland, and in the ovary from the site of the thrombosis, too.
Conclusions: In the cases with DVT in the common iliac veins the symptom "ironed out gluteal sulcus" is positive. In the cases with DVT in the external iliac veins, but without DVT in the common iliac veins the symptom of the "ironed out gluteal sulcus" is negative.

C0085
PLATELET VOLUME AS A PROGNOSTIC FACTOR OF PULMONARY THROMBOEMBOLISM

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Background: Pulmonary embolism (PE) is a frequent and with a fatality rate of 5-10%. Mean platelet volume (MPV) is a risk factor for cardiovascular complications and cerebrovascular disorders, and inflammatory conditions. Our aim is to evaluate the association between high VPM and 90-day survival after a PE episode
Methods: Prospective cohort of all consecutive adult patients with a first episode of PE were included in the Institutional Register of Thromboembolism (Institutional Registry of Thromboembolic.-Home-ClinicalTrials.gov, NCT01372514) between 2014 and 2015, in the Hospital

Italiano, Buenos Aires, Argentina. MPV was evaluated during the PE event and follow-up was until 90 days or death. MPV was considered high if > 11 fL. Survival was estimated with Kaplan Meier. Cox regression was used to evaluate MPV and death, crude (HRc) and adjusted hazard ratios (HRa) were reported.

Results: We included 147 patients, with a median age of 73 years, 57% were female. The main comorbidities were: 49% cancer, 15% coronary disease, 15% sepsis and 10% stroke. Median MPV was 8 fl (8- 10), serum troponin 22.5 pg/ml (12- 50), proBNP 1055 pg/ml (298-2600). Prevalence of high MPV was 17% (25). Overall mortality was 22.4% (33). 7 day survival estimate was 0.88 (95%CI 0.67-0.95) vs 0.97 (95%CI 0.91-0.99); 30 day survival 0.64 (95%CI 0.42-0.79) vs. 0.91 (95%CI 0.85-0.95); and 90 day survival estimate was 0.52 (95%CI 0.31-0.69) vs. 0.82 (0.74-0.88) for high MPV and normal MPV respectively. Overall survival estimate was statically different (p<0,001). Crude HR of mortality for high VPM was 3.61 (95%IC 1.77-7.35, p<0.001). Age, female gender, sepsis, coronary disease, ProBNP elevation and ventricular dysfunction were not associated with death. TUS over 20pg/dL had a HR of 2.30 (95%IC 1.07-4.96, p=0.033) and cancer had a HR of 3.95 (95%CI 1.83 – 8.50, p<0.001). HR of death for high VPM adjusted by cancer and TUS over 2 pg/dl was 3.45 (95%CI 1.66 - 7.17; p<0.001).

Conclusions: High MPV is an independent risk factor for mortality following an episode of PE.

C0126
THE CORRELATION BETWEEN PLASMA D-DIMER AND PLASMA AND URINE PROTHROMBIN FRAGMENT 1 + 2 IN NON-COMORBID PATIENTS WITH SUSPECTED DEEP VEIN THROMBOSIS.

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Background: D-dimer measured in plasma (pD-dimer) is a feasible test to exclude deep vein thrombosis (DVT) when the clinical probability is low. Prothrombin fragment 1 + 2 (F1 + 2) may also be used as a pretest that can be analysed both in plasma (pF1 + 2) and urine (uF1 + 2). We recently published data that showed positive correlation between pD-dimer, pF1 + 2 and uF1 + 2 in non-selected patients with suspected venous thromboembolism. In the present study we investigated the correlation between these biomarkers in a subset of the population, i.e. in patients with suspected DVT who are otherwise healthy.

Methods: Patients with clinically suspected DVT and without known comorbidities were included. Urine and blood samples were collected before examination with compression ultrasound. The samples were analysed with ELISA kits. To assess differences in biomarker levels between DVT negative and positive patients the Mann-Whitney U test was used. The overall performance was determined with the area under the curve (AUC) of the receiver operator characteristic (ROC) curve. Dependence between the biomarkers was assessed with Spearman`s rank correlation (r_s).

Results: DVT was diagnosed in 39 (22%) of the 176 included patients. Those with DVT had statistically significant higher levels of pD-dimer (2998 ng/mL), pF1 + 2 (460 pmol/L) and uF1 + 2 (53 pmol/L) compared to those without DVT (376 ng/mL, 233 pmol/l and 20 pmol/L respectively), p<0.001. Plasma D-dimer had the highest AUC (0.881) followed by pF1 + 2 (0.835) and uF1 + 2 (0.723). A positive correlation was found between pD-dimer and pF1 + 2 (r_s=0.76) and between pF1 + 2 and uF1 + 2 (r_s=0.44). 86 (49%) patients had levels of uF1 + 2 that were not detectable, i.e. below 20 pmol/L. Exclusion of these patients increased the AUC of pD-dimer and pF1 + 2 with 4% and uF1 + 2 with 9% and the correlation between pF1 + 2 and uF1 + 2 increased (r_s=0.50).

Conclusions: In this selected population significantly higher biomarker levels were found in patients with DVT compared to those without. Plasma D-dimer had the best overall performance followed by pF1 + 2 and uF1 + 2. When excluding patients with non-detectable uF1 + 2 levels, the performance of F1 + 2 in urine increased more than the performance of pF1 + 2 and pD-dimer. In addition, the correlation between uF1 + 2 and pF1 + 2 increased. This indicates that increasing the uF1 + 2 test sensitivity may improve its performance and allow it to be an alternative non-invasive pretest.

C0135
OUR CLINICAL EXPERIENCE IN THE EVALUATION OF MESENTERIC VEIN THROMBOSIS

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Background: Mesenteric vein thrombosis occurs rarely and is responsible for approximately 5-15% of all cases of acute mesenteric ischemia. The aim of this report was to discuss the management of mesenteric vein thrombosis based on our experience with 59 patients.

Methods: In the present study, 59 patients who were admitted to our emergency surgery department between January 2010 and July 2015 with a diagnosis of acute mesenteric ischemia were assessed retrospectively. Patients with peritoneal signs first underwent diagnostic laparoscopy to rule out perforation or bowel necrosis. All patients were administered 100 mg/kg of the anticoagulant enoxaparin twice daily.

Results: CT angiography revealed superior mesenteric vein thrombosis in 14 (23%) patients, portal vein thrombosis in 6 (10%) patients, and splenic vein thrombosis in 2 (3%) patients. Four patients with peritoneal signs underwent diagnostic laparoscopy; two of the patients performed small bowel resection, anastomosis, and trocar insertion. In a patient reactional fluid and edema was seen in 60 cm small intestine and another patient 20 cm segmental edema seen and second look laparoscopy was made.

Conclusions: Early diagnosis with CT angiography, conservative treatment with proper anticoagulation and laparoscopic second look detecting with supportive intensive care are the cornerstones of successful treatment of mesenteric vein thrombosis

C0143
VENOUS THROMBOEMBOLISM IN WOMEN USING HORMONAL CONTRACEPTION. FINDINGS FROM A SINGLE CENTER

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Background: Venous thrombosis including deep-vein thrombosis (DVT) and pulmonary embolism (PE) is considered a multifactorial disease associated with genetic and acquired risk factors. In women of reproductive age, the main cause of venous thromboembolic disease (VTD) is the hormonal contraception. However, other risk factors interact to produce VTD. Identifying these factors, may intervene in risk situations and limit the occurrence of VTD with its potential morbidity and mortality.

Methods: We reviewed the characteristics of our series of 103 women with objectively confirmed VTD associated with hormonal contraception. We analyzed its clinical data and thrombophilia studies which were performed in more than 80% of them and included anticoagulant proteins, genetic tests, antiphospholipid antibodies and factor VIII level. Statistical analysis was performed with SPSS 18.0 software.

Results: See Table 1.

Table 1

Patients, N	103
Clinical characteristics	
Mean age (years ± SD)	29 ± 7.4
Body mass Index (Kg/m² ± SD)	25.8 ± 5.9
Body mass Index >25 Kg/m²	25 (46.3%)
Risk factors for venous thromboembolism	
Immobility	29 (30.9%)
A family history	23 (27.4%)
Polycystic ovary syndrome	9 (9.8%)
Type of combined oral contraceptive	
Including antiandrogen	27 (52.9%)
Including second generation progestogen	3 (5.9%)
Including third generation progestogen	21 (41.2%)
Venous thromboembolism characteristics	
Pulmonary embolism	45 (44.6%)
Proximal deep vein thrombosis	53 (52.5%)
Upper-extremity deep vein thrombosis	3 (3%)
Thrombophilia tests	
Factor V Leiden	11 (12.9%)
Prothrombin mutation	18 (20.5%)
Antiphospholipid syndrome	3 (2.9%)
Protein C deficiency	0 (0%)
Protein S deficiency	2 (2.4%)
Antithrombin deficiency	0 (0%)
Increased factor VIII	14 (18.7%)

Conclusions: Contraceptive use remains the most important risk factor for VTD in women of reproductive age. We observe additional risk factors such as obesity, immobilization, polycystic ovary syndrome or family history of VTD and certain thrombophilic defects. G20210A prothrombin and G1691A factor V Leiden mutations as well as elevated factor VIII (which has been associated to blood group non O) are frequent in women at a fertile age and should be part of thrombophilia study. Defining high risk patients may improve interventions in risk situations (e.g. administering antithrombotic prophylaxis or discontinuing contraceptive use after lower limb trauma) in order to prevent VTD. Finally, the increased thrombotic risk of antiandrogen and third generation contraceptives should be also taken into account.

C0144
INCORPORATION OF DOACS IN CLINICAL MANAGEMENT OF VTE. EXPERIENCE FROM THE HEMOSTASIS UNIT OF A GREEK TERTIARY HOSPITAL

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Background: We have experienced a revolution in anticoagulation by the invention of direct oral anticoagulants. Recently EMEA approved the introduction of DOACs in venous thromboembolism (VTE) management. Although safety and efficacy were documented in the introductory studies of DOACs, still they must prove their value in daily clinical practice.
Methods: The aim of our study is to evaluate safety and efficacy of DOACs in patients on long-term anticoagulation who attended our hemostasis unit, and investigate whether thrombophilia affects the rate of hemorrhagic complications.
Results: A total of 90 patients (51% male), at median age 45.5 (range 15-78) years, were treated for a median of 11.5 (1-39) months, accounting for a total of 88.83 person-years of observation. Indication for anticoagulation was deep vein thrombosis (DVT) (55.6%), pulmonary embolism (PE) (18.9%), concurrent DVT/PE (14.4%), inferior vena cava thrombosis (5.6%), central nervous system thrombosis (2.2%). One or more thrombophiliic factors were present in 64% of patients, the commonest being factor V Leiden in 28%, raised homocysteine in 27%, prothrombin 20210G>A in 17% of patients. Hemorrhagic complications, mainly increase in menstrual loss (4.4%) and nose-bleeds (3.3%), were classified according to the definitions of SSC ISTH (Kaatz et al, 2015). No major bleeding was observed; the incidence rate of clinically relevant non major bleeding was 3.4 and of minor hemorrhage 10.1 events per 100 person-years. The incidence rates of any grade of hemorrhage in patients with any thrombophilia versus none thrombophilia were 7.9 and 27.7 respectively, p=0.02. The incidence rate ratio was 0.28 (95%CI 0.08-0.92). Thrombophilia appears to have a protective effect for hemorrhage in anticoagulated patients. Other adverse events reported were worsening of post-thrombotic syndrome (3.3%), headaches (2.2%), itching (1.1%). Nine patients (10%) discontinued DOACs, due to hemorrhage (5.5%), other adverse events (3.3%), and one patient after acute coronary syndrome.
Conclusions: We have enriched the anticoagulant armamentarium with new promising effective and easy to use drugs. In order to have a clear view on their safety and efficacy long term data and data from Registries are needed. Thrombophilia's impact on bleeding risk of anticoagulated patients seems protective and should be investigated in larger cohorts of patients.

C0149
BILATERAL LOWER LIMBS DEEP VENOUS THROMBOSIS: A STUDY OF 15 CASES

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Background: Bilateral deep Venous thrombosis (DVT) of lower limbs is an uncommon situation. The aim of this study was to identify its epidemiological, clinical and etiological features.
Methods: It's a retrospective study including patients with bilateral lower limbs DVT admitted in an internal medicine department during a period of 15 years. Doppler ultrasonography was used in all cases for DVT diagnosis.
Results: Fifteen patients with bilateral lower limbs DVT were enrolled in this study (0.01% of total patients with lower limbs DVT). The mean age of patients was 48.8 years and the sex-ratio M/F was 2.75. No personal or family history of DVT was found in our patients. Thrombosis was extended to inferior vena cava in 3 patients and pulmonary embolism was seen in 2 cases. DVT risk factors were found in four cases: surgery (n=2) and immobilization (n=2). Behçet's disease, inferior vena cava agenesis and retroperitoneal fibrosis were diagnosed each one in one patient. One patient had an antiphospholipid syndrome and another had a nephritic syndrome. High level of homocystein was noted in one case. Six patients had malignancies: testicular cancer (n=1), vulvar cancer (n=1), lung cancer (n=1), hepatocellular carcinoma (n=1), bladder cancer (n=1) and multiple myeloma (n=1). Malignancy was previously known in 83.33% of cases and was metastatic in 66.66% of cases. Treatment was based on low molecular weight heparins, relayed by oral vitamin K antagonist in all patients. The initial response to therapy was favorable in all cases. Late complications were mainly recurrences (n=4). Six patients were lost to follow up while four patients were referred to other specialists for etiological treatment. The mean treatment's period was of 46.3 months.
Conclusions: Bilateral lower limbs DVT seems to be under-diagnosed, since their incidence was 7% in a study evaluating DVT in patients with single limb or bilateral symptoms and 19.7% in another series of patients who presented with only unilateral symptoms but screened for the 2 limbs. In our hospital, patients are only screened for symptomatic limb. Malignancies especially active ones seem to be a major cause of these thromboses.

C0155
ASSOCIATION OF TISSUE FACTOR PATHWAY INHIBITOR GENE POLYMORPHISMS 399C/T AND 33T/C WITH DEEP VEIN THROMBOSIS

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Background: One of the major causes of morbidity and mortality in India is deep vein thrombosis (DVT). Tissue factor pathway inhibitor (TFPI) plays a vital important role in the blood coagulation pathway. Previous studies reported that low level of TFPI in plasma is risk factor for DVT, however polymorphism in TFPI gene as a risk factor for DVT remains controversial. The aim of present study is to determine the role of tissue factor pathway inhibitor gene polymorphisms at position 399C/T and 33T/C in the development of DVT in North Indian population.
Methods: We examined two polymorphisms of TFPI gene 399 C/T and 33 T/C in 70 patients with DVT and in equal number of age and sex matched healthy controls. All study subjects were typed for 399 C/T and 33T/C polymorphisms using allele specific PCR and PCR-RFLP method respectively.
Results: The genotype frequency of C399T polymorphism was higher in patients (35.7%) compared to controls (12.8%) and this difference was statistically significant (P=0.003). Significantly higher prevalence of 33 T/C Polymorphism in controls (71.4%) compared to patients (52.8%) group (p=0.036).
Conclusions: Both the polymorphisms of TFPI gene were significantly associated with risk of DVT and TFPI 33T/C shows a protective effect in DVT. A study with large sample size representative of the diverse Indian population along with TFPI levels would be required to confirm this finding.

C0185
UPPER LIMBS VENOUS THROMBOSES: A STUDY OF 32 CASES

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Background: The objectives of this study were to describe demographic and clinical features of upper-extremities venous thromboses (VT) and to determinate their causes and outcome.
Methods: A retrospective study of the cases of upper limbs VT seen in an internal medicine department during a period of 15 years. VT diagnosis was confirmed by Doppler ultrasonography in all cases.
Results: Thirty two patients were included in the study. The mean age at the moment of VT occurrence was 48.8 years. The sex-ratio M/F was 1.9. Personal and family histories of VT were found respectively in 4 and 3 patients. Upper extremities symptoms were pain (93.75%) and edema (100%). Thrombosis was deep in 23 cases, superficial in 6 patients and associated in 3 cases. Thromboses locations were humeral vein (n=12), axillary vein (n=12), subclavian vein (n=15), cephalic vein (n=5), basilic vein (n=3), brachial vein (n=2) and radial vein (n=2). Upper limbs thromboses were extended to jugular veins in 7 patients and to brachiocephalic trunk in 3 cases. There were no apparent risk factors in 7 cases. Malignancies (n=9), venous injections or catheters (n=6) and constitutional thrombophilia (n=3) were the main causes of upper limbs thromboses in our patients. Malignancies found in this series were breast cancer (n=3) peritoneal mesothelioma (n=1), endometrial adenocarcinoma (n=1), ovarian cancer (n=1), renal cancer (n=1), lung cancer (n=1) and thyroid cancer (n=1). VT revealed cancer in 2 cases. Behçet's disease and antiphospholipid syndrome were diagnosed respectively in one and two patients. One patient had hyperhomocysteinemia and other was treated by carbamazypin. A hypereosinophilic syndrome was diagnosed in one case. Treatment was based on low molecular weight heparin (n=28), or unfractionated heparin (n=4) relayed by vitamin K antagonist (n=30). The outcome was good in all cases. Recurrence was seen in 5 patients. Nine patients were lost to follow up while four patients were referred to other specialists for etiological treatment. The mean treatment's period was of 21.9 months.
Conclusions: Upper-extremities venous thromboses are uncommon, they must be considered in patients with upper limbs edema or pain, especially in patients with malignancy or catheters. In patients with this atypical location of VT, malignancies must be carefully screened. Constitutional thrombophilia can be main causes in young patients with a family history of VT.

C0190
THE INVESTIGATION OF NATURAL ANTICOAGULANT DEFICIENCIES IN PATIENTS WITH DEEP VEIN THROMBOSIS

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Background: Deep vein thrombosis (DVT) is one of the most common forms of venous thromboembolism (VTE). There is an increasing evidence that patients with deficiency of natural coagulation inhibitors are susceptible to DVT. Since inherited risk factors can influence thrombophilic patients, understanding the influence of natural anticoagulants deficiencies in prevalent regions is essential to provide a comprehensive assessments for accurate identification and differential diagnosis especially in patients with DVT Symptoms.
Methods: In this cross sectional study, we have investigated all the patients with DVT that referred to Iranian Blood Transfusion Organization (IBTO) during Apr. 2013 - Oct. 2015. Of the initial 656 DVT patients, 141 cases without acquired risk factors were included in our study. Protein S, protein C, antithrombin and resistance to activated protein C (APC-R) were measured with coagulometer, using kits of Diagnostica Stago in order to investigate any defect in natural anticoagulant proteins.
Results: Mean age of female and male patients were 37 and 39 years, respectively. Protein S deficiency, with a frequency of 12.7% (18/141), was the most common defect in patients with DVT. Defect in APC-R was found in 4.9% of cases (7/141), following antithrombin and protein C deficiencies which had the lowest rate of 2.8% (4/141) and 2.1% (3/141), respectively. We also found a simultaneous defect of protein C and protein S in our population.
Conclusions: We assess a high prevalence of protein S deficiency compared with other natural anticoagulant in our patients. Our data represent the most comprehensive study with respect to natural anticoagulant deficiencies in DVT patients. We recommend population based studies in different ethnic groups in order to achieve a greater impact of hereditary risk factors in cases with thrombosis.

C0191
VENA CAVA THROMBOSES: A STUDY OF CLINICAL AND ETIOLOGICAL FEATURES OF 42 CASES

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Background: The aim of this study was to describe clinical and etiological features of vena cava thrombosis.
Methods: We conducted a retrospective study of patients with vena cava thromboses diagnosed in an internal medicine department over a period time of 15 years. Patients underwent angio-computed tomography for vena cava thrombosis diagnosis.
Results: Forty two patients with vena cava thrombosis were enrolled. The mean age was 43 years (ranges 18-85) and the sex-ratio M/F was 2.8. Twenty six patients had inferior vena cava thrombosis (IVCT) and 18 patients had superior vena cava thrombosis (SVCT) (2 patients had superior and inferior vena cava thrombosis). Eleven patients had personal history of venous

thrombosis. IVCT was discovered incidentally in 80% of cases, otherwise it was revealed by bilateral lower limbs edema. Patients presented with lower limbs edema (61%), pain (19%) and collateral venous circulation (15%). Concomitant thromboses were found in 80% of patients: lower extremities (19 cases), atypical locations (7 cases), pulmonary embolism (3 cases) and superficial thrombophlebitis (n=2). Six patients had Behcet's disease and 5 had malignancy (bladder cancer, endometrial adenocarcinoma, testicular carcinoma and 2 patients had metastasis with unknown primitive cancer). Inherited thrombophilia was noted in 2 cases and one patient had inferior vena cava agenesis.

SVCT was discovered incidentally in 4 cases and revealed by a superior vena cava syndrome in 72% of cases. Collateral circulation (72%), bilateral upper extremities edema (45%), headache (5%) and dyspnea (22%) were other signs of SVCT. SVCT was associated to other locations in 77.7% of cases: upper extremities (n=8), cerebral (n=2), lower extremities (n=1), retinal (n=1) and sub clavicular (n=1). Pulmonary embolism was diagnosed in 2 cases. Behcet's disease (n=10) and pulmonary carcinoma (n=2) were the main causes of SVCT. Association of superior and inferior vena cava thrombosis were seen in a patient with Behçet's disease and another with hyperhomocysteinemia.

After treatment, thrombosis disappeared in 6 cases, persisted in 4 cases and extended in 2 cases. Two patients had another thrombosis location. Three patients died. The mean follow up was 4 years.

Conclusions: In our series Behcet's disease and malignancies seems to be major causes of vena cava thrombosis.

C0192 A
TYPICAL LOCATIONS OF VENOUS THROMBOSIS: A STUDY OF 47 CASES

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Background: Atypical venous thrombosis (TV) concerns unusual locations other than the lower limbs. These locations are uncommon and require careful etiological approach. The aim of this study is to describe clinical data and topographic and etiological characteristics of atypical venous thrombosis in unusual locations in a group of patients hospitalized in an internal medicine department.

Methods: This is a retrospective study that included 47 patients hospitalized between 1998 and 2014 for an atypical thrombophlebitis location diagnosed by Doppler ultrasound or CT angiography and/or magnetic resonance imaging.

Results: There were 29 men and 18 women. The average age was 49 years (23-84 years). The seat of thrombosis were: upper limbs (n = 11, 23.40%), portal veins (n = 11, 23.40%), vena cava (n = 9, 19.14%), hepatic veins (n = 5, 10.63%), cerebral veins (n = 5, 10.63%), renal veins (n = 2, 4.25%), jugular veins (n = 2, 4.25%), supraclavicular vein (n = 1, 2.12%), innominate trunk (n = 1, 2.12%), and temporal vein (n = 1, 2.12%) An etiological investigation was performed for all patients. The etiologies were neoplasia in 13 cases, Behcet's disease in 5 cases and systemic lupus erythematous in a case. Thrombophilia was diagnosed in 6 patients (resistance to activated protein C = 3 case, protein C deficiency = one case, hyperhomocysteinemia = 2 case). Sepsis was noted in 5 cases and nephrotic syndrome in 3 patients. ANCA vasculitis and an unclassifiable vasculitis were found in 2 cases. Venous thrombosis remained unexplained in 12 cases. All patients were started on anticoagulant associated with etiologic treatment.

Conclusions: Unusual thrombophlebitis locations represent a serious condition that requires careful exploration because of the prevalence of Para neoplastic origin.

C0197
THE SPLANCHNIC VENOUS THROMBOSIS: ABOUT 20 CASES

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Background: The splanchnic venous thrombosis designates the venous thrombosis of carries system extra and intrahepatic including terminal segment of inferior vena cava.

The aim of this study is to describe the epidemiological, clinical and etiological characteristic of the splanchnic venous thrombosis.

Methods: This is a retrospective study that included 20 patients hospitalized in an internal medicine department with splanchnic vein thrombosis diagnosed by Doppler ultrasound or CT angiography between 2000 and 2014.

Results: The sex ratio was 5.66. The average age was 48 years (23-82 years). The location of thrombosis interested mainly the terminal segment of the inferior vena cava in 7 cases. Mesenteric and supra-hepatic vein thrombosis was found in 5 cases each. Portal vein thrombosis was noted in 4 cases. Symptomatology varies according to locations (diffuse abdominal pain, ascites, fever, asymptomatic). Splanchnic venous thrombosis revealed the underlying pathology in 50% of cases. An etiological research was performed for all patients revealing: neoplastic causes in 6 cases, Behcet's disease in 4 cases, resistance to activated protein C in 3 cases. Sepsis was noted in 2 patients, ANCA vasculitis in one case and an unclassifiable vasculitis in one case. Venous thrombosis remained unexplained despite etiological investigation repeat in 3 patients. All patients were put on anticoagulants associated with an etiological treatment with good evolution.

Conclusions: Splanchnic vein thrombosis is a severe and unusual location because it cans life threatening. Careful etiological research must be done because of the high frequency of Para neoplastic forms.

C0198
TOPOGRAPHIC PROFILES OF UNUSUAL LOCATION VENOUS THROMBOSIS DURING VASCULITIS

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Background: It is well established that the vasculitis including Behçet's disease are associated with a significant risk of thromboembolism. The purpose of this study is to raise the topographic profile of unusual location venous thrombosis in the vasculitis in a group of patients in our service.

Methods: Retrospective study that included 47 patients hospitalized between 2000 and 2014 for an unusual location of thrombophlebitis diagnosed by Doppler ultrasound or CT angiography and/or magnetic resonance imaging.

Results: Eight patients had an unusual venous thrombosis associated to a vasculitis. It was seven men and one woman. The average age was 42 years (23-84 years). Behçet's disease etiologies dominate (5 cases). The seat of thrombosis was the inferior vena cava in 2 cases, the cerebral veins in a case, mesenteric veins in one case and the portal vein in one case. The other 2 patients, there was a ANCA vasculitis (1 case) associated with a thrombosis of the superior vena cava (TVC) and unclassifiable vasculitis (1 case) associated with thrombosis of mesenteric, splenic and brain veins. These were revealing thrombosis in 2 patients. All patients were started on anticoagulation associated with etiological treatment

Conclusions: Despite a clear predominance of neoplastic etiologies, venous thrombosis in an unusual location can be a complication or circumstance of discovery of vasculitis mainly Behçet's disease.

C0206
VENOUS THROMBOEMBOLISM AMONG THE POPULATION OF INTERNAL SECURITY FORCES AGENTS IN TUNISIA

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Background: Thromboembolic events are a large motive of hospitalization in internal medicine departments. The aim of our study was to determine the etiologic profile of venous thromboembolism in hospitalized patients in the internal medicine department of Internal Forces Security hospital and to describe its characteristics.
Methods: Patients hospitalized between January 2003 and December 2014 for venous thromboembolism confirmed by imaging were retrospectively studied. Demographic, clinical and evolutionary features were analyzed.
Results: One hundred and thirty six patients were included. They were 92 male and 44 female with a male to female ratio of 2.09. The mean age at diagnosis was 50 years with extremes varying from 17 to 82 years. Eighty nine patients (67.6%) had deep venous thrombosis in the lower limbs among which 17 (18.4%) were proximal and 75 (81.5%) were distal. A pulmonary embolism complicated the deep venous thrombosis in 7 cases and was isolated in 19 (13.9%). Twenty three (16.9%) patients presented one or many unusual location of thrombosis. A superficial vein thrombosis was found in 18 cases. The etiologies of thrombosis were neoplasia in 16 cases (11.76%) largely dominated by digestive cancers (50%), resistance to activated protein C in 7 cases, a protein S deficiency in 5 cases and a protein C deficiency in 3 cases. Hyper homocysteinemia was found in 8 cases. The antiphospholipid syndrome was the cause in 5 cases among which one case was associated with lupus erythematosus. In 2 cases the thrombosis was diagnosed during a Parkinson's disease and in 3 cases in patients with Crohn disease. The thrombosis complicated the course of an intense nephritic syndrome in 3 cases, vasculitis in 2 cases, connective tissue disease in 2 cases and celiac disease in one case. The etiology remained unknown in 82 cases (60.29%) however, 28 patients had thromboembolism risk factors. One hundred twenty five patients were treated with anti vitamin K. A favorable evolution was noticed in 134 cases, recurrence of thrombosis happened in 28 cases (one under anti vitamin K). Two patients died from cancer and acute lung edema.
Conclusions: The male ascendancy and the young age diagnosis in our study can be explained by a bias of recruitment because our patients are mainly professionally active. The relatively high frequency of the digestive cancers may be understandable by the presence of a unit of gastroenterology in our department making the access to the diagnosis of digestive cancers easier.

C0212
INCIDENCE OF PERIPHERAL CATHETER RELATED DEEP VEIN THROMBOSIS IN SURGICAL PATIENTS

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Background: Central venous catheters and peripherally inserted central catheters are well established risk factors for upper limb deep vein thrombosis. There is limited literature on the thrombosis rates in patients with peripheral catheters. A prospective observational study was conducted to determine the incidence of upper limb deep vein thrombosis in surgical patients with peripheral catheters.
Methods: Patients deemed high risk for venous thrombosis with a peripheral catheter admitted to the general surgical unit were considered eligible for the study. An ultrasound was performed on enrolment into the study and at discharge from hospital. Participants were reviewed twice a day for clinical features of upper limb deep vein thrombosis during their admission and followed up at 30 days.
Results: 54 patient were included in the study. The incidence of deep vein thrombosis and superficial venous thrombosis was 1.8% and 9.2% respectively. All cases of venous thrombosis were asymptomatic. Risk factor analysis was limited by the low incidence of deep vein thrombosis. There were no cases of clinically detected pulmonary embolism.
Conclusions: This study revealed a low incidence of deep vein thrombosis in surgical patients with peripheral catheters (1.8%). As the study was underpowered with a low incidence of thrombosis, the association between peripheral catheters and deep vein thrombosis is unable to be determined. Future studies with larger sample sizes are required to determine the association between peripheral catheters and thrombosis.

C0213
A SYSTEMATIC REVIEW OF PATIENT-RELATED RISK FACTORS FOR CATHETER-RELATED THROMBOSIS

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Background: Up to 66% of cases of catheter-related thrombosis are asymptomatic. The first signs of thrombosis may be catheter occlusion or, more worryingly, symptomatic pulmonary embolism. There is, therefore, a clinical imperative to identify patients who are more likely to develop catheter-related thrombosis. Closer monitoring of patients assessed as high risk for developing catheter-related thrombosis may prevent thrombotic complications. There have been no previous systematic reviews focusing on the clinical characteristics of patients who develop catheter-related thrombosis.
Methods: We performed a systematic review of the literature assessing patient-related risk factors for thrombosis related to CVC or PICC. The databases PubMed, Ovid and the Cochrane library were searched for observational studies pertaining to patient-related risk factors for central venous catheter and peripherally inserted central catheter-related thrombosis.
Results: The initial search through PubMed, Ovid and the Cochrane library yielded 516 results. After 71 duplicates were removed, 445 articles were assessed for eligibility based on title and abstract. 411 articles were then excluded and 33 full text articles were manually assessed for eligibility. Eight articles were eliminated as they did not contain content relevant to the review. Twenty-five studies were then selected to assess twenty risk factors. There were no consistent significant associations for catheter-related thrombosis across the twenty-five studies. Multiple studies identified age, malignancy, diabetes, obesity, chemotherapy, thrombophilia and a history of thrombosis as significant risk factors for catheter-related thrombosis.
Conclusions: Inconsistent findings among studies make it difficult to establish which patient-related risk factors are associated with catheter-related thrombosis. Future studies could include larger sample sizes and more cases of catheter-related thrombosis to produce more significant results. Identification of patient-related risk factors could lead to early recognition of upper limb deep vein thrombosis in patients with catheters, thereby preventing complications.

C0232
INFLUENCE OF DECREASED FIBRINOLYTIC ACTIVITY ON VENOUS THROMBOSIS RISK

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Background: Whether plasminogen activator inhibitor-1 (PAI-1) 4G/5G polymorphism increase venous thrombosis risk is controversial. Previous reports yielded inconsistent results, and did not all take confounding fully into account, either by randomization or extensive adjustment. We aimed

to determine whether decreased fibrinolytic activity, or PAI-1 4G/5G polymorphism influenced the risk of venous thrombosis.
Methods: Our case-control study included 100 patients with venous thrombosis, and 100 random controls. When patients were compared with random controls, unconditional logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs).
Results: Decreased fibrinolytic activity yielded a 2.7 fold increase in risk for venous thrombosis than physiological fibrinolytic activity (OR 2.70; 95% CI 1.22-5.98), when comparing patients with random controls. Adjustment for several putative confounders did not change the estimate (OR 3.02; 95% CI 1.26-7.22).Analysis of venous thrombotic risk influenced by PAI-1 genotype, showed no influence of PAI-1 4G/5G gene variant in comparison with 5G/5G genotype (OR 0.57 95% CI; 0.27-1.20).
Conclusions: Decreased fibrinolytic activity increased, while PAI-1 4G/5G polymorphism did not influence venous thrombosis risk in this study.

C0250
THROMBOSIS PREVALANCE AND RISK FACTORS IN CHILDREN WITH LEUKEMIA: ONE CENTER EXPERIENCE

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Background: Acute leukemias are the most prevalent malignant disorders in children. Venous thrombosis is one of the most frequent complications of acute leukemias and its treatments.
The aim of this retrospective study was investigate of acquired and genetical risk factors for venous thrombosis among children with acute leukemia which diagnosed and treated at Ege University Children's Hospital, Department, Pediatric Haematology in Izmir.
Methods: Between 2007 and 2015; 144 patients with acute leukemia were evaluated. Most of the patients were acute lympoblastic leukemia (ALL) (n=122) and others were acute myeloblastic leukemia (AML) (n=12). In five patients (5/144; 3.5%) venous thrombosis was diagnosed during treatment and follow-up periods. All patients with thrombosis were recently diagnosed with ALL (5/122; 4%). Three of them were male and mean age was 10 years. All patients with thrombosis had central venous line and timing of thrombosis were during initial chemotherapy with L-Asparaginase and Steroids during BFM protocols.
Results: Sinus venous thrombosis (SVT) in the brain veins was the most frequent thrombosis location and developed after L-ASP infusions during Protocol-I. Two patients with SVT were male. Other patient was female and she was treated with ostrogen pills for menstruental cylus problem. Other locations were catheter related iliac and femoral venous thrombosis and other one was superficial thrombosis at the right forearm. One male patient was obese. Responsible genetic risk factors were evaluated in thrombotic patients. One of SVT patients had heterozygous prothrombin mutation and have elevated FVIII and FIX levels. Another SVT patient had heterozygous factor V Leiden mutation with factor V H1299R mutation. Third patient had heterozygous MTHFR (C677T) mutation and together with Lupus Anticogulant (LA) positivity and moderate PS and AT deficiency. Patient with DVT had no genetical risk factors. Patient with superficial thrombosis had heterozygous MTHFR mutation and had obesity.
Conclusions: In conclusion, even though venous thrombosis risk was lower more than expected in acute leukemia patients, all patients were ALL. Moreover most of thrombotic patients had diagnosis with Steven though most leukemia patients without thrombosis had also central venous line and same chemotherapy protocols; genetic risk factors as F Vleiden and protrombin mutation may be responsible for development venous thrombotic complications together with acquired risk factors.

C0252
NON –CATHATER THROMBOEMBOLIC EVENTS IN CHILDREN

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Background: Although the incidence of thromboembolic events has increased over the last decade, non catheter-relatedthromboembolism is uncommonly seen in childhood. This study was aimed to analyze the data of 65 thromboembolic events in children who were followed up in our hematology–oncology clinic between 2000-2015, retrospectively.
Methods: Information of 65 patients were retrieved from patient files and from the records contained in the electronic information processing environment created after 2005.
Results: Thirty eight of the patients were males and 27 were females. The age range was between four months-16 years. Presenting ages of the patients were changing from one day to 12 years. Of the children 11 (16.9%) of the cases were neonates, 20 (30.1%) were infants less than 1 year old, and 34 (52%) were children over than one year old. Thromboembolic events were mostly located in central nervous system 37 (56.9%), deep venous system of the limbs 11 (16.9%), portal vein 7 (10.7%), renal vein 2 (3%), intracardiac 2 (3%), inferior vena cava 2 (3%), peripheral artery 2 (3%) and pulmonary embolism 2 (3%). Inherited risk factors were present in 41 (63%) of the children. Ten of the patients carried two risk factors (%). MTHFR was the most common inherited risk factor. Acquired risk factors were present in 31 (50.7%) of the children. Trauma was the most common underlying risk factor. Acquired and inherited risk factors were present simultaneously in 13 (20%) of the patients.
Conclusions: Thrombosis in children is an important complication with high morbidity and mortality. Thrombosis in children is gaining increased awareness, as advanced medical care has increased treatment intensity of hospitalized pediatric patients. Better predictors of prognosis in relation to risk factors, treatment and prophylaxis are therefore urgently needed. Future respective studies may help to assess the risk profile and therapy.

C0253
NEW DEVELOPMENTS IN THE DIAGNOSIS OF ACUTE DEEP VEIN THROMBOSIS (DVT) AND PREVENTION OF DVT RECURRENCE AND POSTTHROMBOTIC SYNDROME IN THE MULTIDISCIPLINARY PRIMARY CARE, HOPITAL AND ACADEMIC MEDICINE SETTING ANNO 2016 AND BEYOND

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Background: The sequential use of complete compression ultrasonography (CCUS) followed by a sensitive D-dimer test and a clinical score assessment is a safe and effective noninvasive strategy to exclude and diagnose DVT and AD in patients with suspected DVT in the primary care and hospital setting (Michiels et al 2016).
Methods: Compression Ultrasonography (CUS) rules in and out deep vein thrombosis (DVT) and picks up alternative diagnoses (AD) including Baker's cyst, muscle hematomas, old DVT, and superficial vein thrombosis. CCUS from the femoral and popliteal region and calf veins has become since 2005 the diagnostic objective test in our Medical Diagnostic Center Rotterdam to diagnose distal and proximal DVT. Acute DVT patients are recommended to wear medical elastic stockings (MECS) for symptomatic relief of swollen legs during the acute phase of DVT, and when objective clinical signs of postthrombotic syndrome (PTS) become evident at 3 to 6 months post-DVT. About half to two third of DVT patients on anticoagulant treatment do not develop symptomatic PTS at time point 3 to 6 months post-DVT obviating the need to wear MECS (cost-effective). The Maastricht Rotterdam DVT

PTS working Group of primary care physicians, internists, radiologist and vascular surgeons proposed to use the C in the CEAP for objective grading of PTS and the Villalta score by the patients and nurses at thrombosis services at time point 6 and 12 months post-DVT. On top of the C of CEAP we plan to introduce objective testing with serial CUS at time points 1, 3 and 6 months post-DVT for reflux or residual vein thrombosis as a main risk factor for DVT recurrence and PTS evolution (Michiels et al 2015). Rapid and complete recanalization on DUS within 1–3 months post-DVT is associated with no reflux and low risk on DVT and PTS (1.2% of 100 patient/years, obviating the need of MECS and anticoagulation at 6 months post-DVT (cost-effective). Delayed recanalisation and residual vein thrombosis (RVT) of popliteal/femoral LET class II DVT with delayed recanalization on CUS at 3 months post-DVT is associated with reflux PTS due valve destruction on CUS and a high risk of DVT recurrence (20%-30%) and symptomatic PTS indicating the need to extend anticoagulation for a few to several years and to wear MECS for subjective relief of symptomatic PTS and maintenance of good quality of life.

Results: DVT recurrence in patients with subclinical and symptomatic reflux type PTS are best prevented by extended anticoagulation for a few to several years with low dose Direct Oral Xa (DOXa) inhibitor. MECS do not prevent DVT recurrence and only provide relief of subjective signs without affecting the degree of PTS according to the clinical (C) criteria of the Maastricht-Rotterdam PTS scale. Acute ileofemoral DVT and proximal popliteal/femoral/ileofemoral (LET class III DVT) are at high risk of DVT recurrence and severe obstruction type PTS (partial recanalization with outflow obstruction). Consequently, Acute Thrombosis Symptoms (ATS) with LET class III DVT are candidate on day zero of ATS presentation for the randomized clinical trial comparing Catheter Accelerated thrombolysis Versus Anticoagulation (CAVA) to immediately restore the outflow obstruction and prevent subsequent PTS by anticoagulation and additional stenting if indicated in high qualified phlebology intervention centers.

Conclusions: A prospective cost-effective safety outcome management study to bridge the gap between ATS with LET class I, II and III DVT and the risk of PTS at 6 to 12 months post-DVT in patients with distal, proximal and iliofemoral thrombosis on complete CUS is warranted to reduce the overall DVT recurrence rate and symptomatic PTS from about 30% to 3% patient/years during long-term follow-up. We intend to design in 2016 a multidisciplinary prospective management outcome study in the primary care, hospital and academic medical setting to bridge and close the gaps between DVT and PTS, with the aim of reducing the overall DVT recurrence rate and PTS in ATS patients to less than 3% patient/years during life long follow-up.

C0262
ELASTOGRAPHY OF VENOUS THROMBI AT THE ER: IS IT A HELPFUL TOOL?

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Background: The stiffness of a thrombus increases with increasing age. Ultrasound elastography can provide information about elastic properties of thrombi and estimate the exact age of them, which is difficult using gray scale sonography alone. The main aim of our study was to distinguish thrombi of age ≤ 6 days. Older thrombi are adherent to the vessel wall and do not pose a risk of pulmonary embolus as acute thrombi do.

Methods: We examined 483 patients in one year, from the ER (emergency room) who mentioned/inferred with clinical history and/or symptoms of DVT (deep vein thrombosis). Gray scale and elastography was performed to all patients of the group twice; at the admission day and ten days after, trying to differentiate the acute, sub acute and chronic thrombus.

Results: 192 patients were diagnosed with DVT. Initially was successfully distinguished acute from chronic thrombus. Some difficulties have been in categorizing the sub acute cases.

Conclusions: Elastography can be useful in diagnosing acute DVT in ER patients preventing the risk of pulmonary thromboembolism and response to treatment.

C0268
POST-TRAUMATIC PORTAL VEIN THROMBOSIS: A RARE INCIDENT

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Background: Abdominal trauma is a very rare cause of portal vein thrombosis. When thrombosis of the portal vein occurs, involving abdominal trauma, a complete search for all the known main causes must be carried out before confirming this diagnosis.

Methods: We report a case of a 19-year-old male with no previous medical history who was referred to the ER department of our hospital after a violent blunt trauma, occurred during a motorbike accident.

Results: Emergency abdominal ultrasonography showed free fluid in the peritoneal cavity, indicative of hemoperitoneum and hepatic parenchyma irregularity. Abdominal CT scan with iv contrast media confirmed the diagnosis of liver laceration and the follow up CT scan after two days also showed thrombosis of the left branch of the portal vein. In this young man, none of the other potential causes of portal vein thrombosis was found and the only triggering factor was the recent abdominal trauma

Conclusions: After an 18-month follow-up and 6-month anticoagulant therapy the thrombus totally regressed and no other element was observed which could have caused thrombosis of the portal vein.

C0270
VENOUS INJURY: THE ROLE OF MULTI DETECTOR COMPUTED TOMOGRAPHY (MDCT)

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Background: MDCT is an accurate modality to evaluate the abdominal vascular injuries, after direct or blunt abdominal trauma, most of them life threatening emergencies.

Methods: we report two cases of abdominal trauma with injury and subsequent thrombosis of the IVC and the internal iliac vein. The first case was a blunt trauma from car accident and the second one a direct pin trauma.

Results: MDCT showed in the first case retroperitoneal hematoma indicative an injury of the midline vascular structures and leak of blood from the IVC was confirmed after iv contrast media. In the second case with multiple internal organ injuries from a pin organ there was also internal iliac vein laceration. In both cases CT showed distal vein thrombosis.

Conclusions: MDCT is a non-invasive, accurate, diagnostic approach for the evaluation of vascular structures and potential vascular trauma in the Emergency Room (ER).

C0277
PREGNANCY AND DELIVERY IN WOMEN WITH HISTORY OF VENOUS THROMBOEMBOLIC COMPLICATIONS

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Background: Despite intensive research, thromboembolism still accounts for significant maternal. Our aim was to determine thrombophilia in patients with thromboembolism during pregnancy and to evaluate the efficiency of antithrombotic prophylaxis in patients with thrombophilia for prevention of recurrent thromboembolism.

Methods: Group I: n= 57 (28.7±4.2 years), subgroup I (n=20) women with history of thromboembolism, subgroup (n=19) women with

thromboembolism during current pregnancy, group II (control) – healthy pregnant women (n=60) were screened for genetic thrombophilia and antiphospholipid antibodies (APA). Subgroup I received prophylaxis in preconception period, during pregnancy and at least 6 weeks postpartum: low molecular weight heparin (LMWH), omega-3-acides, vitamins of B group, folic acid (up to 4 mg/day), aspirin (80 mg/day).
Results: In group I 54.4% had familial history of venous thromboembolism, and 68.4% had personal history of pregnancy complications (fetal loss syndrome, preeclampsia, placental abruption) (p<0.05 vs. control). In the group I thrombophilia was detected in 94.1%: MTHFR C677T (11.7% +/+, 52.9 ±), FV Leiden (23.5% ±), prothrombin G20210A (13.7% ±), multigenic fibrinolytic defects (64.7%); APA (49%), hyperhomocysteinemia (45%) (p<0.001 vs. control). Recurrent thrombosis occurred in 1 woman from subgroup I before the start of LMWH and in 5 pts from subgroup II (26.3%) (p=0.091). In subgroup I no one had severe obstetrics complications. All pts were delivered at term and all babies were alive. In subgroup II moderate to severe obstetrics complications were noted: preeclampsia, IUGR grade I-III, critical maternal-placental-fetal blood flow disturbances (43.7%). Preterm delivery was required in 43.7% pts from subgroup II.
Conclusions: Thrombophilia might be the essential pathogenetic mechanism of thromboembolism associated with pregnancy. LMWH was effective for prevention of recurrent thromboembolism and obstetric complications. Women with personal or family history of thromboembolism or with history of obstetric complications should be screened for thrombophilia.

C0283
MESENTERIC VENOUS THROMBOSIS IN FUENLABRADA UNIVERSITY HOSPITAL. 28 CASES SERIES ANALYSIS

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Background: Mesenteric venous thrombosis is an entity which incidence is out of 2.7 cases per 100,000 habitants, which key risk factors are cirrhosis, neoplasms and thrombophilias. The diagnosis is established by radiological technique. Currently morbimortality is 10-20% due to an early diagnosis and treatment.
Methods: Twenty-eight patients were included, in which the diagnosis of mesenteric venous thrombosis was stablished by ultrasonography or CT scan (27 patients) or intraoperative (1 patient) in the Fuenlabrada University Hospital between 2004 and 2015. We analysed relevant epidemiological variables and comorbidities registered along the medical history up to the moment of the diagnosis as well as the prevalence of them and the therapeutical approach.
Results: Twenty-eight patients have been studied, 53.6% were men, with an average age of 60.28 years (range 27-82); the 46.4% were smokers. Almost the 86% of the patients presented at least one key risk factor. From the other four, two of them were immobilized during hospitalization. From the other two, one deceased without completing the study. In the remaining case, despite the study was completed, factors cannot be determined.
Systemic factors: 39.3% presented active neoplasm to the diagnosis. None of the women of our series was pregnant. Only one of them was taking oral contraceptives. Thrombophilia tests were realized on the 43% of the patients, determined the JAK2 mutation in two of them (7%). No mutations were found.
Local factors: The 35.7% presented cirrhosis. The 28.6% presented breakthrough infections, and 17.9% had an operation in previous days.
The satisfactory evolution, defined as survival to that event, was 78.6%. The 81.8% of them was treated with conventional anticoagulation (LMWH plus anti-vitamin K agent).
Conclusions: Our data are not far from the published on the literature. Practically all of our patients presented at least one major risk factor which justifies the pathology, with active neoplasm as the more relevant. Thrombophilia does not appear to be an important risk factor, although we only analyzed less than half of the cases. Most patients had a good outcome with anticoagulation.

C0287
UNUSUAL LOCALIZATIONS OF DEEP VENOUS THROMBOSIS ABOUT 21 CASES.

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Background: The aim of our study is to describe the etiologic profile, clinical presentation and outcome in patients with unusual localization of deep venous thrombosis.
Methods: A retrospective descriptive study including patients with an unusual localization of thrombosis confirmed by imaging and hospitalized in our department.
Results: Twenty one patients were included. There were 13 male and 8 female with a male to female ratio of 1.6. The mean age at diagnosis was 48.3 years old with extremities varying from 17 to 78 years old. The thrombosis were located in the upper limb (n=9), portal vena (n=7), cerebral vessels (n=3), spleno-mesenteric trunk (n=2), inferior vena cava (n=2) and BuddChiari syndrome (n=2). Three of our patients presented more than one unusual location of venous thrombosis. Etiologies were dominated by: cancers in 4 cases (hépatocellular carcinoma n=2, stomach cancer n=1 and lymphoma in one case), antiphospholipid syndrome in two cases, Behçet disease in one case, hyperhomocysteinemia in one case and extramembranous glomerulonephritis in one case. No etiology was found in 4 patients. Fifteen of our patients were treated with antivitamine K, and two among them presented an overdose: a digestive hemorrhage and ecchymosis. Recurrence occurred in 4 patients including 3 in the same site. One case of death was noted related to the evolution of hepatocellular carcinoma. The outcome was favorable in 13 cases and three patients were lost to follow up.
Conclusions: Even though their low incidence the recognition and the exploration of an unusual location of thrombosis remain important and the search of the etiology allows to adapt the treatment to the cause.

C0289
PARKINSON'S DISEASE, HYPERHOMOCYSTEINEMIA AND THROMBOSIS: THE DANGEROUS COMBINATION

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Background: Hyperhomocysteinemia is an independent risk factor of thrombosis and stroke. Many studies have recently shown a high blood level of homocysteinemia in patients with Parkinson's disease (PD). This high level seems to be multifactorial, partially due to the drugs used in the management of the disease. Besides, mutations in the gene coding for the enzymes of homocysteine's metabolism and particularly Methylene tetrahydrofolate reductase (MTHFR) occur more frequently in patients with Parkinson's disease.
In addition, thrombosis may be promoted by the posture abnormalities in advanced forms of PD.
The aim of our study is to look into the relation between PD and thrombosis through two cases.
Methods: We report here two cases of patients with PD and who presented with venous thrombosis.
Results: Case 1: A 45 years old man diagnosed with PD since two years and who was treated by dopaminergics, was admitted in our department for a proximal deep venous thrombosis on the left lower limb and pulmonary embolism. Physical examination revealed deep venous thrombosis symptoms, rigidity of lower limbs and a bending attitude. The laboratory tests showed hyperhomocysteinemia (92 μmol/l) and vitamin B 12 deficiency (43 pg/ml). He was treated with acenocoumarol, compression stockings and vitamin B12 supplementation.
Case 2: A 72 years old patient suffering from PD for ten years and treated with dopaminergics was transferred for recurrent venous thrombosis. He had a past medical history of a superficial thrombosis of the right lower

limb 7 years ago, a deep venous thrombosis of the same limb 3 years ago and a superficial thrombosis of the controlateral limb a month ago. Physical examination didn't reveal any posture abnormalities. Etiologic Investigation of thrombosis especially to rule out cancers was negative .He had hyperhomocysteinemia (18 μmol/l) and a mutation in the gene coding for MTHFR. He was treated with acenocoumarol and compression stockings.
Conclusions: The challenge facing the clinician thrombosis is to find an etiology. The careful questioning of patients and the search for a drug intake should be part of the etiological research.

C0291
MULTIPLE MYELOMA AND THROMBOSIS

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Background: The relation between cancer and venous thromboembolism (VTE) is well known. The underlying mechanisms include the interactions berween the nature of the disease and treatments, acquired disorders of coagulation, extrinsic pressure of tumor mass on vessels, immobility, surgery, central venous catheters, and presence of congenital hypercoagulability states. The aim of our study is to investigate the prevalance and related factors of VTE in patients with MM.
Methods: 80 patients with the diagnosis of MM according to International Myeloma Working Group (IMWG) criteria between 2010-2015. General features, stage, treatments and thromboembolic complications were recorded.
Results: 14 patients had VTE (17.5%) and 11 had arterial thromboembolic episode (ATE) (13.75%). 10 patients with VTE (71.4%) and all patients with ATE had either thalidomide or lenalidomide treatment. Body mass index of all patients were normal. Mean age of patients with VTE was 66.93 with a female dominancy (10/4). 85.7% of the patients were stage III according to International Staging System (ISS) with ECOG performance score 3 or 4 in 64.28%, and 71.4% had taken 3 or more treatments (anthracyclines, proteozome inhibitors and imids). 10 years-cardiovascular risk were 3-8%. This risk was similar with studies on patients with same age groups without myeloma. Mean age of patients with ATE was 69.18 with a female/male ratio of 5/6. All patients were ISS stage III with ECOG performance score 3 or 4 in 81.81%.10 years-cardiovascular risk were 11%. This risk was similar with studies on patients with same age groups without myeloma. Age were similar in patients with VTE and ATE though ECOG performance score, stage and 10 years-cardiovascular risks were significantly higher in patients with ATE ($p<0.005$) and VTE was significantly more frequent in women ($p<0.005$). In regard with thromboprophylaxis, 2 of the patients with VTE was on low molecular weight heparin and all patients with ATE were on acetilcalycylic acid. Adherence to medication, polypharmacy and skipping dose may be additional confunding factors.
Conclusions: Venous and arterial thromboembolism is frequent in patients with MM. Use of IMIDs, poor performance status, advanced disease and cardiovascular risks were the contributing factors of ATE and VTE in our study. Thromboembolic events are frequent and managable complications, though preventive measures are essential at all times.

C0295
CEREBRAL VENOUS THROMBOSIS

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Background: Is a rare, multifactorial disorder, being 3 times as frequently in women (increased risk on pregnancy and with oral contraceptive use). Clinical features depend on: extension and localization of the thrombosis, and the time between onset of symptoms and hospital admission. Headache is present in 90% of the cases. In the International Study on Cerebral Veins and Dural Sinus Thrombosis (ISCVT) cohort, 44% of the patients had more than one risk factor. We discuss 4 clinical cases with different etiology.
Methods: See Table 1.
Results: In 3/4 patients we could identify an underlying risk factor. Other prothombotic situations helped, to cause CVT. In case 1, we consider pregnancy, iron deficiency anaemia, an independent variable for development of CVT, and dehydration. In case 2, he was on specific treatment for Crohn´s disease. 1.6 % cases of CVT are associated with inflammatory bowel disease. In case 3, the precipitating factor was done hard gym, in a patient with thrombophilia. In case 4, contraceptive use and smoking, provoked CVT. In the ISCVT high oestrogen levels were identifiable as a risk factor in 65% of the patients (contraceptive use, pregnancy). Patients 1, 2 and 4 were diagnosed in acute phase and managed with anticoagulation doses of low molecular weight heparin (LMWH) improving their symptoms. In case 3 the diagnosis was made one month after the onset of symptoms so, with high levels of lipoprotein(a) we started oral anticoagulation with warfarin.
Conclusions: Thrombophilia was present in most patients, but a precipitating factor was needed to provoke a CVT. All the patients improved their symptoms with anticoagulation management.

C0315
MANAGEMENT OF VENOUS THROMBOEMBOLISM IN CHILDREN IN A SINGLE-PEDIATRIC TERTIARY CARE MEDICAL CENTER.

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Background: The aim of this retrospective study was to summarize our experience regarding pediatric venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE) in a single tertiary care medical centre
Methods: We revised 22 patients (pts) under 16 years old diagnosed of VTE and follow-up at our institution between March 2006 and August 2014. We reviewed clinical data, thrombotic risk factors, thrombophilia test results, DVT location, management for enoxaparin therapy and outcomes.
Results: The diagnosis of VTE was at a median age of 5 years (0.5–16 years); out of 22 pts, 14 were boys and 8 girls. The lower extremities ± PE were the site for DVT in 10 pts, upper extremities in 2 pts, the portal and

Table 1. Abstract C0295
Clinical cases

	Sex	Age	Site of thrombosis	Clinical features	Thrombophilia	Other conditions
1	female	42	Internal cerebral veins, straight, transverse and left sigmoid sinuses	Headache, vomiting, speech disturbances, right hemiplegia	AAC, LA, (+)	Pregnancy, iron deficiency
2	male	22	Left sigmoid sinus and superficial vein	Headache, speech disturbances	FII20210A heterozygote, AAC (+)	Inflammatory bowel disease
3	male	66	Transverse and left sigmoid sinuses, and proximal internal jugular vein	Persistent headache	High lipoprotein(a), gym	Arterial hypertension, ischemic cardiopathy
4	female	32	Superior sagittal sinus and cortical veins	Right sensory deficits, speech disturbances	Negative	Contraceptive use, smoking

inferior vena cava in 3 pts and cerebral venous sinus thrombosis in 7 pts. In 8 cases no risk factors for VTE were registered. Oncologic diseases and systemic sepsis were found in 6 and 4 pts respectively, 4 central venous catheter (CVC) carriers, 6 patients underwent a previous surgery, 1 pt required invasive mechanical ventilation and 1 pt was affected by *perinatal hypoxic*-ischemic *encephalopathy.* 11 cases (50%) presented a pattern of inherited thrombophilia; 4 pts methyl tetrahydropholate reductase (MTHFR) mutation, 1 pt factor V Leiden, 1 both thrombin mutation G20210A and MTHFR, 1 pt *protein C deficiency and 2 pts antiphospholipid syndrome.* Anticoagulation therapy was initiated in 3 pts with unfractioned heparin to achieve therapeutic activated partial thromboplastin time and 18 patients received enoxaparin at a mean dose of 1 mg/kg/12 h to achieve anti-Xa therapeutic level. The median duration of anticoagulation was 3 months. The overall recurrence rate of VTE (including 1 PE) was 22% (5/22) and the mortality rate 10% (2/22). Mortality was related to the underlying disease: 1 pt perinatal hypoxic encephalopathy and 1 pt tumor progression. 1 *episode* of gastrointestinal bleeding related to anticoagulant therapy was observed.
Conclusions: The distribution of VTE in our patients was similar to already published. In our experience, multiple underlying conditions (sepsis, recent surgery, malignancies) were associated with VTE. Hospitalized children with high-risk factors for VTE should be candidates for thrombophilia screening. Adjustment in enoxaparin dosage to achieved target anti-Xa level has shown to be a valuable anticoagulant therapy for pediatric VTE.

C0322
PARTICULARITIES OF PULMONARY EMBOLISM: AN INTERNAL MEDICINE DEPARTMENT EXPERIENCE

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Background: The aim of our study is to analyze the epidemiological, clinical and evolutionary characteristics of pulmonary embolism in patients hospitalized in a polyvalent internal medicine department and to deduce the main particularities.
Methods: A retrospective study including patients hospitalized for pulmonary embolism in an internal medicine department from January 2003 to January 2015. The pulmonary embolism was confirmed by CT angiography.
Results: During the study period, 26 patients were included: 13 male and 13 female making the male to female ratio equal to 1. The mean age was 56.2 years with extremes varying from 24 to 82 years. The pulmonary embolism was associated with deep vein thrombosis in 7 cases (26.9%), with a portal thrombosis in one case and with a thrombosis of inferior vena cava in one case. The etiological factors were dominated by cancers found in four cases among which 3 cases of digestive cancer. Thrombophilia was observed in 3 cases (11.5%): one case of resistance to active protein C, a case of protein S deficiency and a case of a deficiency in both protein S and C. A hyperhomocystenemia was found in one case. The pulmonary embolism was a complication of systemic diseases in 3 cases (11.5%): a case of systemic erythematosus lupus, a case of Behçet disease and a case of antiphospholipid syndrome. It also occurred in a patient with extra membrane glomerulonephritis. The etiology wasn't found in 14 cases (53.8%). Thirteen patients among 26 had one or many thrombosis predisposing factors. All patients were treated with heparin which was switched to anti vitamin K. We noted a favorable course of the disease in 25 cases (96.15%) and only a case of death related to a hepatocellular carcinoma. A recurrence was observed in 4 (15.38%) cases in patients with deep vein thrombosis after stopping the treatment with antivitamine K and 3 cases of asymptomatic overdose of anti vitamin K were observed.
Conclusions: The pulmonary embolism is a serious condition which should be actively sought each time we are faced to a deep venous thrombosis. Seeking for the etiology may facilitate the management of the disease and prevent the recurrences.

C0354
PLASMA TOTAL HOMOCYSTEINE LEVELS AND OTHER BIOCHEMICAL PARAMETERS IN ALGERIAN PATIENTS WITH DEEP VEIN THROMBOSIS

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Background: We studied total plasma homocysteine levels (tHcy) in Algerian patients with a deep venous thrombosis (DVT).
Methods: We measured tHcy levels in a total of 99 subjects enrolled in this study, including 40 patients with DVT and 59 healthy controls. The mean tHcy level in the patients was 12.62 ± 8.7 μmol/L and that in the controls was 10.2 ± 2.1 μmol/L.
Results: In a univariate regression model, tHcy concentrations were correlated with triglycerides (TG) (r= 0.358; p= 0.023) and total cholesterol (TC) (r = 0.454; p = 0.003) concentrations. Logistic regression analysis showed that tHcy after adjustment was significantly associated with the following factors: TC (p = 0.003) and TG (p = 0.023). The analysis in DVT patients showed that variables independently associated with tHcy were TC [odds ratio (OR) 2.1, 95% confidence interval (CI) 1.7–2.6], lowdensity lipoprotein cholesterol (OR 2.0, 95% CI 1.6–2.5), creatinine (OR 2.2, 95% CI 1.7–2.6), and smoking (OR 2.1, 95% CI 1.7–2.5).
Conclusions: In conclusion, these results indicate that tHcy levels and other biochemical parameters are important determinant factors for DVT diseases in Algerian patients.

C0359
ELEVATED RISK OF THROMBOPHILIA IN AGENESIS OF THE VENA CAVA AS A FACTOR FOR DEEP VEIN THROMBOSIS

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Background: Congenital absence of the inferior vena cava (AIVC) is a rare malformation which may be associated with an increased risk for deep vein thrombosis (DVT). However, the role of thrombophilia in AIVC and DVT is unknown.
Methods: Between 1982 and 2013, 41 patients (12 female, 29 male, mean age 28 S.D. 11 years) were detected at the University of Düsseldorf, Germany, with AIVC. Based on medical history, clinical examination, imaging and coagulation studies, we performed on this collective a risk characterisation. Extensive literature research added further 123 published cases during 1993 and 2013. AIVC-patients were compared with iliocaval DVT-patients without AIVC (n = 168) treated during the same period in our clinic (90 female, 78 male, mean age 38 S.D. 17 years).
Results: In contrast to classical DVT younger men were more often affected. Factor-V-Leiden-mutation, 5,10-methylenetetrahydrofolate reductase (MTHFR) polymorphism and hyperhomocysteinemia individually are associated with an increased risk of DVT in patients with AIVC. Aplasia/hypoplasia of the right or left kidney is also associated with IVCA.
Conclusions: AIVC should be considered in young patients who present with DVT involving the vena cava. Analysis of publications with AIVC and our patients yielded a typical spectrum of AIVC-associated DVT characteristics: AIVC occurs in young male adults, is revealed by proximal DVT, not necessarily accused by precipitating factors like immobilisation, and is mostly located bilateral. Hereditary coagulation abnormalities seem to be more often a contributing factor for DVT in AIVC.
Reference:
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C0365
BRANDED AND COPIES OF THE LOW MOLECULAR WEIGHT ENOXAPARIN. ARE THEY SAME?

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Background: The patent protection of LMWHs expired so the definition of criteria for the biological similarity between LMWH copies and the original product is a real need. The present *in vitro* study compared copies and branded enoxaparin using the specific anti-Xa activity and the calibrated automated thrombogram assay.
Methods: Samples of platelet poor (PPP) and platelet rich plasma (PRP) from 15 healthy volunteers were spiked with branded enoxaparin (Lovenox®) or its copies (Cutenox®, Dilutol®, Enoxa®, Fibrinox®, Loparin®, Lupenox®, Novex®, Noxprin®, Versa®). The specific anti-Xa activity was measured in PPP and thrombin generation was assessed in PPP and PRP in the presence of tissue factor or pancreatic cancer cells BXPC3.
Results: The anti-Xa activity of enoxaparin copies ranged from 0.072 to 0.088 IU/μg, being lower as compared to the branded enoxaparin (0.095 anti-Xa IU/μg). The potency of each copy to inhibit thrombin generation varied in the three experimental systems. The presence of platelets or pancreatic cancer cells BXPC3 in human plasma induced significant modifications of the inhibitory efficiency of enoxaparin copies on thrombin generation which distinguished them from the branded product.
Conclusions: Enoxaparin copies showed significant variability regarding their inhibitory potency on thrombin generation. Platelets and cancer cells significantly increased the variability of the antithrombotic efficiency of the copies as compared to the branded enoxaparin. The present study underlines the need for the elaboration of additional functional criteria to evaluate the global antithrombotic capacity of enoxaparin copies in order to evaluate their potential sameness with the branded drug.

C0366
SELECTION OF BIOLOGICAL MARKERS OF HYPERCOAGULABILITY FOR THE IDENTIFICATION OF HIGH VTE RISK PATIENTS WITH LUNG ADENOCARCINOMA. THE ROADMAP STUDY.

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Background: In patients with lung adenocarcinoma (LA), metastasis (MTS), advanced stage and chemotherapy (CTx) are risk factors for thromboembolism (VTE). Routine thromboprophylaxis is not recommended but individualized risk assessment is encouraged. The selection of the most relevant hypercoagulability biomarkers (HB) for incorporation into the risk assessment models (RAM) for VTE.
Methods: Patients with documented LA eligible for CTx at distance of at least 3 months from surgery or hospitalization were included. They were either CTx naive (NG) or had received CTx (OTG). Control group (CG) consisted of 30 healthy age & sex-matched individuals. We assessed them for thrombin generation (TG), P-Selectin, heparanase (HPA), procoagulant phospholipids (PPL), factor VIIa, D-Dimers (DDi) and Tissue Factor activity (TFa).
Results: Patients showed significantly shortened PPL and higher levels of TFa, DDi and HPA as compared to the CG. FVIIa levels were lower in patients compared to CG. The NG showed significantly shorter lag-time and lower ETP as compared to the OTG. It also showed significantly higher levels of HPA as compared to the OTG. The increase of TG and of HPA, P-Selectin, FVIIa was associated with the stage. Patients with MTS had higher levels of P-Selectin, TFa, DDi, FVIIa, TGT and HPA than those with localized or advanced disease. Patients with VTE had higher baseline levels of DDi, TGT, shorter PPL and lower levels of HPA as compared to those without. Patients who died within 3-months had higher baseline levels of DDi and lower HPA levels as compared to those who were alive.
Conclusions: Increased PPL, TF pathway up regulation, DDi and HPA increase is a universal phenomenon in LA. CTx has an impact on TGT and HPA levels. Baseline values of TGT, PPL, HPA, DDi were related with mortality and thrombosis. The incorporation of HB in VTE-RAMs might improve their predictive value. This concept is being studied on an ongoing trial.

C0367
A NEW RISK ASSESSMENT MODEL FOR VTE IN AMBULATORY PATIENTS WITH LUNG ADENOCARCINOMA ON CHEMOTHERAPY. THE ROADMAP STUDY

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Background: In ambulatory patients with advanced or metastatic stage of lung adenocarcinoma (LA) the risk of VTE increases during chemotherapy. But individual risk factors cannot identify patients at risk. The available RAM are not applicable in patients already on chemotherapy.
The prospective longitudinal non interventional study ROADMAP was designed to elaborate a RAM for VTE specific for ambulatory patients with LA on chemotherapy.
Methods: Patients with LA on chemotherapy were included and followed up at 3, 6 and 12 months. Documented symptomatic VTE was the end-point of the study. Blood samples were collected at inclusion and assessed for thrombin generation (TG) and procoagulant phospholipids (PPL-ct). Assays and reagents were from Diagnostic Stago (France). Multivariate analysis was performed and the RAM was developed using the logistic regression. Sensitivity, specificity and the predictive value of the RAM were calculated. The ROC Curve was plotted.
Results: The study included 150 patients (mean age 65 years, 73% male). The LA diagnosis was done within 6 months before inclusion in 70% of them and 90% had advanced or metastatic disease at inclusion. In 85% of patients the ECOG performance status was <3. In one year follow up 12 symptomatic VTE episodes occurred (8%), 75% of which occurred within the 3 months from inclusion. The RAM includes the following variables: Recent hospitalisation, Time since diagnosis of the cancer, Mean Rate Index of TG and PPL-ct. The ROC analysis gave an AUC value of 0.84. The sensitivity of the RAM was 89% and the specificity was 70%. The positive predictive value is 16% and the negative predictive value is 98%
Conclusions: The new RAM for VTE is specific for ambulatory patients with LA on chemotherapy and can reliably predict VTE using simple clinical variables and biomarkers of hypercoagulability. This RAM can be used by physicians for the identification of ambulatory lung cancer patients eligible for thromboprophylaxis.

Diagnostic and laboratory methods

C0033
CHANGES OF FIBRINOLYTIC HOMEOSTASIS LINK OF ELDERY PATIENTS WITH POLYORGAN PATHOLOGY

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Background: To study activity of fibrinolytic and proteolytic systems of the blood of patients with concomitant course of ischemic heart disease (IHD) and chronic noncalculous cholecystitis (CNC), pancreatitis (CP).
Methods: 105 sick and 20 healthy old-age persons were examined. In the first group were included patients with concomitant course of IHD and CNC (average age-69.3⁺6.2 years); in the second group – 51 patient with concomitant course of IHD and CP (average age-71.3⁺6.2 years). IHD has been presented with exercise stenocardia of II functional class. Sex ratio in the both groups was equal. Determination of total plasma fibrinolytic activity (TFA), nonensymatic fibrinolytic activity (NFA) and enzymatic fibrinolytic activity (EFA) was conducted by means of lysis of azofibrin ("Simko Ltd"). With the similar method the plasma proteolytic activity by means of lysis of azoalbumin (low molecular weight proteins' lysis), azocazein (high molecular weight proteins' lysis), and azokol (collagen lysis) was determined.
Results: In the first group was obtained increase of TFA in comparison with indices of healthy persons, accordingly 1.58⁺0.1 ml/hour and 1.31⁺0.08 ml/hour (p<0.05). This increase occurred mostly at the expense of NFA 0.77⁺0.05 ml/h (in healthy-0.48⁺0.04 ml/h, p<0.01), by almost invariable EFA-0.81⁺0.05 ml/h (healthy-0.48⁺0.04 ml/h, p>0.5). In the second group decreasing of TFA-0, 83⁺0.03 E_{440}ml/h, (p<0.05) at the expense EFA-0.51⁺0.02 E_{440}ml/h (p<0.05) and less-NFA-0.40⁺0.01 E_{440}ml/h (p<0.05). In both patients groups activation both of unlimited and limited proteolysis with maximal rise of intensity of proteolytic degradation of high molecular weight proteins, accordingly 4.17⁺0.79 ml/h and 4.55⁺0.18 ml/h, with the normal range-1.93⁺0.11 ml/h, (p<0.05) is observed.
Conclusions: Dynamics of changes of fibrinolytic and proteolytic activity of the blood by concomitant course of IHD and CNC or CP can serve as a base for determination of pathological process activity and substantiation of differential treatment of the given group of patients.

C0043
NORMAL RANGES OF INNOVANCE® PFA-200 TESTS FOR THE URBAN POPULATION OF CENTRAL RUSSIA

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Background: Platelet Functional Analyzer (PFA) does models platelet aggregation like nature conditions with blood flow and vessel damaged site. Establishing reference ranges for PFA tests might be weakly applicable in Russia due to differences in average age, sex and race distribution compared to European population. The aim was to determine PFA tests reference intervals based on the screening data from adult population living in Moscow.
Methods: Study's population consisted of ninety healthy volunteers (males – 66, females – 24). We used S-Monovette PFA (Sarstedt, Germany) blood collection system (CN 3.8%; pH 5.5). INNOVANCE® PFA-200 (Simens, Germany) cartridges with collagen and ADP (COL/ADP); with collagen and epinephrine (COL/EPI) and cartridge P2Y were applied. Reference intervals are presented as 5th-95th percentile. Obtained reference ranges were compared with reference intervals for European population. Besides gender differences were evaluated for reference range of each test type. Differences were detected using Mann — Whitney test (MedCalc ver. 12.5, Belgium).
Results: CT reference interval for COL/ADP had 96-115 sec that was narrower in comparison to European population (CT 68-121 sec). No significant differences related to volunteers gender were found (p>0.05). In compare to European population the COL/EPI testing showed more wide CT range having differences for men and for women (161-200 sec and 131-193 sec, respectively; p<0.05). By PFA manual P2Y normal values are lower 106 sec. Obtained reference range for P2Y consists 73-88 sec regardless of sex.
Conclusions: The analyzer 200 INNOVANCE® PFA using supposes that each laboratory should set his own range of expected values of the test COL/ADP, COL/ EPI and P2Y. The obtained data are indicative ranges for urban population of central Russia. It should be considered the normal PFA aggregation might have different CT ranges for men and for women.

C0070
DISTRIBUTION OF PLATELET AND PLATELET INDICES DUE TO AGE

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Background: Platelet and platelet indices which include plateletcrit (PCT), platelet distribution width (PDW) and mean platelet volume (MPV) have been analysed by automated blood cell counters for several years. The aim of this study is to investigate the distribution of platelet and platelet indices due to age.
Methods: The patients who admitted to TOBB ETU Hospital between the years 2005-2015 for check-up or routine pediatric control were taken in this retrospective study. The groups were divided according to age as newborn, 1 month-1 year, 1-5, 5-18, 18-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90 and 90-100 year old. The groups include 285 (150 male, 135 female), 361 (200 male, 161 female), 3177 (1685 male, 1492 female), 4036 (1999 male, 2037 female), 6479 (2102 male, 4377 female), 15357 (5080 male, 10277 female), 9868 (4768 male, 5100 female), 8332 (4840 male, 3492 female) , 6829 (4016 male, 2813 female), 4893 (2415 male, 2478 female), 2265 (983 male, 1282 female), and 137(54 male, 83 female) patients, respectively Platelet count, PCT, PDW and MPV were measured in whole blood using Sysmex XT 2000i (Sysmex Co., Japan) and the results were analysed by SPSS 18 (Chicago, IL,USA).
Results: We observed no correlation between newborns and 5-18 year and 50-100 year old group for PLT values. For PDW and MPV, no difference were seen between ages 18-100 and 50-100, respectively. For PCT, no correlation was found except between newborns and 1 month- 1 year, 1-5 year and 50-60 year old group and between 18-30 year and 70-100 year old group. Moreover, for platelet count and PCT after an elevation in 1 month-1 year and a downtrend in 18-30 year period, a plato phase was seen. Additionally, for PCT after a second fall in 50-60 years and again a rise to plato phase was observed. Before plato phase, on the contrary a rise in MPV, a fall in PDW in 1-5 year old period was seen (Figure 1).

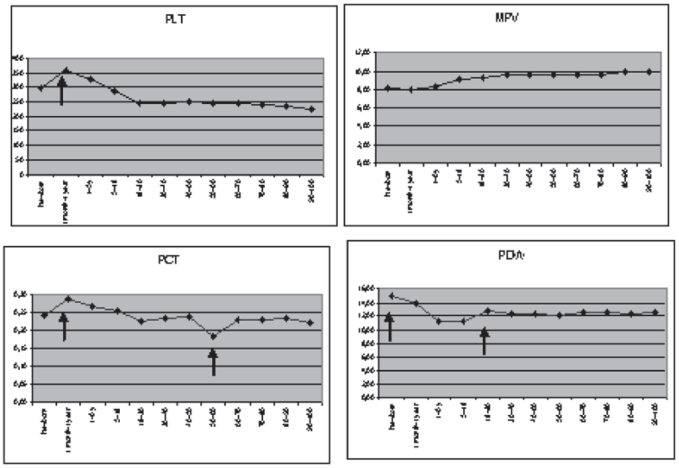

Fig. 1. Distribution of PLT, MPV, PCT and PDW due to age.

Conclusions: In the first 18 years, platelet and platelet indices seem to differ from other periods of life and afterwards, except a fall in PCT levels in 50-60 year period all parameters stand stable. These results also indicate that a reference value for PLT and PLT indices should be determined for certain life periods.

C0089
EVALUATION OF VITAMIN K ANTAGONISTS ANTICOAGULATION EFFECT

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Background: Despite the new oral anticoagulants (NOAC), vitamin K antagonists (VKAs) are still most frequently used drugs for long term thromboprophylaxis in patients with atrial fibrillation (AF) and venous thromboembolism (VTE). VKAs' efficacy and safety are closely related to the level of INR control achieved, and VKA-treated AF patients often have INRs outside the therapeutic range.
Our goal was to determine patients' time spent in therapeutic range (TTR), proportion of INR measurements in range (PINRR) and adverse events in relation to INR in AF and VTE patients using VKAs.
Methods: The anticoagulation effect of Acenocoumarol was estimated by measurement of the proportion of the INR values in rang in 786 AF and VTE patients (07-09. 2015). The TTR was estimated in 219 AF patients who were taking VKAs at least 3 years in the period of 2012-2015.
Results: The PINRR out of 786 measurements was as follows: 331 (42%) < 2 (~1.5); 408 (52%) 2-3.5 and 47 (6%) >3.5 (~ 4.8). The estimation of the TTR in 219 AF patients showed the following: 31% INR <2, 54% INR 2-3 and 15% INR >3. The mean age was 72 years for AF patients and 40 years for VTE patients. The average number of control INR measurements to achieve the therapeutic rang was 3-5 for both groups. The incidence of minor bleeding episodes was 5.4% in AF patients and they were not associated with INR >3. Thromboembolic events were observed in 3 patients (2 recurrent VTE while INR was <2, and one transient ischemic stroke episode with the INR in the therapeutic rang).
Conclusions: VKA-treated patients' INRs were in therapeutic range 54% of the time, and PINRR assessments were within range a mere 52% of the time. During the periods in which the patients were outside the therapeutic range, they were significantly more likely to be below the range. According to our opinion VKAs' efficacy and safety are closely related to the level of INR control achieved, and VKA-treated AF patients often have INRs outside the therapeutic range. Further selection of anticoagulants, the introduction of NOACs, as well as patient education are necessary for the improvement of the long term thromboprophylaxis efficacy and safety.

C0093
THE ROLE OF PLATELET-TO-LYMPHOCYTE RATIO IN THE DIAGNOSIS OF INFECTIOUS MONONUCLEOSIS

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Background: The aim of this study is to investigate the role of Platelet-to-Lymphocyte Ratio (PLR) in the diagnosis of infectious mononucleosis (IM).
Methods: 116 patients who admitted to TOBB ETU Hospital between the ages 0-15 were taken in this retrospective study. Complete blood count, Ebstein-Barr Virus Immunglobulin M (EBV IgM) serology were studied concurrently. Analysing C-reactive protein and ferritin levels and also leucocyte count 40 patients were taken as healthy controls.
Complete blood count was analysed using Sysmex XT2000i (Sysmex Co., Japan), C-reactive protein and ferritin levels using Cobas 6000 (Roche Diagnostics Co., Mannheim, Germany) and EBV IgM (Anti-VCA GP 125 IgM, anti-VCA P19 IgM, anti EBNA-1 IgM, anti P22 IgM and anti-EA-D IgM antibodies) using Euroline Anti- EBV Profile 2-IGM (Euroimmun Medizinische Labordiagnostika AG, Lübeck Germany).
PLR was calculated in both groups. In order to determine the cut-off values ROC analysis was performed (SPSS 18, Chicago, IL, USA).
Results: Out of 116 patients 24 (20.7%) were diagnosed as IM due to serological tests. Mean PLR was found 112±70. In 67 of 116 patients (57.7%), PLR were less than 112 and 19 of 67 patient (28.3%) were found EBV IgM positive. 19 of 24 patients (79%) diagnosed as IM have PLR less than groups' mean value.
According to the ROC analysis, 24 IM patients and 40 healthy controls were found to have PLR less than 48. Due to these values, sensitivity and specificity of PLR were found 50% and 95%, respectively. Also, positive predictive value was determined as 85.7% and negative positive predictive as 76% ($p>0.001$).
Conclusions: According to these data, high values of PLR can be used to rule out IM disease, However low values may indicate the necessity of serological tests for EBV.

C0120
LABORATORY DETECTION OF THROMBOPHILIC MARKERS

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Background: Thrombophilia means increased tendency for venous or arterial thrombosis. Potential laboratory markers for it are antithrombin III (ATIII), protein C (PC) and protein S (PS) deficiencies or inherited thrombophilic defects such activated protein C resistance (APCR), factor V Leiden (fVL) or prothrombin (II G20210A) mutation.
Methods: 100 patients (21 to 70 years old) with a history of DVT, PE and AIM. Biological activity of AT III, PC, PS with Simens BERICHROM ATIII, BERICHROM PC, PROTEIN S Ac kits and resistance to activated PC (ProC® Ac R, Simens Bechring) were measured on automated coagulation analyser (BCS-XP). According to reference values ATIII, PC and PS activity below 60 % were regarded as deficiency. A ratio of activated PC below 2.1 indicated APCR. fVL and II G20210A polymorphism were detected with PCR specific polymorphism detection kits (both Applied Biosystems) on a ABI Prism 7000 equipment.
Results: 29 patients from 100 had APCR (1.64±0.22 v.s.2.24 ± 0.51). 15 patients from all had decreased level of PC (40.13 %±18.36 v.s. 101.47%± 39.91) and 19 patients had decreased level of PS (43.11%±12.93 vs. 89.6%±39.68). All examined had normal ATIII (96.82%±16.96). 15 patients were heterozygotes and one was homozygote for f.VL. 9 patients were heterozygotes for II G20210A.One patient with AIM was heterozygote for fVL and II, and one patient with Phlebothrombosis was homozygote for fVL and heterozygote for II. These patients were APCR (1.51±0.44). 14 patients with heterozygote fVL were at same time APCR (1.68±0.16).
Conclusions: The availability of new lab tests for thrombophilia has opened a new era for its diagnostic, prevention and prophylaxis. Decreased concentration of ATIII, PC, PS and APC Resistance are very useful laboratory markers for thrombophilia. Recognition of thrombophilic defects (fVL and II G20210A polymorphism) are complementary and changed the diagnostic approach for thrombophilia.

C0154
ANTIBODIES TO FACTOR XII DIAGNOSED AT THE TIME OF LABOR FOLLOWING VARICELLA INFECTION DURING PREGNANCY: A CASE REPORT

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Background: Factor XII (FXII) is a component of the contact system of the blood coagulation. It's required for a normal activated partial thromboplastin

time (aPTT) but it doesn't appear to be required for normal coagulation. FXII deficient patients may experience thromboembolic events. Otherwise, antibodies to FXII (FXIIabs) are less reported than antibodies to FVIII or FIX and showed curiously a strong association with fetal loss. In this report, we presented a 20-year-old asymptomatic Tunisian woman whose laboratory tests showed a severely prolonged aPTT with normal prothrombin time (PT) at the time of labor induction at 36 weeks amenorrhea because of intrauterine fetal death following maternal varicella infection and who was subsequently diagnosed with FXIIabs.

Methods: Platelet poor plasma was prepared by a double centrifugation of the citrated whole blood. PT, aPTT, thrombin time (TT) and factors clotting activity were measured using the STA Compact (Diagnostica Stago, Asniers, France). The correction of aPTT after 1:1 mixing with normal plasma was assessed before and after 2 hours of incubation at 37°C and then the Rosner index (RI) was calculated. The screening of Lupus anticoagulant (LA) was also investigated.

Results: Laboratory tests at the time of labor induction were as follows: PT was 90%, aPTT was 81s/30s, TT was 18s/19s and fibrinogen was 3,5g/l. The prolongation of aPTT was checked on another sample. Mixing the plasma with an equal volume of normal plasma corrected the patient's prolonged aPTT (39s, RI of 10%). Clotting factor levels of the intrinsic system were as follow: FVIII: 120%, FIX: 90%, FXI: 81% and FXII: 1.5%. FXIIabs were so suspected. Surprisingly, aPTT was no longer corrected with normal plasma after 2 hours of incubation at 37°C (54s, RI of 29%). FXIIabs was confirmed by Bethesda method. The screening of LA was negative.

Conclusions: The patient was born of non consanguineous parents and had not previous prolongation of aPTT. The monitoring of aPTT and FXIIabs titer were planned. The varicella infection may be the cause of FXIIabs.

C0157
THROMBOPHILIA ASSESSMENT IN PATENTS WITH VENOUS THROMBOEMBOLISM

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Background: The role of mutations in the prothrombin and factor V genes and other thrombophilic abnormalities as risk factors for thromboembolism especially in women during pregnancy and the puerperium is well known. Testing for thrombophilia has increased tremendously for various indications, but whether the results of such tests help in the clinical management of patients has not been settled. The purpose of this study is to evaluate the justification of thrombophilia testing.

Methods: Hereditary thrombophilia was assessed in 38 patients with apparently unprovoked or spontaneous VTE and 4 patients with postpartum stroke. We measured the activity of antithrombin, protein C, protein S and AFA. We also performed genetic analyses to detect the G1691A mutation in the factor V Leiden gene (FVL), the G20210A mutation in the prothrombin gene, and the C677T mutation in the methylenetetrahydrofolate reductase (MTHFR) gene. Blood samples were obtained at least 2 weeks after the cessation of anticoagulant therapy.

Results: Genetic thrombophilic factor alone or in combination with plasma anticoagulant deficit was found in 33 (78.6%) of the patients. In 9 (21.4%) of them thrombophilia testing was negative. There was no case with elevated AFA. Single heterozygote mutation was found in 48% of the patients (24% in FVL gene, 18% in the prothrombin gene and 6% in MTHFR gene). Double heterozygote mutation was found in 39% of the patients (including the women with postpartum stroke) from which 28% had combined FVL and prothrombin mutation and 12% patients had prothrombin and MTHFR mutation. In one VTE patient homozygous mutation of prothrombin together with heterozygous MTHFR mutation was found. Genetic testing revealed the same mutations alone or in combination in his parents and siblings. The estimated high frequency of combined mutations is probably due to the highly selected group of patients. The mean age was 38 years for VTE patients and 29 years for the women with postpartum stroke.

Conclusions: Screening for thrombophilia in VTE patients as well as in pregnant women with thrombotic complications might help to identify those at higher risk of recurrences. Screening for thrombophilia should be performed particularly in young patients with unprovoked venous thromboembolism and in their relatives to identify asymptomatic carriers who may benefit from thromboprophylaxis.

C0173
LEMIERRE SYNDROME: CASE REPORT

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Background: Lemierre's syndrome is a condition characterized by thrombophlebitis of the internal jugular vein caused by anaerobic organisms, following a recent oropharyngeal infection. *Fusobacterium* spp. are the causative organisms. Patients typically present with high fevers, neck pain, and pulmonary symptoms. Conservative treatment with an extended course of antibiotics and anticoagulation for jugular vein thrombosis led to a good recovery. Here we present a 2-year-old male developed Lemierre syndrome after suppurative lymphadenitis and abscess.

Case report: A 2-year-old previously healthy male was admitted to hospital with a history of cough, fever and swelling in the left side of the neck. His temperature was 37 C and there was tonsillar hypertrophy and inflammation. On neck examination he has lymphadenopathy in the left anterior region that sized 4x5 cm. Skin, chest, cardiac and abdominal examination were normal. Laboratory investigations revealed white blood count of 14.120/mm3, hemaglobin of 10.7 gr/dl, platelet count of 627,000/mm3 and normal coagulation profile. Liver function tests, urea and creatinine were within normal limits. The level of C-reactive protein was 13.6 (normal range 0–0.5) and the erythrocyte sedimentation rate was 106. Ampicillin-sulbactam therapy was started. Neck ultrasound showed abscess and suppurative lymphadenitis. Blood culture grew Streptococcus anginius, prompting revision of the antibiotic therapy to clindamycin. Computed tomography (CT) scan showed thrombosis of the left jugular vein. Thrombosis was corrected with Doppler ultrasound and enoxaparin therapy was started. After 2 months CT showed complete resolution of the abscess and jugular vein thrombosis.

C0174
COMMON THROMBOSIS IN THE BOTH TRANSVERSE, BOTH SIGMOID SINUSES AND LEFT INTERNAL JUGULER VEIN IN A CHILD WITH ULCERATIVE COLITIS

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Background: The incidence of childhood cerebral vein and sinus thrombosis is 0.3 per 100,000 children per year. Cerebral vein and sinus thrombosis may present with a variety of symptoms that range from headache to impairment of consciousness and coma. It may be associated with inherited thrombotic risk factors, systemic disease, drugs (steroids, oral contraceptives), trauma, malignancy, vasculitis, mastoiditis and a variety of other less frequent causes. Ulcerative colitis (UC) is a chronic inflammatory disease characterized by local and systemic inflammation predominantly affecting the gastrointestinal tract but that may be associated to extra-intestinal manifestations including thrombosis. The pathogenesis of thrombosis in UC is probably multifactorial. Transient abnormalities of the coagulation system, including thrombocytosis, elevated factor V, factor VII, factor VIII, fibrinogen, and lipoprotein a, and deficient antithrombin III and protein S are reported. Most of the thrombotic events occur in the lower extremities, whereas the incidence of central nervous system involvement is rare and

variable. We report a case of cerebral vein and sinus thrombosis associated with ulcerative colitis.

Case report: A 13-year old female presented with sudden and severe headaches. In the medical history ulcerative colitis was diagnosed 2 months ago and confirmed by intestinal colonoscopy and biopsy. One day prior to her admission steroid and salazopyrin therapy was started for her colitis. Physical examination showed a temperature of 36.7 C, blood pressure of 120/75 mmHg, heart rate of 80/min. Skin, chest, cardiac and abdominal examination were normal. Neurological examination was within normal limits and the fundoscopic examination did not reveal papilledema. A complete blood count revealed white blood count of 21,000/mm3, hemoglobin of 11 gr/dl, platelet count of 214,000/mm3. Liver function tests, urea and creatinine were within normal limits. The level of C-reactive protein was 1 (normal range 0–0.5) and the erythrocyte sedimentation rate was 25. Further laboratory evaluation showed prothrombin time of 12.3 s, INR 1.1, partial thromboplastin time of 25.6 s, fibrinogen level 437 mg/dl (normal, 200–400 mg/dl). MRI brain scan was suspicious for the left transverse and sigmoid sinuses thrombosis. MR angiography demonstrated lack of vein flow of the both transverse, both sigmoid sinuses and left internal jugular vein. Thrombosis tests were planned and enoxaparin therapy was started.

C0207
REVIEW OF D-DIMER PROFICIENCY TESTING DATA WITH RESPECT TO DIFFERENT CONTROL SAMPLE TYPE

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Background: D-dimer test (DD) has been established as a rule-out test for venous thromboembolism. So far, proficiency testing demonstrated poor comparability of the DD results between different methods, reflecting poor standardization of the test. The aim was to critically review DD proficiency testing results with respect to different control sample types provided by Croatian Centre for Quality Assessment in Laboratory Medicine in the last four cycles of testing.

Methods: Ready to use commercial control sample (sample A) with different level was provided at each cycle of proficiency testing in 2013 and 2014 (one cycle per year). In 2015, a lyophilised control sample (sample B) of different origin was used for the two cycles of proficiency testing. Criteria used in assessing preferable sample type and performance of all participating laboratories were comparison of coefficients of variation (CV) with claimed criteria of 25% and calculation of success rate (SR), considering >70% as the good one, regardless of and according to a method.

Results: Number of participants in DD EQA scheme in years 2013 and 2014 was 24 and 30, whereas in two cycles in 2015 was 31 and 33. The most widespread method for DD determination among participants was Siemens Innovance/imunnoturbidimetric method (depending on cycle n=16-22). Other methods, such as Roche/imunnoturbidimetric, Roche/imunocromatography, AbbotAxsym/MEIA, Beckman Coulter/imunnoturbidimetric, Biomerieux Vidas/imunnoturbidimetric between laboratories were less utilised (n<5). Consequently, estimation according to a method was performed just for the Siemens Innovance users. Regardless of the method obtained CVs for the Sample A in 2013 was 34.4% whereas in 2014 was 41.1% with SR of 33%. Considering Sample B, obtained CVs for the two cycles were 18.4% and 30.6% with SR 77.4 and 48.4%, respectively. Considering Siemens Innovance method, obtained CV for sample A in 2013 (n=14) was 6.75 and in 2014 (n=16) 9.5% with SR of 31.3. Results obtained for the cycles carried out with sample B were 7.2% (n=21) and 11.3% (n=22) with SR 91% and 73%, respectively.

Conclusions: Considering obtained CVs and SR, sample type was not critical point for the results obtained by Siemens Innovance method. Regardless of the method implemented, the lyophilised specimen improved between centre agreements. Despite improvement, substantial different successful rate was obtained and therefore further efforts must be invested in finding the best way of proficiency testing and harmonisation.

C0221
SHORT EVALUATION OF FIBRINOGEN DETERMINATION BY DADE THROMBIN REAGENT ON SYSMEX CA 1500 ANALYSER

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Background: The aim of the study was to perform short evaluation of fibrinogen determination by Dade Thrombin Reagent on automated coagulation analyzer Sysmex CA1500 and compare results with those obtained by Multifibren U on the same analyzer (all Siemens Diagnostics, Germany).

Methods: Analytical validation included: within-run imprecision, between-run imprecision and accuracy on three levels of commercially controls (L1=0.9g/L; L2=2.6g/L; L3=7.5g/L). Within-run imprecision was determined by five consecutive measurements each of two human plasma sample (A=2.9g/L; B=3.9g/L). Between-run imprecision was determined on control samples during 7 days. Imprecision was expressed as coefficient of variation (CV) whereas inaccuracy as a percentage of bias (B%). Results were compared to manufacturer's criteria for within- and between-run imprecision (<10%), national proficiency testing for bias (<20%) and Ricos goals (desirable bias 4.8%; imprecision 5.4%; allowable total error, TEa 13.6%). Comparison study was performed by analysing 30 plasma samples by both methods. Methods agreement was evaluated by Passing-Bablok regression and Bland Altman.

Results: Obtained CVs for samples A and B, by run imprecision were 4.51% and 2.24%, respectively. Between-run imprecision yielded CVs for L1, L2 and L3 of 7.59%, 2.38% and 1.79%, whereas obtained biases were -15.5%, -3.85% and 4.53%, respectively. Calculated TEa were as follows: -2.98% (L1), 0.13% (L2) and 7.48% (L3). The method met manufacturer's criteria for within and between-run imprecision. Minimum goals for between-run imprecision given by Ricos were met at L2 and L3 but not at L1. Obtained bias for L2 and L3 were within, whereas at L1 was higher than Ricos recommendation. However all met national proficiency testing allowable bias. Obtained TEa at all levels met the Ricos goals. In considered comparison study, the linearity test performed on Passing-Bablok regression (y=0.1327+0.8273x) showed no significant deviation (P>0.10). In addition, no constant (95%CI for intercept: -0.2233-0.4524), but proportional difference was obtained (95%CI for slope: 0.7320-0.933). The agreement between methods showed important dispersion of the differences (±1.96SD: 44.5%) despite the low mean difference (9.6%).

Conclusions: Dade Thrombin Reagent assay achieved minimum analytical performance goals and as such is suitable for most routine purposes. However, comparison results indicate poor agreement between methods and results obtained by each should not be unambiguously used.

C0222
COAGULATION LABORATORY NETWORK IN REPUBLIC OF CROATIA

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Background: Laboratory coagulation tests are important components of clinical and affected outpatient management whereas lack of expertise may affect patient outcome. In 2015, a strategy is developed to evaluate the status of current practices of coagulation testing among laboratories in

Republic of Croatia (RH). The first step and objective of this study was to assess coagulation laboratory network in RH.
Methods: The last census of the health institutions in the RH (obtained from Ministry of Health and Croatian Institute for Health Insurance) was compared with the data on laboratories network (obtained from the Croatian Chamber of Medical Biochemists) and a list of coagulation proficiency testing participants (provided by Croatian Centre for Quality Assessment in Laboratory Medicine).
Results: The above investigation established that at present there are 177 coagulation services, of which 11 are transfusion and 166 medical biochemistry laboratories. The type and category of institutions with associated laboratories, some of which have substations at different locations were as follows: Clinical Hospital Centers (n=5) with 9 laboratories, Clinical Hospitals (n=3) with 4 laboratories, Clinics (n=5) with 4 laboratories, General Hospitals (n=20) with 22 laboratories, Special Hospitals (n=25) with 13 laboratories and two policlinics with 2 laboratories. The majority of transfusion services are located in general hospitals (n=8). Furthermore, core laboratory services for coagulation at most general hospitals provide a comprehensive range of services both to the hospital and to the local primary care sectors. Most primary care laboratories (n=96) act within or as substation of Health Centers (n=49) and according to the lease contract are expected to perform prothrombin time only. Private laboratory medicine services (n=25) are mainly associated with small private clinics with specialized services.
Conclusions: The results confirmed assumption that different types of laboratories are involved in the implementation of coagulation tests in Croatia. A full test directory and other relevant information about services provided should be available as soon as comprehensive online survey related to current practices is conducted.

C0260
RETROSPECTIVE EVALUATION OF PATIENTS WITH FACTOR XI DEFICIENCY: RESULTS FROM A SINGLE CENTRE

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Background: Bleeding phenotype in patients with cogenital factor XI (FXI) deficiency is not correlated with FIX activity. The aim of this retrospective study is to evaluate the bleeding frequency and related complications in FXI deficiency in our centre.
Methods: A total of 23 patients who are diagnosed with FXI deficiency and are followed at Outpatient Clinics of Cerrahpasa Medical Faculty Department of Haematology between 2000-2015 were included in the study. Demographic data, bleeding history and information on the factor activity, complications and clinical course including complications were obtained from the medical records.
Results: There were 14 females and 9 males; the mean age of diagnosis was 40.3±16.1 years (ranging between 8 – 73). Presenting sign and symptom on admission was bleeding symptoms in 9 (40%), presurgery evaluation in 8 (34%) and post surgery bleeding in 6 (26%) of the patients. Mean FXI activity and activated partial thromboplastin time were 5.21 ± 10 % (range: 0.1-33.4) and 76.09 ± 15.1sec, respectively. No inhibitors were detected in our cohort. Only one of the patients had a family history FXI deficiency. Bleeding types were given in Table 1. The most frequent modes of treatment used in case of bleeding was fresh frozen plasma (FFP) and tranexamic acid. Prophylactic FFP infusion was administered before surgeries. No red blood cells transfusion was used in patients who underwent surgery.
Conclusions: Spontaneous bleeding was usually not observed in patients with congenital FXI deficiency. Our patients who bled postoperatively were successfully treated with FFP transfusions. We could not show any association between FXI activity and clinical severity. Most of the patients were asymptomatic and diagnosed coincidentally while evaluated for prolonged aPTT. Treatment decision should be individualised and based on clinical bleeding phenotype not on factor activity.

Table 1

Symptom	N=23	FXI Level(mean)
Echymosis	3 (13%)	1.5%
Postoperation bleeding	6 (26%)	10.95%
Epistaxis	2 (8.6%)	2.25%
Presurgery screening	8 (34%)	4.8%
Oral mucosal bleeding	3 (13%)	1.9%
Menorrhagia	1 (5.4%)	1%

C0274
ASSOCIATIONS BETWEEN COMPLETE BLOOD COUNT RESULTS AND D-DIMER LEVEL IN PATIENTS WITH ARTERIAL OR VENOUS THROMBOSIS

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Background: Arterial thrombosis is characterized by white thrombi that are rich in neutrophils and platelets, whereas venous thrombosis is characterized by red thrombi that are rich in red blood cells. An automated hematology analyzer can provide complete blood counts (CBCs) and differential leukocyte counts rapidly and economically. Certain hematological parameters, including those for platelets (e.g., MPV), red blood cells (e.g., RDW), and white blood cells, have been reported to be associated with arterial thrombosis or venous thrombosis. However, there are no clear reports of erythrocyte, leukocyte, platelet values and D-dimer levels having been investigated simultaneously during these conditions. The aim of this study was to assess the clinical utility of CBC parameters together with D-dimer level for predicting arterial thrombosis and venous thrombosis.
Methods: Two hundred and forty patients aged 2 to 80 years who presented with clinically suspected thrombosis were enrolled. Thrombosis was diagnosed in 215 patients based on positive D-dimer level and/or radiological findings indicating thrombosis. The remaining 25 patients were analyzed as controls. Data collected for each of the 240 patients were the International Classification of Diseases, tenth revision (ICD-10) coded diagnosis for “thrombosis”, and procedure information available from standard hospital data. Patients were categorized according to the presence of arterial or venous thrombosis. A CBC (determined by Coulter® LH 780 autoanalyzer) and plasma D-dimer levels were compared in the patient and control groups. Data were statistically analyzed using the SPSS vs. 15.0, Chicago, IL
Results: Means for leukocyte count, neutrophil count and erythrocyte indices (e.g. MCV, MCH, and MCHC) were significantly higher in patients with arterial thrombosis than in those with venous thrombosis. Among patients with arterial thrombosis, there was a moderate correlation between D-dimer level and neutrophil count (r>0.47, p=0.004). Cut-off values for leukocyte count (>9000/μL) and neutrophil count (>6000/μL) were highly sensitive (81%) and specific (88%) for predicting arterial thrombosis (p=0.03).
Conclusions: Among patients with suspected thrombosis, presence of arterial thrombosis is likely if leukocytosis and neutrophilia are detected in combination with high D-dimer level and positive radiological findings indicating thrombosis.

C0317

MULTIFACTORIAL MODEL TO PREDICT LONG-TERM OUTCOMES IN PATIENTS SURVIVED AFTER UNSTABLE ANGINA

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Background: The aim of the present investigation is the development of the multifactorial model for the long term unstable angina (UA) outcomes prognosis on the basis of the predictors of the thrombogenic risk.
Methods: 180 patients with UA included in the study. They were admitted to the Republican Scientific and Practical Center "Cardiology" and the 4th Minsk City hospital.
All patients included in the study, performed physical examination, 12-lead ECG, echocardiography, Holter ECG monitoring, and coronary angiography. Laboratory studies included: General blood analysis, biochemical blood analysis with determination of lipid profile, determination of the level of high-sensitivity troponin (hsTnI), C-reactive protein (CRP), homocysteine, brain natriuretic peptide (BNP), myeloperoxidase (MPO); coagulation hemostasis (level of fibrinogen (FG), antithrombin III (AT III), D–dimer, factor XA).
Results: During the 3 years of observation of 180 patients who had unstable angina in 64 (35.5%) persons identified recurrent progressive angina requiring CABG in 25 (13.8%) patients, angioplasty and stenting of the coronary arteries by urgent reasons in 22 (12.2 %) patents. Nonfatal myocardial infarction occurred in 11 (6.1%) patients. Rhythm disturbances (short paroxysms unstable ventricular tachycardia) was observed in 6 (3.3%) patients and were treated with medication (cordarone, β-blockers). Three patients with unstable angina died suddenly from acute coronary insufficiency. Mortality was 1.6%.
In the subgroup with adverse outcomes was found to be increasing from 1 of the above-mentioned biomarkers in 12 (15.4%) persons, 2 - 47 (60%) of persons and 3 - 19 (24.3 %) patients. The obtained data confirm the diagnostic significance of laboratory parameters of homocysteine, BNP, MPO, hsTnI, CRP.
Conclusions: Developed the multifactorial scale for the long term outcomes (3 years) in patients survived after UA included such predictors as the baseline level of CRP>5.99 mg/l (sensitivity – 92%, specificity– 69%), troponin I 0.01ngml (sensitivity– 86%, specificity– 91%) and myeloperoxidase >344 pmol/ml (sensitivity– 86%, specificity– 77%). It was established that for the patients at a high risk the probability of the recurrent coronary events in a 3 years of follow up increases in 12.5 times.

Disseminated Intravascular coagulation

C0166

PLATELET COUNT, AND GLOBAL MARKERS OF COAGULATION AND FIBRINOLYSIS DURING EARLY PHASE OF OUT-OF–HOSPITAL CARDIAC ARREST AND RESUSCITATION

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Background: Hypoxia and ischemia influence blood coagulation and fibrinolysis, if sufficiently severe like cardiac arrest and resuscitation, cause disseminated intravascular coagulation (DIC). We investigated prognostic implication of early DIC diagnosed during 24 hours after admission.
Methods: Patients with established out-of-hospital cardiac arrest (OHCA) who underwent cardiopulmonary resuscitation with subsequent return of spontaneous circulation were retrospectively enrolled. Patients were divided two subgroups with DIC (208) and without DIC (180) by the Japanese Association for Acute Medicine (JAAM) DIC criteria. Platelet count, global markers of coagulation and fibrinolysis were measured 4 times after admission to emergency department (T1, 0-6; T2, 6-12; T3, 12-18; T4, 18-24 hr).
Results: DIC patients showed significantly lower platelet counts, fibrinogen and antithrombin levels, and more prolonged prothrombin time throughout the study period. FDP and D-dimer levels of DIC patients were extremely higher than those without DIC, which was associated with increased lactate levels. Higher sequential organ failure assessment score (SOFA) (9 vs. 6, $p<0.001$) associated with increased prevalence of multiple organ dysfunction (23.6% vs. 3.9%, $p<0.001$) in DIC patients were observed, which leads to poor hospital outcome evaluated by hospital mortality of DIC patients (54.8% vs. 23.9%, $p<0.001$).
Conclusions: DIC immediately after cardiac arrest and resuscitation shows increased fibrinolysis, which may affect morbidity and mortality in patients with OHCA.

C0227

GASTRIC ADENOCARCINOMA WITH BONE MARROW CARCINOMATOSIS COMPLICATED WITH CANCER RELATED THROMBOTIC MICROANGIOPATHY: CASE REPORT

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Background: We report the case of a 38-year-old man affected by metastatic gastric adenocarcinoma, who first presented with thrombotic microanghiopathy (TMA) and melena. Esophagogastroduodenoscopy revealed advanced gastric cancer (AGC). The signet ring cell gastric cancer was diagnosed by biopsy. He was considered as cancer related thrombotic microanghiopathy (CR-TMA). Bone marrow biopsy led to a diagnosis of disseminated carcinomatosis of the bone marrow caused by AGC. We initiated combination chemotherapy with 5-flourouracil (5-FU) and cisplatin (CIS), which led to a significant improvement of the CR-TMA. CR-TMA was considered to be caused by AGC. CR-TMA can be initial presentation of the underlying cancer. This severe and poor-prognosis disease requires prompt diagnosis and rapid initiation of specific chemotherapy.
Introduction: Thrombotic microangiopathy (TMA), is a common complication in cancer patients. Thrombotic microangiopathy occurs in association with a variety of malignancies, especially adenocarcinomas [1]. The prognosis is not as favorable as in classical TTP. Presentation may be either at an early stage of cancer or associated with disseminated disease. Occasionally, TMA may be one of the first manifestations of an occult cancer [2]. ADAMTS13 activity is not significantly reduced in these patients [2].The pathogenesis of cancer-related TMA (CR-TMA) is unclear, but probably the most important factor is endothelial damage. However, cancer-associated TMAs show some different hallmarks. Weakness, cough and dyspnoea, fever, weight loss, bone and abdominal pain are the most common presenting symptoms of CR-TMA. Blood chemistry reveals markedly increased LDH levels, increased alkaline phosphatase and the blood smear shows erythromyelemia. Bone marrow biopsy is a valuable tool in order to show malignant seeding. Treatment of the underlying neoplasia is the mainstay of therapy and there is no role for plasmapheresis or plasma infusions
Case: A 38 year-old male patient with a past medical history of Crohn disease, receiving mesalazine and azathiopurine therapy for the last three years was admitted to the emergency room with melena. Gastroscopy revealed intact gastric mucosa and bleeding ulserated gastric advanced gastric cancer (AGC) (Figure 1). The signet ring cell gastric cancer was diagnosed by biopsy. In admission, Laboratory results showed anemia, thrombocytopenia and schistocytes in peripheral blood smear. Clotting tests revealed elevated D-dimer (1170 µg/mL) level, normal level of fibrinogen (210 mg/dL) and a low platelet count ($6000 \times 10^3/\mu L$), a slightly higher level of INR, low haptoglobulin levels, elevated serum LDH and indirect bilirubin levels which led us a diagnosis of cancer related thrombotic microanghiopathy (CR-TMA). His electrolyte panel was normal with a BUN 12 and a creatinine 0.8. The remainder of his chemical profile was normal. Despite receiving intensive therapy for CR-TMA, his clinical status worsened.

Bone marrow biopsy led to a diagnosis of disseminated carcinomatosis of the bone marrow caused by AGC (Figure 2). We initiated combination chemotherapy with 5-flourouracil (5-FU) and cisplatin (CIS), which led to a significant improvement of the CR-TMA. Thrombocytopenia of uncertain origin with slightly high INR, APTT, elevated D-dimer, normal fibrinogen, proves of intravascular hemolysis and schistocytes in peripheral blood smear led us the diagnosis of TMA. This process warrants searching for bone narrow metastases.

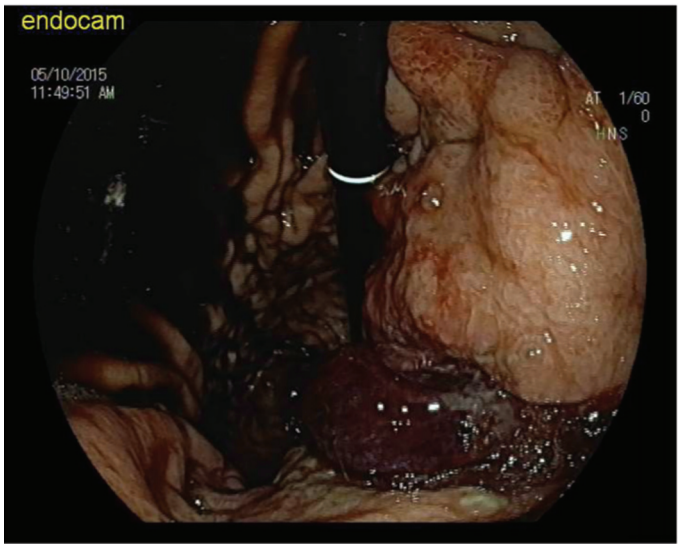

Fig. 1. Lesion lies from posterior wall of corpus to antrum with slightly deppressed and ulserated base.

Discussion: Cancer-related thrombotic microanghiopathy (CR-TMA) can complicate the development of a variety of cancers is characterized as microangiopathic hemolytic anemia (MAHA) with fragmented red blood cells. Although patients may have an established diagnosis with documented metastases, cancer related thrombotic microanghiopathy (CR-TMA) can be a presenting feature of an occult malignancy. While a severe ADAMTS13 deficiency seems not to be the underlying pathophysiologic mechanism, bone marrow infiltration by carcinoma cells is strongly associated with TMA. We present herein a case of gastric adenocarcinoma complicated with CR-TMA. The patient is a 38-year-old man with advanced gastric carcinoma(AGC) that had metastasized to his bone marrow. The results of a bone-marrow biopsy confirmed the involvement by metastatic carcinoma. He is completing the 5th cycle of a planned six cycles of his treatment. Before any form of therapy is initiated, several questions have to raised, such as whether TMA is primary or secondary to a metastatic carcinoma.

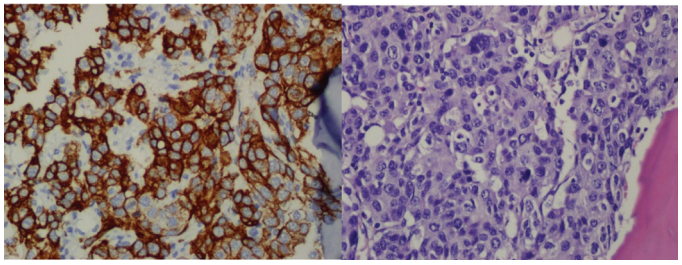

Fig. 2. Bone marrow biopsy showing 40x pan CK7 positivity(left), bone marrow biopsy showing 40x magnification abundance of signet ring cells (right).

C0311
THERAPEUTIC PLASMA EXCHANGE FOR THROMBOTIC MICROANGIOPATHY

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Background: Thrombotic microangiopathy (TMA) is a syndrome characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, fever and renal dysfunction. Therapeutic Plasma Exchange (TPE) is a standard treatment approach for the patients. Our aim is to determine the clinical characteristics and outcome of patients with TMA treated with TPE in our center.
Methods: We retrospectively evaluated 46 patients who have been diagnosed as TMA at Ankara University Department of Hematology between 2007 and 2015. Patients were treated with TPE (Frensenius Kabi AG, Hamburg, Germany) until the normalization of laboratory parameters. The plasma exchanged was 1.5 times the predicted plasma volume with fresh frozen plasma for the first procedure, and usually 1.0 time the predicted volume thereafter until remission.
Results: 22M/24F was included in the study with a median age of 55 (range, 18-83). 10 of 46 patients (22%) were consulted from intensive care units, 7/46 (15%) from emergency unit and 6/46 (13%) from nephrology unit. The most common presenting symptom was purpura in 52%, followed by neurological disturbance 48%, renal function abnormality in 43% and fever in 28% of patients. At diagnosis the median hemoglobin (g/dl), leucocyte count (10^9/L) and thrombocyte count (10^9/L) were as follows: 9.4, 11.4 and 58.6. Median time period of procedure was 99 minutes (range, 64-313). 5/46 (11%) patients had femoral catheters and central venous catheters were the access for the rest of patients. None of the patients had severe adverse events during procedures. 21 patients achieved complete response (46%) after 2-40 sessions and 2 of them were died during follow-up. Responders were diagnosed mostly with infectious related TMA (47%). 21 patients (46%) who had progressive disease died within 30 days after diagnosis. 2 non-responder patients to TPE had diagnosis of Thrombotic thrombocytopenic purpura and treated with successfully with Rituximab.
Conclusions: TPE is safe treatement modality in patients with TMA however there is still a high mortality rate. Patients should be evaluated on individual bases. PTE should be started immediately after diagnosis and new treatment approaches should be considered for non-responders.

C0369
COMPARISON OF THE COAGULATION ABNORMALITIES IN PATIENTS WITH DIC COMPARED TO WARFARINIZED PATIENTS

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Background: Disseminated intravascular coagulation (DIC) occurs as a complication of many underlying diseases. DIC is characterized by a systemic activation of the coagulation and fibrinolytic systems and the ongoing activation of coagulation can exhaust coagulation factors, ultimately leading to bleeding. The International Society of Thrombosis and Hemostasis (ISTH) criteria for DIC consists of a scoring system that includes decreased platelet count, increased D-dimer/Fibrin degradation products, prolonged PT, and decreased fibrinogen. Patients receiving warfarin for anticoagulation also have a prolonged PT/INR. Although the goal on therapy is to increase the INR between 2.0 and 3.0, during the initial phase of therapy it is less than 1.5. The purpose of this study was to compare the coagulopathy observed in patients with DIC and in patients in the initial phase of warfarin therapy.
Methods: Citrated plasma samples were collected at baseline from patients diagnosed with sepsis-associated DIC (n= 100) and from patients in the initial phase of warfarin therapy (n=100). These plasma samples were evaluated for PT/INR, APTT, fibrinogen, and functional and antigenic levels of Factors IX and X.

Results: The PT/INR values were statistically significantly higher in warfarinized patients compared to DIC patients (p<0.001). The APTT showed no correlation with the INR in warfarinized patients but increased with an increase in the INR in the DIC group (p<0.001). Similarly, the fibrinogen levels showed no correlation with INR in warfarinized patients; however, in DIC patients, the fibrinogen levels decreased with an increase in the INR. In the factor assays, both the functional and antigenic levels of factors IX and X were decreased in the anticoagulated patients as INR increased, but showed no variation with INR in the DIC patient group. Factor VII levels were decreased with an increased INR in both the anticoagulated and DIC patients.
Conclusions: An increase in INR correlated with an increase in both APTT and fibrinogen in DIC patients but not in patients receiving anticoagulation. Interestingly, in DIC patients, there was no decrease in either the functional or antigen Factor IX or X levels while the Factor VII levels showed a decrease. This contrasts with patients receiving warfarin anticoagulation, where the Factor VII, IX, and X levels all decrease with an increasing INR. These result suggest that the coagulopathy observed in a patient with INR ≥ 1.4 is fundamentally different in a patient receiving warfarin anticoagulation, where changes in coagulation factor levels but not in global coagulation parameters such as APTT and fibrinogen should be expected, than in a patient with DIC, where greater changes in global coagulation parameters but less consistent changes in coagulation factor levels should be anticipated.

C0374
DIFFERENCES IN THROMBIN GENERATION MARKERS AT BASELINE IN PATIENTS WITH SEPSIS ASSOCIATED COAGULOPATHIES

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Background: Severe sepsis remains the most common cause of death in critically ill patients thrombin plays a crucial role in the pathogenesis of sepsis associated disseminated intravascular coagulation (DIC). The purpose of this study was to compare the baseline values of prothrombin fragment (F1.2), thrombin antithrombin complex (TAT) and d-Dimer (DD) in patients enrolled in the Phase 2B and the Phase III study for the effect of recombinant thrombomodulin.
Methods: Plasma samples from seven hundred and fifty eight patients enrolled in the ART-123 study, a phase 2b, international, multicenter, randomized controlled trial, and patients enrolled in the ongoing (n=200) Phase III clinical trial groups were analyzed for various parameters using ELISA methods for F1.2 and TAT and a functional method for AT. Plasma levels of F1.2, TAT, and AT were analyzed at baseline prior to the first dosage of recombinant thrombomodulin or placebo.
Results: The inclusion criteria for the phase 2b study included revised ISTH criteria and the phase III study used and INR>1.4, 30K=<PLT<150K, Shock and/or Respiratory organ dysfunction as criteria at baseline. The median values were TAT (7.5 ng/ml Phase 2b study; 12.4 ng/ml Phase III), F1.2 (305 pmol/L Phase 2b; 401.8 pmol/L Phase III) and AT (72.8%, Phase 2b; 50.3%, Phase III). There was a difference noted in the markers of thrombin generation between the two studies. The TAT and F1.2 were higher and the AT was lower, indicating consumption. This new data is based on n=176 patient baselines.
Conclusions: Therefore the strict criteria used in the Phase III study shows that this patient group had more activation of coagulation compared to the Phase 2b patients. Therefore strict entrance criteria for patient included in sepsis studies is important for good clinical outcomes.

Fibrinogen and other coagulation factors

C0108
CHANGES OF BLOOD FIBRINOGEN CONCENTRATION, CONNECTED TO GEOMAGNETICAL EVENTS, IN HEALTHY RATS POPULATION

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Background: There is a deep and close interconnection between electromagnetic events on the Sun, the Earth, and Cosmos and biological processes, that had been shown by Russian investigators - A.L. Chischevsky, V.Z. Vernadsky, P.V. Florensky. It is a hard problem till now to explain the mechanism of this global phenomenon because the solar and terrestrial magnetism is a natural factor of living matter existence and could not be excluded from variety of another influences on the organism. So science progress represents collection data in this field especially in human practice sphere.
Methods: In joint research with institute ISMERAN (Institute Of Earth Magnetism) it had been studying the influence of terrestrial magnetic tension on process of haemostasis and fibrinolysis in healthy rats during 6 months (July-December) in Moscow region. There were blood probes taken in rats from v. jugularis once every month. There were determinated the parameters of haemostasis (fibrinogen level, recalcification time, soluble fibrin-monomer complexes (SFMC) concentration) and fibrinolysis parameters - euglobulin clot lysis time (ECLT) and functional activity of t-PA on fibrin plates.
Results: From July till December it was observed the growing of plasma thrombotic properties and decreasing of fibrinolytic activity. The fibrinogen level increased from 3.5 ±0.21 g/l to 6.6±0.41 g/l, (p<0.01), SFMC level risen from 0.08±0.007 g/l to 0.136±0.009 g/l (p<0.001). ECLT prolonged from 190 till 280 min. (p<0.05), t-PA activity decreased 1.5 times. These data were evidence of increase of thrombotic state in healthy animals blood to December season, that could lead to thrombosis in case of sufficient provocation. Besides there was observed the rhythmic character of these changes. The fibrinogen level reached the value 8±0.9 g/l, SFMC – 0.2±0.002 g/l, the ECLT - 1060 min. in maximal point in November. The rhythm and amplitude of TMT was well synchronized with rhythm and value of t-PA activity, but partially differed from fibrinogen rhythm changes. The last was fully coincided with SFMC changes, the main marker of thrombin generation.
Conclusions: The rhythmic fluctuations of fibrinogen and other factors.s levels in healthy organism can lead to such their occasionally combinations, that will be sufficient to provide for spontaneous thrombosis or other catastrophe. It is particularly dangerously in winter.

C0124
PAMUKKALE SUMMER CAMP EXPERIENCE

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Background: In Hemophilia summer schools, Hemophilia patients and their families get together with health care providers with the aim of education and social activities. In our country, from the year that Hemophilia Association founded in 1996, Hemophilia summer camps are organized in June of each year. Camps for hemophilic patients give chance to identify their disease and improve their skills. Patients and their families take an opportunity to come together with patients diagnosed of same disease and realize that they are not alone. Besides, in summer camps, self-infusion education is given to hemophilia patients and their families.

Methods: Pamukkale Hemophilia Summer Camp is the first national organization of Pamukkale Hemophilia Union attached to Hemophilia Association. This organization achieved by foundation administration, Hemophilia patients and families. There is 160 participators in summer camp, in whom there is 130 hemophilia patients and their families from Turkey. Health workers dealing with hemophilia gave theoretical and practical education. Also participators had chance to swim in Pamukkale Thermal water, made trip to Laodikeia and Hierapolis cities.
Results: Communication in the summer camp has had positive effect on improving self-confidence and respect in Hemophilia patients
Conclusions: Pamukkale summer camp was a good example of physician, patient and family collaboration.

C0131
A HEMOPHILIA CASE WHO IS DIAGNOSED LYMPHOMA AND TREATED WITH CHEMOTHERAPY

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Background: Hemophilia A is an incorrect synthesis of factor 8 and X linked hereditary disease. It is more common than the other factor deficiencies (1). Our case report was a Hemophilia A patient with multiple lymphadenopathy and hard palate mass in application and then diagnosed NHL. Also we presented an assembly of literature for the incidence of lymphomas and the other cancers field on hemophilia and whether there is a sensitivity for malignancies in hemophilic patients.
Results: An 60 year old male patient with mild hemophilia A (factor level % 12). In September 2008, multiple lymphadenopathy and hard palate mass was detected in the patient the factor inhibitor is negative. HIV (-), HBsAg: (-), Anti-HCV: (-) were reported. It was reported there was a destructive image in the posterior wall of the left maxillary sinus and a wall thickening of the hard palate left sided in paranasal sinus tomography clinic biopsy of the mass was made. At the pre-operative first day we gave 90 U/kg (target factor level 100) factor 8 to the patient. We gave 2x45 U/kg (first dosage was one hour before the operation) at the operation day, post-operative first day 2x45 U/kg, post-operative second day 2x45 U/kg and third day 2x45 U/kg plasma-derived factor 8 infusion to the patient and there was no hemorrhage. In the operation, factor 8 level was 100 U/ kg and pre-operative or post-operative factor inhibitor were negative. The result of the pathology was diffuse large B cell lymphoma CD 20(+)(NHL). We gave R-CHOP 8cycles, the patient were complete response. He has monitored as remission for seven years.
Conclusions: In the last years -with the usage of factor preparations- causes of the major mortality became age-related cardiovascular diseases and cancer because of advanced ages in hemophilic patients instead of hemorrhages (2-3). In the literature there has been lots of investigations about the possible sensitivity of malignancies in hemophiliac patients.
The HIV infection is the most important factor of cancer related mortality in hemophilic patients. NHL is the most frequent malignancy in HIV positive patients.
Similar to other studies in the literature, we detected hemophilac patients had increased sensitivity for malignancies in our study. We especially notified the incidence of the lymphomas increased in both HIV positive hemophiliac patients associated with immunosuppression related to AIDS progression and also HIV negative patients. But more studies are needed about this subject in literature.

C0179
AN ACQUIRED FVII DEFICIENCY AND HYPOFIBRINOGENAEMIA FOLLOWING A HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: Acquired factor VII (FVII) deficiency in hematological diseases can be caused by vitamin K deficiency, infections, disseminated intravascular coagulation, hepatic dysfunction or intensive chemotherapy.
Methods: We described a 47-old patient presenting prolongation of the prothrombin time (PT) and hypofibrinogenemia 2-3 weeks following hematopoietic stem cell transplantation (HSCT). The PT and the fibrinogen level were normal at the time of admission. The nadirs were in the 28th day post HSCT: PT was 46% and fibrinogen level was 0.46. The plasma factor VII clotting activity was 24%. Those of factors II, V, and X were normal. Protein C activity was normal. Screening for factor VII specific autoantibody was negative.
Results: There was no response to vitamin K supplementation. No bleeding complications were reported. However, a thrombotic microangiopathy had been suspected 5 days following the nadirs necessitating the cyclosporine discontinuation. One day later, PT was completely corrected and fibrinogen slightly improved. Fibrinogen level reached a value of 2.1 over the next four days. The patient died at day +173 post HSCT following a septic shock although hemostatic parameters were conserved.
Conclusions: Few similar cases were reported in the literature. The clinical manifestations of this uncommon acquired deficiency state are variable and its mechanism remains to be defined. Could cyclosporin be considered as responsible of this hemostatic defect?

C0313
ACQUIRED DEFICIENCY OF VITAMIN K-DEPENDANT CLOTTING FACTORS, DESCRIPTIVE REPORT OF 3 CASES, SINGLE CENTRE EXPERIENCE

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Background: Combined deficiency of vitamin K-dependent coagulation factors (CDVKF) is a rare disorder that can be either inherited or acquired, characterized by the deficiency of factors II, VII, IX and X (VKCF). This disorder can be caused by a mutation in the c-carboxylase gene (VKCFD1) or by a defect in the VKOR complex (VKCFD2) and causes bleeding.
Methods: We report here 3 cases of CDVKF diagnosed at our centre between 2004-2013.
Results: All patients were female and none of them showed evidence of malabsorption, liver disease or coumarin intoxication. First patient, 31 year-old, was referred due to bleeding from operation site on left foot. Her medical history revealed no bleeding following appendectomy and spontaneous delivery at the ages of 9 and 19, respectively. Prolonged bleeding had been observed after rhinoplasty at the age of 21. There was no family history of bleeding. Laboratory was unremarkable prolonged PT/aPTT. Mixing study indicated factor deficiency. VKCF levels were low. Vit. K and FFP (15 ml/kg) was started to stop bleeding. However, bleeding persisted and PT/aPTT did not normalize. The molecular genetic analysis of the VKORC1- and the GGCX- genes did not reveal any mutation at known loci. Bleeding ceased and PT/aPTT normalised following aPCC infusion. The patient is still on aPCC.
Second patient, 41 years old, was referred due to prolonged menstrual bleeding, hematuria and epistaxis. She had been diagnosed with CDVKF at the age of 19. Parenteral administration of 10 mg/wk Vit. K normalized PT/aPTT. She receives Vit. K and FFP for occasional epistaxis.
Third patient was 26 years old. She admitted to hospital due to ruptured ovarian cysts. Her bleeding persisted after surgery which led to a second

operation for oophorectomy and removal of intraabdominal hematoma. She had prolonged PT/aPTT, and low levels of VKCF. FFP and Vit. K was started. Administration of 20 mg/day Vit. K and 10-20 ml/kg FFP decreased the hemorrhage in 2 weeks. She is still on 10 mg/day Vit. K.
Conclusions: CDVKF is a rare and usually inherited disorder. Sporadic acquired forms have been reported. Diagnosis depends on reduced levels of vitamin K–dependent coagulation factors. Factor levels usually improve with vitamin K, FFP or aPCC. Prophylaxis replacement may be required in patients with recurrent major bleeding.

C0314
HYPOFIBRINOGENEMIA; DESCRIPTIVE REPORT OF 5 CASES, SINGLE CENTRE EXPERIENCE

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Background: Inherited fibrinogen disorders are rare and primarily include type I which covers cases with hypo- and afibrinogenemia and type II consisting of cases with dys- and hypodysfibrinogenemia. There are also acquired forms of hypo and dysfibrinogenemia.
Methods: Here, we report 5 cases of hypofibrinogenemia diagnosed at our centre between 2002-2016.
Results: Four patients were male. Mean age at diagnosis was 39 (range: 20-52). Two of our patients were siblings. Only the female patient had a history of bleeding, that occurred during delivery. She gave a bleeding history for all of her deliveries; the last one leading to partial hysterectomy due to prolonged bleeding. All patients had a family history of hemorrhagic diathesis. In 3 of the patients PT, aPTT could not be measured due to absence of clot formation. Two patients had prolonged PT and aPTT (PT: 42 and 26.2 sec, aPTT: 170 and 44 sec). Mean fibrinogen level was 27 mg/dl (range: 14-85 mg/dl). Thrombin time was prolonged in all of them. Hemoglobin level, liver and renal function tests were normal in all cases. One patient had been successfully operated for left scrotal hernia, after 4 units of FFP replacement. No bleeding was observed. During follow up he had a tooth extraction without bleeding after replacement of 2 units of FFP. One patient has developed liver cirrhosis which did not reveal any underlying disorder 11 years after the diagnosis of hemorrhagic diathesis. All patients are alive and still on follow up.
Conclusions: Hypofibrinogenemia is a rare disorder and patients are usually asymptomatic. Bleeding usually occurs after surgical procedures or if there is a concomitant bleeding disorder. Some patients with hypofibrinogenemia develop chronic liver diseases during follow up. This can be because of accumulation of aggregates in hepatocyte endoplasmic reticulum during impaired abnormal fibrinogen release.

C0320
HEMOPHILIA: A SINGLE-CENTRE EXPERIENCE OF 12 YEARS

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Background: The hemophilias A and B (HA, HB) are the most common X-linked inherited bleeding disorders. If the patients are not properly managed and informed, it can lead to high morbidity. Development of neutralizing inhibitory antibodies to FVIII and FIX is the most challenging treatment-related complication of hemophilia.
Methods: We report a retrospective case series between 2003-2015 at Cerrahpasa Medical Faculty Pediatric Hematology Outpatient Clinic which consists of 37 severe HA, 42 moderate-mild HA, 8 severe HB and 9 moderate-mild HB patients.
Results: Twenty one of the 37 severe HA patients were under primary prophylaxis, whereas 16 patients had on-demand treatment. Three of the 21 patients whom were getting primary prophylaxis, were treated with plasma derived factors and the other 18 patients were treated with recombinant factors. Nine of the patients getting primary prophylaxis (42%) presented to hematology clinic with joint bleeding and their history revealed irregular use of factors. Four of the 9 patients also had bleeding problem at circumcision. Nine of the 42 moderate-mild HA patients had primary prophylaxis (4 patients with plasma derived factors, 5 patients with recombinant factors) and none of them developed inhibitors secondary to treatment. Four of the eight severe HB and two of the nine moderate-mild HB patients were treated with primary prophylaxis and only one of them received recombinant factor. Three of the severe HA patients who were under primary prophylaxis with recombinant factors developed inhibitors to FVIII. Only one of them had stable inhibitors, whereas the other two patients' inhibitors were permanently eradicated with the prophylaxis of the same factor at 6 and 8 months of the treatment, respectively.
Conclusions: Hemophilia is a serious congenital bleeding disorder that requires early diagnosis, intensive family and patient education, and regular comprehensive care to prevent life-threatening complications and potentially lifelong disability.

Fibrinolysis and thrombolysis

C0051
EFFECT OF ANTIHYPERTENSIVE DRUGS ON THE ACTIVITY OF PROTEASES OF THE FIBRINOLYTIC SYSTEM IN VITRO

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Background: The fibrinolytic system (FS) and the renin-angiotensin system are involved in hemo-vascular regulation. Hypertension increases the risk of thrombosis. Inhibitors of angiotensin-converting enzyme (ACE) are used as antihypertensive drugs. Elucidation of the possibility of a direct effect of ACE inhibitors having different structures on the activity of enzymes of the FS *in vitro*.
Methods: The effect of enalaprilat (0 - 10 mM), captopril (0 - 5 mM) and lysinopril (0 - 25 mM) on amidase activities of tissue plasminogen activator (tPA), urokinase (uPA) and plasmin as well as on the rate of Glu-plasminigen activation by tPA (in presence of soluble fibrin) and uPA has been studied.
Results: Enalaprilat and lysinopril had no effect, but captopril inhibited the amidase activities of 1-10 nM plasmin, 20-75 nM uPA and tPA (IC_{50} = (2.0-2.6) ± 0.1 mM). Enalaprilat had no effect and captopril inhibited Glu-plasminogen activation by tPA and uPA (IC_{50} - (1.50-1.80) ± 0.06 mM). Effect of lysinopril on the activator activities of the two activators was opposite: in the presence of 25 mM lysinopril, the rate of Glu-plasminogen activation under the action of tPA was reduced by 70% and was increased by 120% under the action of uPA (IC_{50} = 12.0 ± 0.5 mM).
Conclusions: Depending on the structure, the three antihypertensive drugs have different effects on the activity of proteases of the FS. Lysinopril containing lysine group has opposite effect on Glu-plasminogen activation by t-PA and by uPA. Captopril containing SH-group inhibits the amidase activities of plasmin, uPA and tPA as well as the conversion of Glu-plasminogen into plasmin induced by the tPA and by the uPA. Hence, the use of captopril that suppress activity of FS may increase in risk of thrombosis.

C0214
CHANGES OF HAEMOSTASIS AND FIBRIINOLYSIS AFTER PER OS USING OF THROMBOLYTIC PREPARATION LNGOLYTIN

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Background: Thrombolytic preparations from micromycetes is very intensively studying in eastern countries particularly. There was found the new way of thrombi dissolution by fungi proteases - administration of thrombolytic preparation per os. We studied the new thrombolytic preparation longolytin - obtained from micromycete Arthrobotrys longa. Longolytin dissolved experimental thrombi in v. jugularis in rats after intravenous introduction and external thrombi formed in superficial ear marginal rabbit's vein after application. The aim of this work is to study fibrinilysis and haemostasis in rats after per os administration of longolytin. It is at the first step of future investigation of thrombolytic action of lngolytin after its per os using.
Methods: Preparation longolytin (30 mg/ml) in glycerol) introduced to mouth (0.1 ml) by special soft catheter during 10 days every day. Blood for analysis was taken from v.jugularis 3 times: before experiment, on 7 day and 20 day. There were determined parameters of haemostasis APTT- activated partial thromboplastin time (sec), fibrinogen level (g/l) and parameters of fibrinolysis: ECLT - time of lysis of euglobulin clot (min); t-PA - tissue plasminogen activator (mm^2 on fibrin plates).
Results: There were observed moderate fibrinolysis activation, diminished to 20 day: on 1-st day ECLT increased on 22% compared to data before experiment, on 7 day - on 36%, on 20 day - 2%. Simultaneously t-PA activity raised from 25±2.8 mm^2 before to 52.6±7.1 mm^2 on first day ($p<0.02$), to 74.2±6.8 mm^2 on 7 day ($p<0.05$), to 30.6±3.3 mm^2 on 20 day ($p<0.5$). There were not noticed phenomenon of rethrombosis, often accompanied intravenous administration of thrombolytic preparations. Parameter of haemostasis (APTT) demonstrated prolonged activation of anticoagulant properties of blood during 20 days of experiment. APTT raised from 42±4.1 sec to 58±4.9 sec on first day ($p<0.05$), till 68±5.9 sec (7 day) ($p<0.05$), till 59±5.6 sec (20 day) ($p<0.05$). Fibrinogen level did not change during 20 days of observation.
Conclusions: Per os administration of longolytin stimulated gentle, moderate and prolonged increasing of fibrinolytic and anticoagulant properties of blood. It was very favourable factor for person with depressed fibrinolysis in different diseases: diabet, cardiovascular and renal pathology, stroke.

C0230
INFLUENCE OF HEPARIN-LIKE PLANT COMPONENT ON ANTICOAGULATING AND FIBRINOLYTIC PROPERTIES OF BLOOD PLASMA

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Background: It is known that low molecular weight heparin of animal origin are anticoagulants and antithrombotics.
The present study deals with the isolation from plants (Paeonia suffruticosa Andrews). Components influencing anticoagulant and fibrinolytic properties of blood plasma of animals.
Methods: We studied the ability of components to modify the fibrin polymerization with simultaneous activation of anticoagulant activity. The lyophilized samples obtained from peony roots were used. Using a variety of methods have shown that molecular weight, spectral characteristics (mass spectroscopy, infrared spectroscopy) plant component indicate its similarity with heparin or low molecular weight of animal origin. The test drug plant heparin was administered intramuscularly to rats at a dose of 1 mg/kg of body weight.
Results: 1 hour after the introduction of the drug observed in plasma of rats a significant increase in anticoagulant activity 2.5 times, fibrinolytic and fibrin depolymerizing activities - 2 times, reduction of the level of inhibitors of plasmin - 1.5 times. These changes persisted after 3 hours after drug administration. 24 hours after the introduction of the plant component of anticoagulant and fibrinolytic activity reduced, but still higher than in the control.
Conclusions: Thus, heparin-like plant component of the peony contributes to prolonged increase in blood flow and fibrin depolymerizing and anticoagulant properties of blood plasma within 24 hours after injection.

C0266
REAL-TIME MONITORING OF DRUG-INDUCED FIBRINOLYSIS UNDER INTENSIVE FLOW CONDITIONS IN VITRO

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Background: Failures in hemostasis system functioning can cause such serious and deathly diseases as strokes, heart attacks, thrombosis of the lower limbs and sudden cardiac death. Methods that traditionally are used for hemostasis control, are invasive or relatively prolonged. So, that's why we try to develop effective non-invasive and real-time method for hemostasis monitoring. As a core of our method we used ultrasound. It was shown earlier that the blood coagulation processes under flow conditions in vitro can be reliably detected by ultrasonic methods [*Uzlova S.G., Guria K.G., Guria G.Th. Acoustic determination of early stages of intravascular blood coagulation// Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences. 2008*]. In present work ultrasonic approach is used for real-time monitoring of drug-induced fibrinolysis in flowing blood.
Methods: Bloodstream was modeled in the closed system of silicon tubes. Liquid therein was moved by peristaltic pump. We used human fresh-frozen blood plasma and whole blood that were taken from healthy donors. The evolution of blood coagulation and fibrinolysis was monitored simultaneously by two channels: optical and acoustical. Specially designed automatic injector allowed us to inject the fibrinolytic agent precisely at certain stages of thrombosis processes in accordance with acoustic data. We used three types of fibrinolytic agents: urokinase, streptokinase and tissue plasminogen activator. The efficiency of fibrinolysis was estimated by special index, based on quantitative parameters of acoustic signal.
Results: Developed experimental setup has allowed to registrate in details processes of fibrinolysis as well as blood coagulation. The kinetics of drug-induced fibrinolysis under flow conditions was investigated. It has been demonstrated that the efficiency of fibrinolysis essentially depends not only on the dose, but also on the clot formation stage the drug was injected on. Experiments revealed that a timely injection of any studied drugs may lead to fast and complete clot dissolution.
Conclusions: The designed software-hardware complex can be used for testing novel fibrinolytic agents and developing real-time administration protocols. The developed approach is of interest for the aims of diagnostic and monitoring in clinic.
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C0371
FIBRINOLYTIC DYSREGULATION IN ARTHROPLASTY PATIENTS MAY CONTRIBUTE TO POSTOPERATIVE HEMOSTATIC COMPLICATIONS

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Background: The pathogenesis of the alterations of fibrinolytic components in inflammatory joint disease and their post-surgical modulation are not clearly understood. Preexisting hemostatic dysfunction may lead to both thrombotic and bleeding disorders in these patients. To profile fibrinolytic parameters in patients undergoing arthroplasty prior to and after surgery and compare with normal, healthy controls.
Methods: 100 arthroplasty patients were included in this study. Blood samples were drawn at preoperative (preop) and postoperative (postop) day 1. Citrated plasma samples from 50 healthy individuals constituted the control group. Antigenic level of D-Dimer, PAI-1 and tPA were measured using a commercially available ELISA kit. Antiplasmin activity was measured by using functional method.
Results: Preop PAI-1, D-Dimer, tPA levels were significantly higher from healthy controls ($p<0.0001$) ($p<0.0001$), ($p<0.0001$); respectively. Preop antiplasmin levels were lower than controls ($p=0.045$). Postop levels of PAI-1 and D-Dimer were increased compared to preop values ($p= 0.023$), ($p<0.0001$); respectively. Postop antiplasmin values were lower than preop levels ($p=0.024$). Changes in tPA were not significant ($p=0.115$). There was no correlation between preop PAI-1 and D-Dimer levels. Pre and postop % changes of each individual were also calculated for PAI-1, D-Dimer, tPA and antiplasmin. There were significant correlation between D-Dimer and PAI-1 ($p=0.003$). Negative correlations between antiplasmin and D-Dimer ($p=0.0013$) and antiplasmin and PAI-1 ($p=0.023$). There was no correlation between tPA and PAI-1, D-Dimer and antiplasmin.
Conclusions: These results confirm the preexisting perturbation of the fibrinolytic system of patients undergoing arthroplasty. Surgical intervention may further enhance the observed changes. The alterations in the fibrinolytic system may lead to the observed hemostatic complications in these patients.

Genetics and genomics in thrombosis and Hemostasis

C0047
PREVALENCE OF PROTHROMBOGENIC GENES POLYMORPHISM OF HAEMOSTASIS SYSTEM IN THE NENETS AUTONOMOUS DISTRICT NENETS POPULATION

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Background: Far North indigenous population resistance to changing environment largely depends on its gene pool condition and genetic predisposition to diseases, including cardiovascular. The object of the study is a sample of Nenets from the Nenets Autonomous District.
Methods: The number of investigated samples was 191. The object was genomic DNA received from peripheral venous blood leukocytes. Genotyping was held with the use of polymerase chain reaction with allele-specific primers and electrophoretic detection in agarose gel.
Results: According to our data, the population of the indigenous ethnic group "genetically" healthier than those in the European sample in relation to cardiovascular diseases. Analysis of multigene carriage of prothrombogenic allelic variants of genes revealed that the Nenets are much less carry 3 of those polymorphisms at once (χ^2=5,54, P=0,018). Also unlike the ethnic Russian, in the Nenets sample there were no carriers of 4 prothrombogenic gene variants. Among the allelic variants of studied genes the so-called "wild-type" prevails in the indigenous ethnic group sample. In the current sample the carriage of alleles 1691A of F5 gene and 1565C of ITGB3 gene was significantly associated with the development of cardiovascular diseases: these alleles increase the pathology risk at 14 and 2 times respectively (P=0,046 and P=0.05 respectively). One of the genetic features of the Nenets sample was a significant percentage of PAI-1 gene 4G/4G variant carriage (32%). This polymorphism is associated with a more active synthesis of plasminogen activator inhibitor. Function of PAI-1 is a thrombolysis restriction at vascular injury location, which prevents the uncontrolled fibrinolytic system activation and bleeding.
Conclusions: In the harsh conditions of the Far North and the lifestyle associated with an increased risk of injury, bleeding stop is a vital factor. In this regard, this polymorphism had been so distributed in the population of the indigenous ethnic group, in contrast to the sample of ethnic Russian (P=0.026).

C0048
POLYMORPHISMS OF METHYLENETETRAHYDROFOLATE REDUCTASE GENE AS A HYPERHOMOCYSTEINEMIA RISK FACTOR IN NATIVE POPULATION OF NENETS AUTONOMOUS DISTRICT

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Background: In the metabolic processes study and many common diseases preventing a human ethnic origin should be taken into consideration. Cardiovascular diseases risk factors study and the development of early preventive measures are of particular topicality.
Aim: to investigate the prevalence of methylenetetrahydrofolate reductase gene polymorphisms MTHFR C677T and A1298C, the level of homocysteine in blood and lifestyle of the Nenets Autonomous District (NAD) population.
Methods: Inclusion criteria: Nenets ethnicity; constant residence in NAD; presence of informed consent. The study approved by the NSMU local ethics committee (protocol ?6, 8.06.2011). Questioning – data on diet, smoking, alcohol intake from survey respondents (n = 226). The homocysteine level in the blood serum (n = 90) was determined by solid-phase ELISA using reagents Axis Shield Diagnostics Ltd. Identification of polymorphisms MTHFR C677T (n = 121) and A1298C (n = 90) was performed in CSRL of NSMU. Genome DNA received from peripheral venous blood leukocytes was used in PCR molecular genetic analysis with allele-specific primers with detection by agarose gel electrophoresis.
Results: The age of the study sample Me = 42 [30;51] years. Among the modifiable risk factors of hyperhomocysteinemia smoking (25%) and alcohol intake (51%) were present. In smoking men 52% smoke more than one cigarette pack per day.By to the results they were divided into three groups according to thrombosis risk (Shmeleva V, 2008): < 10.5 nkM (normal amount), 10.5–13.5 mkM (thrombosis risk increased 1.3–3 times) and more than 13.5 mkM (thrombosis risk increased 3–5 times). The results were following: 8.07 [7.2;9.3] for the 1st group (n = 27), 11.5 [11.2;12.0] for the 2nd group (n = 22) and 17.2 [14.6;19.8] for the 3rd group (n = 40). Frequency of T677T polymorphism in Nenets population significantly less than in Russian population in Tomsk (v2 = 10.59, P = 0.001). A1298C polymorphism frequency significantly differ in compared populations (v2 = 6.17, P = 0.01). Assessment of interlinkages of homocysteine level in the blood serum with different allelic MTHFR gene variants carriage was performed using Kruskal-Wallace test (P = 0.05). Significant differences were revealed: 0.03 for MTHFR C677T and no significant differences: 0.531 for MTHFR A1298C.
Conclusions: We revealed a high percentage of hyperhomocysteinemia in Nenets population. It should be in connection with polymorphisms of MTHFR gene C677T and external modifiable factors.

C0102
SCREENING OF EPCR VARIANTS AND THEIR CORRELATION WITH FACTOR V LEIDEN AND PROTHROMBIN 20210A MUTATIONS IN TURKISH PEDIATRIC PATIENTS WITH ACUTE LEUKEMIA

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Background: Pediatric patients with acute leukemia are at high risk for thromboembolic events (TE). Recent studies showed that prevalence of thrombosis is between 2.4-11.5% in pediatric patients with acute leukemia. EPCR is a member of activated PC anticoagulant pathway. In the literature, 23bp insertion at position c6367 in exon3, c6333CT in intron2, c6936AG in exon4 and c4678GC substations in 3UTR were reported. The 23bp results in truncated translation of protein. Thus, it leads to reduction of PC activation and causes risk of TE. *EPCR* has common 4 haplotypes. A1 haplotype is associated with increased circulating levels of APC and reduced risk of VTE. We aimed to investigate the 23bp *EPCR* and A1in 3UTR in Turkish pediatric acute leukemia patients and to correlate with *FVL* and *PT*20210A mutations.
Methods: The study group consisted of 123 patients aged between 1-15 years who were admitted to Losante Hospital for Children with Leukemia with the diagnosis of acute leukemia. DNA was extracted from leukocytes with DNA isolation instrument (Roche). Determination of 23bp and A1 of *EPCR* were performed by using the PCR. Then PCR products were analyzed by gel electrophoresis. *DdeI* was used for the digestion process and sequencing of different band profiles was performed by sequencer (Beckman Coulter). Genotyping of *FV*1691GA, *PT*20210GA were screened with realtime PCR using fluorescence melting curve detection analysis by means of the Light Cycler (Roche).
Results: We detected 23bp in 3 (2.5%), A1 in 1 (0.8%) of 123 patients. *FVL* and *PT*20210A were also screened in study group. A1 positive patient had heterozygous *FVL* mutation. DNA sequencing analyze of this patient was shown in Table 1. 4 (3.25%) of the 123 patients had TE. Neither of these 4 patients had *EPCR* variants. However, 1 of these patients that experienced TE had homozygous and the other had heterozygous mutations in *FV*nt1691.

Table 1
Genotype distributions in patients for FV1691GA, PT20210GA and EPCR 23-bp insertion

FV 1691	n=123 (%)	PT 20210	n=123 (%)	EPCR23-bp insertion	n=123 (%)
G/G	110 (89.4)	G/G	119 (96.7)	wild type	120 (97.5)
G/A	10 (8.1)	G/A	4 (3.3)	w/ins	3 (2.5)
A/A	3 (2.5)	A/A	0	–	

Conclusions: We showed A1 variation at 0.8% in study group. Found variation in 3UTR of *EPCR* may disturb regulation and stabilization of mRNA. 23bp insertion was found at 2.5% in patients. Akar et al presented a study showing prevalence of 23bp was 0.8% in Turkish healthy. Our percentage was higher compare to healthy. Therefore we conclude that these variants may contribute to development of thrombosis in acute pediatric leukemia. To the best of our knowledge *EPCR* variants were not screened previously in patients. This study results seem to be the first screening results in the literature however needs further investigation associated with sEPCR levels.

C0106
THE ASSOCIATION OF THE PLASMINOGEN ACTIVATOR INHIBITOR-1 (PAI-1) 4G/5G POLYMORPHISM AND FACTOR V LEIDEN (FVL) MUTATION IN PEDIATRIC ACUTE LEUKEMIA PATIENTS

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Background: One of the important complication in pediatric ALL patients is thrombosis. The reported prevalence of thrombosis changes from 2.4 to 11.5%. Its occurrence may complicate the treatment course with a poor prognostic impact. Multiple hereditary factors may play predisposition of thrombosis. PAI1 is the major inhibitor of tissue type plasminogen activator. Increased plasma levels of PAI1 plays a crucial role in the pathogenesis of diseases associated with thrombosis. The *PAI1* located in 7q21.3-22 and contains 9 exons. The gene encoding PAI1 is highly polymorphic and an insertion 5G/deletion 4G polymorphism in the *PAI1* promoter may have functionally important in *PAI1* expression. The 4G homozygous allele had increased concentrations of PAI1 compared to ones with the 5G allele. Previous studies reported that in presence of both 4G homozygous allele and *FVL* may bring a risk for thrombosis. The aim of study was to determine genotype distribution and allele frequencies of *PAI1* polymorphisms and to correlate *FVL* in the Turkish pediatric acute leukemia patients and their association with thrombosis.
Methods: The study population consisted of 147 patients aged between 1-15 years who were admitted to Losante Hospital for Children with Leukemia with the diagnosis of acute leukemia. Healthy individuals were selected among healthy unrelated subjects from Turkey (n: 181) DNA was extracted from leukocytes with DNA isolation instrument (Roche, Germany). Genotyping of PAI1 4G/5G polymorphism and FV1691GA were screened with realtime PCR using fluorescence melting curve detection analysis by means of the Light Cycler System (Roche, Germany).
Results: Genotype distributions and allele frequencies of *PAI1* polymorphism in Turkish pediatric acute leukemia patients to compare with healthy were given in Table 1. No significant difference for *PAI1* genotypes frequency between pediatric leukemia patients and healthy individuals were found [(OR 1.5 (0.9-2.7), CI%95; p=0.07)]. The co-existence of PAI1 polymorphism and *FVL* were not found statistically significant in our study group (p>0.05). Table 2 summarizes the correlation of PAI1 polymorphism and *FVL*.

Table 1
The genotype distribution of polymorphism in pediatric ALL and healthy individuals

PAI	Patients n=147 (%)	Controls n=181 (%)	OR (95% CI)	P value
Genotype				
5G/5G	46 (30.8)	41 (22.7)		
4G/5G	64 (44.2)	94 (51.9)	1.5 (0.9–2.7)	0.07
4G/4G	37 (24.8)	46 (25.4)	1.3 (0.7–2.5)	0.2
Allele				
5G	0.46	0.48	1	
4G	0.53	0.51	1.08 (0.6–1.8)	0.7

Table 2
Correlation of PAI-1 polymorphism and FVL mutation

	Patients n=147 (%)	Controls n=181 (%)	OR (95% CI)	P value
$PAI\text{-}1^{+}/FVL^{-}$	135 (90)	167 (92)	1	
$PAI\text{-}1^{+}/FVL^{+}$	14 (10)	14 (8)	0.8 (0.3–1.7)	0.5

Conclusions: No statistically difference was observed in the frequency of *PAI1* 4G/5G polymorphism between the pediatric acute leukemia and healthy. To the best of our knowledge *PAI1* polymorphism was not screened previously in pediatric acute leukemia patients. In conclusion, our study

suggests that analyses of *PAI1* polymorphism in pediatric acute leukemia is not necessary.

C0118
THE GENETIC CHARACTERISTICS OF THE HEMOSTATIC SYSTEM IN ATHLETES AT ARKHANGELSK REGION

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Background: Under the action on the body of high physical activity clotting component of the hemostatic system is activated by moving it factors in the active state and start the coagulation cascade. In the following, simultaneously fibrinolysis and anticoagulation system is activated. Failure of one of the components of the hemostatic system leads to its imbalance and most commonly at risk of developing thrombophilic states. Internal factors of disorders include the presence of certain genetic polymorphisms. In sports genetics there are alleles, limiting the possibility of sports, they include protein genes of hemostatic system.
Methods: The study involved 82 athletes, of which 67% of boys and 33% girls. Athletes have the sports category of the 1st and higher, kind of sports represented are boxing, skiing, hockey, gymnastics, powerlifting, athletics, etc. Material is EDTA venous blood. The method used to detect polymorphism - polymerase chain reaction with detection on agarose gel.
Results: Polymorphisms were identified in six genes: the gene of factor V (Leiden mutation), the gene of methylenetetrahydrofolate reductase, gene of prothrombin, gene of plasminogen activator inhibitor, gene of fibrinogen, gene of platelet fibrinogen receptor GpIIIa.
3.6% of the athletes (CI: 0.6 - 8.5%) have the polymorphism Leiden mutation, that corresponds the frequency in Europe and the US (3-7%).
The incidence of the gene of methylenetetrahydrofolate reductase (polymorphism 677 C> T) among European race of 35-55%. 45.2% of the athletes (CI: 34.1 - 56.5%) found this kind of polymorphism.
At the frequency of occurrence gene of prothrombin (polymorphism G20210-A) in the population of 1-4%, the surveyed athletes this polymorphism was not detected. 77.4% of the athletes (CI: 67.9 - 85.7%) have gene of plasminogen activator inhibitor (polymorphism 675 5G> 4G). The European population incidence of 53-61%. Polymorphism -455 G-> A gene of fibrinogen is found in 40.5% of athletes. Compared with the incidence of the European polymorphism 20%, athletes frequency twice as high.
In athletes frequency of gene of platelet fibrinogen receptor GpIIIa (polymorphism 1565 T> C was 25% (CI: 16.3 - 34.8%); the European population rate - 13%.
Conclusions: There has been a significant increase in the incidence of unfavorable alleles proteins of the fibrinolytic system, leading to its suppression. Also a high frequency of alleles responsible for the increase in the concentration of fibrinogen in the blood was identified.

C0169
ASSOCIATION OF MDR1 C3435T AND G2677T/A POLYMORPHISMS WITH PLASMA PLATELET ACTIVATING FACTOR LEVELS AND ADP-INDUCED PLATELET FUNCTIONS IN CORONARY ARTERY DISEASE PATIENTS

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Background: Coronary artery disease (CAD) is a complex disease resulting from potential multiple genetic and environmental factors. Platelets have significant functions in thrombosis, hemostasis and cardiovascular disease. Platelet activating factor (PAF) correlates with transmembrane transporter multidrug resistant 1 P-glycoprotein (MDR1 P-gp) expression and activity. MDR1 polymorphisms can affect the expression and activity of P-gp and plasma PAF levels. Our aim is to identify the association of MDR1 gene polymorphisms with plasma PAF levels and ADP induced platelet functions and the risk of CAD.
Methods: The study population consisted of 198 patients angiographically documented CAD, including 113 cases with at least 1 coronary artery with ≥50% luminal diameter stenosis and 85 control subjects with strictly normal coronary angiograms. Genotypes of the MDR1 C3435T and G2677T/A polymorphisms were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Plasma PAF levels were detected by enzyme-linked immunosorbent assay (ELISA). Platelet aggregation functions were also analyzed by ADP stimulation light transmission aggregometry of blood samples.
Results: The plasma levels of PAF were significantly higher in CAD patients than in controls (P<0.001). There was no significant differences among plasma PAF levels in regard to MDR1 C3435T and G2677T polymorphisms in CAD patients and controls (Table 1). Furthermore, analysis of MDR1 haplotypes did not show any associations with increased plasma PAF levels and the risk of CAD (Table 2). There was no significant differences among platelet aggregation functions to MDR1 C3435 and G2677T polymorphisms.
Conclusions: Our results suggest that plasma PAF levels are not associated with MDR1 gene polymorphisms. These results may be biased by the relatively small number of subjects, therefore need to be validated by larger studies.

C0182
FIRST OBSERVATION OF TUBB1 GENE MUTATIONS IN TURKISH PATIENTS WITH MACROTHROMBOCYTOPENIA

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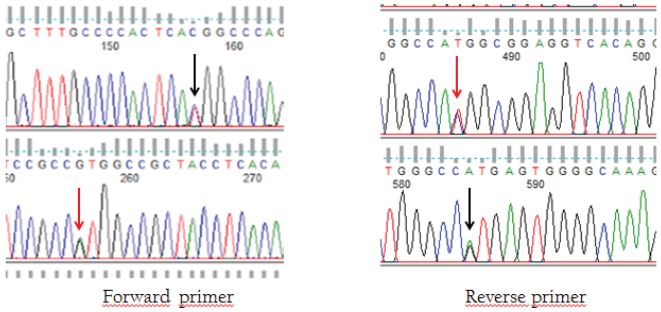
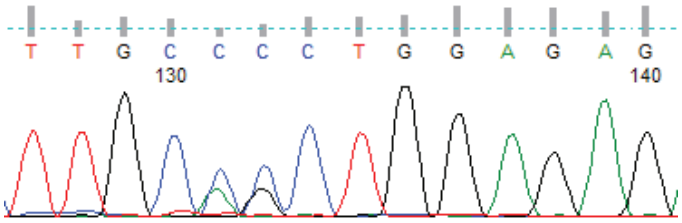
Background: Macrothrombocytopenia (giant platelet syndrome) is an autosomal dominant disorder associated with Myosin Heavy Chain 9 *(MYH9)* mutations. 17 out of 52 mutations that are defined in MYH9 gene between 2004 and 2014 (Human Gene Mutation Database) are defined in patients with macrothrombocytopenia. The membrane skeleton and the link between actin filaments of skeleton and microtubules are important for the normal platelet morphology and the defects on these systems results in macrothrombocytopenia. There are 2 known mutations of *TUBB1* gene defined in macrothrombocytopenia which are potentially responsible for the improper megakaryocytes- microtubule organization and platelet morphology in the disease. Here, for the first time we analyzed the *TUBB1* mutation frequency in Turkish macrothrombocytopenia patients using exon sequencing.



Methods: A written informed consent for genetic analysis was obtained from the patients. The patient blood was collected from various hematology clinics in Turkey. In this study, *TUBB1* gene mutation analysis was performed by using the blood of patients diagnosed with macrothrombocytopenia following the DNA isolation. Then samples were sequenced using a DNA sequencer (Beckman Coulter, USA) and the data were analyzed using the FinchTV program.

Results: *TUBB1* gene analysis of Turkish patients with macrothrombocytopenia revealed a novel heterozygous Cytosine to Timin nucleotide change at 821 at exon4 (p.T274M/ Threonin to Methionine), at a child and his father in the same family, 99 nucleotide ahead which is at nucleotid 920, there is a novel heterozygous Guanine to Adenin nucleotide change, this situation caused to change of Arginine amino acid to Histidine amino acid at 307 position (p.R307H) in protein. We also identified a double base pair substitution at nucleotide positions 130-131 at exon 2, this transition encodes the Q43P (p.Gly43Pro, p.Gly43His) mutant form of the protein.



Conclusions: In this study, we identified the first *TUBB1* mutation; combined 821C>T and 920 G>A mutations in a family and these mutations are not defined previously in Human Gene Mutation Database (HGMD). And Q43P single nucleotide polymorphism is defined firstly at Turkish population, so they are very important findings in terms of explaining the relationship of macrothrombocytopenia and TUBB1 gene.
Funding: This research is financially supported by Starting R&D Projects Funding Program (3001) of The Scientific and Technological Research Council of Turkey (TUBITAK)

C0194
ASSOCIATION OF CANDIDATE GENES POLYMORPHISM WITH PLATELET FUNCTION AND CARDIOVASCULAR EVENTS ZAPROVALNA O. SI "L.T.MALAYA THERAPY INSTITUTE NAMSU", KHARKIV, UKRAINE

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Background: Several clinical and genetic variables can be associated with aspirin resistance (AR). The aim of the study was to propose a path model explaining an impact among variables influencing AR candidate genes polymorphism (Cyclooxygenase-1 (COG-1), PlA1/A2 polymorphism of glycoprotein IIIa) and its association with platelet function and ischemic events in patients with ischemic heart disease (IHD).
Methods: In this prospective study polymorphisms COG-1 (C50T in the PTGS1 (rs3842787)) and PlA1/A2 (T1565C in the ITGB3 (rs5918)) alleles and platelet function (urine level 11-dehydro-thromboxane B2; ADP- and arachidonic acid-induced light transmittance aggregometry) were assessed in 173 patients IHD on chronic aspirin therapy (75 mg/day). The control group included 28 healthy individuals. The rates of major adverse cardiac events (MACE) were recorded during a 36-month.
Results: There were no statistically significant difference of C/T allelesCOG-1 frequency between studied and control groups (p> 0.05) was found. The total index of arachidonic acid-induced platelet aggregation in T-allele patients was not only significantly higher than that of the C-allele patients (p= 0.001). There were no statistically significant difference in ADP-induced aggregation and the urine 11-dehydro-thromboxane B2 level between patients with CC and (CT+TT) genotypes.
The difference T/C allelesPlA1/A2 frequency between studied and control groups (p> 0.05) was no statistical. There were also no statistically significant differences in arachidonic acid-induced, ADP-induced platelet aggregation and the urine 11-dehydro-thromboxane B2 level between patients with CC and (CT+TT) genotypes. In 20 patients during the observation period have taken place MACE. The probability of MACE developing for mutant T-allele COG-1 polymorphism patients was significantly higher (Odds ratio=3.39; 95% CI [1.39-8.77], p= 0.019), than for C-allele patients.
The probability of MACE developing for mutant C-allele PlA1/A2 polymorphism patients was significantly higher (Odds ratio= 2.42; 95% CI [1.18-5.12], p= 0.03), than for T-allele patients.
Conclusions: The risk of MACE in patients with IHD associates with mutant alleles in the PTGS1 and ITGB3genes.

C0205
RELATIONSHIP BETWEEN ACROMEGALY AND GROWTH ARREST-SPECIFIC GENE 6

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Background: The mortality rate of patients with acromegaly appears to be increased and is primarily from cardiovascular disease. The evidence suggests that it is largely the hypertension and diabetes associated with acromegaly that predisposes patients to the development of atherosclerotic disease. Molecular mechanism is unknown. GAS6 protein, a new member of vitamin K dependent proteins, has been indicated in a relation with obesity, insulin sensitivity, inflammation and endothelial dysfunction. A *GAS6* polymorphism (c.834+7AA genotype) was identified as a common SNP in the general population and gave the strongest association with stroke. Others found similar association with acute coronary syndrome, and type 2 diabetes. We can predict a relationship between acromegaly and GAS6 thereby considering the relationship between diabetes, cardiovascular disease and serum GAS6 levels. The hypothesis of this study is that GAS6 polymorphism (c.834+7AA genotype) may exist in correlation with acromegaly and its complications.
Methods: In order to prove this hypothesis, *GAS6* gene Hha-1 c.834+7G>A polymorphism and serum GAS6 concentrations were analyzed together noting parameters for insulin resistance, GH, IGF-1 and duration of illness. An acromegaly group (n=35) was formed from patients in the care of Marmara University School of Medicine Department of Endocrinology and a control group formed from 39 healthy volunteers. *GAS6* gene c.834+7G>A polymorphisms were detected by PCR-RLFP method. Serum GAS6 concentrations were determined by the ELISA method (CUSABIO Human GAS6 ELISA Kit).
Results: *GAS6* c.834+7G>A polymorphism was compared in acromegaly and control groups. There was no significant difference (p>0.05). In the control group AA, AG and GG genotypes were detected at 42%, 48% and 10%, respectively, whereas in the acromegaly group at 45.8%, 43.7%, and 10%. Serum GAS6 protein concentration was 7.38±2.30 ng/ml in the acromegaly group whilst 8.59±0.20 ng/ml in the control group. Statistically, serum GAS6 levels were lower in the patient group than the control group (p<0.05).
Conclusions: The results of this study, for the first time, demonstrated that serum GAS6 protein levels were lower in the acromegaly group despite the fact that *GAS6* gene c.834+7G>A polymorphism were the same across all groups. These results need to be confirmed through further comprehensive studies.

C0220
THE INFLUENCE OF CYP2C9 AND VKORC1 GENE POLYMORPHISMS ON THE RESPONSE TO WARFARIN IN EGYPTIANS

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Background: Warfarin is the most commonly used drug for chronic prevention of thromboembolic events, it also ranks high among drugs that cause serious adverse events. The variability in dose requirements has been attributed to inter-individual differences in medical, personal, and genetic factor. Cytochrome P-450 2C9 is the principle enzyme that terminates the anticoagulant effect of warfarin by catalyzing the conversion of the pharmacologically more potent S-enantiomer to its inactive metabolites.

Warfarin exerts its effect by inhibition of vitamin K epoxide reductase. This protein is encoded by vitamin K epoxide reductase complex subunit 1 gene (*VKORC1*). The current study aimed to investigate the pharmacogenetic effect of CYP2C9 and VKORC1 gene polymorphisms on the patients response to warfarin.

Methods: One hundred cases starting warfarin treatment and 20 healthy controls were enrolled. The mean daily dose of warfarin was calculated from patient's medical records. For each patient, less than 10% variability in warfarin dose and a target international normalized ratio (INR) within the therapeutic target range were required for at least 3 months for one of the following indications (Deep vein thrombosis, Pulmonary embolism, cerebrovascular stroke and Myocardial infarction) prior to inclusion in the study. Tetraprimer amplification refractory mutation system (T-ARMS) PCR was performed to determine *CYP2C9**2, *CYP2C9* *3, and the *VKORC1* 1639G > A genetic polymorphisms. Plasma warfarin determination was performed using rapid flouremetric assay.

Results: Plasma warfarin concentration ranged from 2.19 - 10.98 μg/ml with a median 3.52 μg/ml. Supratherpeutic INR was observed in 11% of the cases. Thromboembolic complications occurred in 7% of the cases and 8% of cases experienced major bleeding. High maintenance dose (>7 mg/day) was associated with the combined non VKORC1*2 and homozygous wild type CYP2C9 (CYP2C9*1*1) alleles, while low maintenance dose was associated with the Variant (AG + AA)/ Wild (*1/*1). (p value <0.001). CYP2C9 variant was a risk factor for supratherapeutic INR in the multivariate logistic regression model. Thromboembolic complications and incidence of supratherapeutic INR were observed in patients carrying combined VKORC1 Variant (AG + AA) and CYP2C9 Variant (*2/*3).

Conclusions: Together with the clinical factors, VKORC1 and CYP2C9 polymorphisms are important contributors to warfarin dosing and may help predict adverse effects in Egyptian patients.

C0265
MTHFR C677T POLYMORPHISM AND THROMBOTIC COMPLICATIONS IN SICKLE CELL DISEASE PATIENTS

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Background: Sickle Cell Disease (SCD) is a hemoglobinopathy characterized by hemolysis and acute vasoocclusion. Hypercoagulable state, increased risk of venous thromboembolism (VTE) and ischemic stroke are also noted. Methylene Tetrahydrofolate Reductase (MTHFR) gene polymorphism C677T leads to a thermolabile form of this enzyme with decreased activity, associated with hyperhomocysteinemia, a risk factor for cardiovascular diseases and VTE, especially under folate depletion. Aim is to compare MTHFR C677T genotype frequencies of Greek SCD patients with and/or without VTE /ischemic stroke and healthy controls.

Methods: In 74 Greek SCD patients (10 homozygous S/S, 19 beta0/S, 40 beta+/S heterozygous for beta thalassemia and sickle cell anemia, 5 other beta gene mutations/S) receiving folate supplementation and 41 controls peripheral blood was collected and genomic DNA was isolated. MTHFR genotype was assessed with PCR-RFLPs. Genotype frequencies were compared with Pearson X^2 and Fischer Exact test, whether applicable.

Results: See Table 1.

Table 1.

MTHFR C677T genotype	CC	CT+TT
SCD patients (n=74)	25 (33.8%)	49 (66.2%)
SCD patients with VTE (n=8)	1 (12.5%)	7 (87.5%)
SCD patients without VTE (n=66)	24 (36.4%)	42 (63.6%)
SCD patients with ischemic stroke (n=3)	0 (0%)	3 (100%)
SCD patients without ischemic stroke (n=71)	25 (35.2%)	46 (64.8%)
Healthy (n=41)	21 (51.2%)	20 (48.8%)

Of the 8 patients with VTE, 4 were beta+/S, 3 beta0/S, 1S/S. With regard to MTHFR C677T polymorphism, 1 was TT, 1 CC and 6 CT. MTHFR C677T CT and TT genotypes were more common in SCD patients (P=0.06) than in controls. In the dominant model, there was statistically significant difference between SCD patients with VTE and healthy controls (P=0.048), but not between SCD patients with and without VTE (P=0.172). Of the 3 patients with ischemic stroke, 2 were beta+/S and 1 S/S. With regard to MTHFR C677T, 2 were CT and 1 TT.

Conclusions: Increased prevalence of MTHFR 677CT and TT genotypes among SCD patients may partly contribute to the hypercoagulability and may constitute a risk factor for VTE and ischemic stroke, but larger studies are needed to confirm the above findings. 677CT heterozygosity seems to confer at least as much risk as homozygosity for thrombotic complications, even under folate sufficiency.

C0351
CUTANEOUS NECROSIS REVEALING PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA. A NEW CASE

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Background: Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal disorder of hematopoietic cells characterized by intravascular hemolytic anemia, hypercoagulable state and bone marrow aplasia. Venous thrombosis generally arise in hepatic, intra-abdominal, cerebral, and extremity veins and represent the most common cause of death in patients with PNH. Despite being recognized as a complication, cutaneous thrombosis is uncommon and a variety of findings have been reported, including bullae, petechiae, leg ulcers, and purpura.

Methods: We report an exceptional case of cutaneous necrosis of the earlobe and the scalp revealing PNH.

Results: We report the case of a 37-year-old male patient with minor-thalassemia diagnosed at the age of 5. He presented with necrotic lesions mainly located in the neck, the scalp and the left earlobe. Laboratory analysis revealed bicytopenia (hemoglobin 9 g/dl; platelet count 33 g/L), with biological inflammation (CRP of 195 mg/l) and hemolysis with a negative coombs test negative and hematuria with no other serological, immunological or coagulation alteration. Skin biopsy revealed superficial and deep dermal vessels with foci of necrosis; without vasculitis. The presence of microvascular occlusion in cutaneous histology, associated with the presence of hemolytic anemia, with thrombopenia, suggest the PHN diagnosis. Flow cytometry of peripheral blood leucocytes and mononuclear cells confirmed the presence of a PHN clone with 90-95% of positive cells. Anticoagulant therapy was started with enoxaparin 1 mg/kg twice a day associated with corticosteroids (prednisone 1 mg/kg/day). After 1 week there were only residual hyper pigmented macules

Conclusions: PNH is a clonal stem cell disorder resulting from a mutation in the PIG-A (phosphatidylinositol glycan class A) gene that block glycosyl-phosphatidylinositol (GPI) anchor biosynthesis. This case is reported because of the rarity of this complication and the importance of its correct and timely diagnosis. The risk of thrombosis appears to be significantly related to the size of the abnormal PNH clone. Both corticosteroid therapy and anticoagulants may be useful in the treatment of thrombotic episodes. The role of eculizumab (a monoclonal antibody inhibits the terminal stage of the complement cascade) in the treatment of acute thrombosis is under consideration.

C0352
MOLECULAR GENETIC PREDICTORS OF ASPIRIN RESISTANCE IN RECURRENT MYOCARDIAL ISCHEMIA

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Background: Gene mutations ITGB3, GP1BA, NOS3, P2RY12 associated with disturbances in the hemostatic system and the presence of both homozygous and heterozygous defines increased risk of arterial thrombosis.
Methods: We studied 196 patients with CHD with aspirin resistance to Kazakh nationalities (165 - men, 31 - women, average age 58.1 ± 2.1 years), including after revascularization - 118 patients. The control group comprised 196 healthy subjects, matched by sex and age with the group of the study. Availability of aspirin resistance was evaluated by the test of platelet aggregation in vitro. Genetic studies were identified the polymorphisms: Leu33Pro gene ITGB3, Thr145Met gene GP1BA, C786T gene NOS3, mutations in the platelet ADP receptor (P2RY12, H1/H2) and used commercial test systems companies Liteh, Moscow (Russia).
Results: In analysis the significance of the presence mutant allele Leu33Pro revealed 41.3% (40.3% - heterozygotes, 1% - mutant homozygotes) in healthy individuals and 47% in patients with ischemic heart disease (33.7% heterozygotes and mutant homozygotes 13.3%). The differences between the groups in the application of statistical criteria were significant ($\chi 2$ = 22.289; p <0.005).
In the analysis of the mutant alleles identified Thr145Met 39.8% (37.8% heterozygotes and mutant homozygotes 2.0%) in healthy individuals and 54.1% in patients with ischemic heart disease (39.8% heterozygotes and mutant homozygotes 14.3%). Differences between groups Pearson were statistically significant ($\chi 2$= 21.874; p <0.001).
In the analysis of C786T revealed 75.3% (51.5% and 13.8% heterozygous homozygous mutation) in healthy patient and 78.6% in patients with ischemic heart disease (38.8% heterozygotes and mutant homozygotes 39.8%). Differences between groups were significant ($\chi 2$= 34.448; p <0.001).
In the presence of mutant alleles H1/H2 differences between groups of patients (63.3%) and healthy individuals (53.5%) were highly significant ($\chi 2$= 33.45, p <0.001).
Conclusions: The identified high levels of statistical significance of gene mutations ITGB3, GPIB/IIIA, NOS3, especially gene mutation P2RY126 in patients of Kazakh nationality, indicates predominant clinical significance of the mutant gene in the homozygous state, and is associated with progressive coronary heart disease, the development of recurrent ischemia after myocardial revascularization.

C0357
THE EFFECT OF TMRPSS6 (RS2235324, RS855791, RS2111833) POLYMORPHISMS ON RED BLOOD CELL LEVELS IN IRON DEFICIENCY ANAEMIA

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Background: Transmembrane Protease, Serine 6 (TMPRSS6) has an important role in iron homeostasis and its mutations have been recently associated with iron-refractory iron deficiency anaemia (IRIDA). Several variants of TMPRSS6 have been already identified; however it was investigated the association between these variants and hematological parameters. In our study we investigated TMPRSS6 polymorphism on 144 patients with iron deficiency anaemia and compared hematological parameters. Serum iron, iron binding capacity, transferrin saturation, haemoglobin, Hct, ferritin, MCV, RBC, MCH and MCHC levels of patients were saved.
Methods: Genomic DNA was isolated from whole blood. TMPRSS6 (rs2235324, rs855791, rs2111833) polymorphisms were detected by Lightcycler (Roche Diagnostics, Mannheim, Germany) hybridization probe and specific primer pairs.
Results: We showed that there is a significant association between these polymorphisms and red blood cell levels (p=0.036, p=0.037, p=0.036, respectively).
Conclusions: The present study is the first study about TMPRSS6 (rs2235324, rs855791, rs2111833) SNPs in patients with iron-deficiency anaemia in Turkish population. Our study will go on with more patients and adding control groups.

Hemostasis and inflammation

C0094
EVALUATION OF CERTAIN HAEMOSTASIS AND ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

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Background: To establish the markers of haemostasis in patients with community-acquired pneumonia and estimate in dynamic.
Methods: Non-randomized, clinical- laboratory, prospective study. We studied hemostasis (D-dimers, soluble fibrin-monomer complex, time fibrin self-assemblance, antitrombin III, fibrinogen), endothelial dysfunction (F. Willebrand, endothelin-1 and activity of plasminogen activators inhibitor type 1) and C-reactive protein in 61 patients with community acquired pneumonia in the day of admission and before discharge from hospital. Exclusion criteria: malignancy, chronic kidney disease, refusal to participate in the study. 17 patients had a severe pneumonia, 6 people died.
Results: The levels of all markers (except antitrombin-III) were increased on admission (D-dimers (median = 1.76 (quartiles = 0.84;3.2), time fibrin self-assemblance (median = 0.68 (quartiles = 0.5;0.8)), endothelin-1 (median = 0.44 (quartiles = 0.29;0.77)), vWF (median = 199 (quartiles = 127;271)), PAI-1 (median = 14.1 (quartiles = 7.8;33.2)) and were reduced before discharge, but within the normal range to include only F.Willebrand, C-reactive protein and time fibrin self-assemblance. D-dimers, C-reactive protein and plasminogen activators inhibitor type 1 were dependent on the severity of the pneumonia, severity of SIRS and extent of the inflammatory process. The risk of severe pneumonia increased with the level of D-dimers in the onset of the disease more than 2.0 mkg/mL (OR = 21.8, 95% CI: 3.09-154.8), with the results of time fibrin self-assemblance less than 0.5 (RR = 2.68, 95% CI: 1.23-5.84), with C reactive protein greater than 200 mg/l (OR = 4.6, 95% CI: 1.87-11.45) and PAI-1 activity more than 30 U/l (OR = 2.05, 95% CI: 0.88-4.74). Rg-CAP outcomes best reflect the level of D-dimers, measured prior to discharge patients. When the level of D-dimer greater than 1 mkg/ml increases the risk of delayed resolution of pneumonia (OR 1.8, 95% CI: 1.08-2.99, p=0.018).

C0116
ENDOTHELIAL DYSFUNCTION IN TRANSCAROTID FLIGHTS IN THE ARCTIC

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Background: The creation of a system of monitoring, forecasting of population health prakticheskogo region of the Arctic based on the comprehensive assessment of the status of endoecology of a person in transcarotid flights. To determine the features of formation and endothelial dysfunction in conditions transhiatal flight in the Arctic
Methods: Study participants healthy adults aged 18 to 46 years in the marine Arctic expedition. The study was performed in July 2015. Investigated the levels of homocysteine, CRP, PAI-1, von Willebrand factor, as well as

a non-invasive method for evaluation of the endothelium to the sea, and in the highest point of the Arctic voyage expedition. Used method for the assessment of vasoreactive on the device EndoPAT-2000.
Results: The data obtained indicate the development and progression of endothelial dysfunction in conditions of the Arctic voyage. The growth of the activity level of PAI-1, CRP and von Willebrand factor. Biochemical markers of endothelial dysfunction correlated with the index of RHI (1.42 ±0.02).
Conclusions: Our study showed the formation of endothelial dysfunction in conditions of the Arctic. Further research on this issue.

C0121
STUDY OF THE EFFECT OF COMBINED ORAL CONTRACEPTIVE (DUOFEM) ON FIBRINOGEN ANT INTERLEUKIN-6 IN FEMALE WISTAR RATS

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Background: It is estimated that 38% of all women worldwide between the ages of 15 – 40 years use combined oral contraceptives, which now differ significantly in formula and concentrations from previous ones. Duofem, a third generation combined oral contraceptive contains desogestrol. The formation is anticipated to give lower risks of thromboembolism, myocardial infarction, stroke and autoimmune diseases. This research priority included efforts to discover the effect of combined oral contraceptive (DUOFEM) on fibrinogen and interleukin-6 in female wistar rats.
Methods: Forty (40) female wistar rats weighing 180-250 g were used for the study. They were divided into four groups of 10 rats each comprising 5 treated and 5 control rats. The treated rats received 0.6mg/kg body weight of COC intragastrically for 36, 48, 60 and 72 days. All groups were given fresh water at ad libitum daily for the period of the experiment. Interleukin-6 was determined using rat ELISA kit (Karmiya Biomedical Company, USA). Fibrinogen was estimated by Clauss Assay (Clauss, 1957).
Results: DUOFEM reduced the serum levels of both fibrinogen and interleukin-6 in all the treated groups compared to controls (P<0.05). Lowest serum levels of fibrinogen and interleukin-6 was observed in group D (72 days).
Conclusions: By lowering IL-6 and fibrinogen, estrogen can negatively suppressed the body's immune response, triggering a predisposition to autoimmune and cardiovascular diseases.

C0180
SELF-TESTING AND SELF-MANAGEMENT OF ORAL ANTICOAGULATION THERAPY (OAT) IN CHILDREN WITH CONGENITAL HEART DISEASE (CHD). FROM THE BEDSIDE TO HOME. A PILOT STUDY IN SPAIN

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Background: OAT self-control has shown an improvement in the time in therapeutic range *(TRT)* with a significant reduction in thromboembolic and bleeding events. Children and adolescents on OAT, present also other special challenges in terms of rapid fluctuations in International Normalised Ratio (INR) values and interruption in daily life due to frequent hospital visits. Limited data are available on the safety and efficacy of this modality of anticoagulation control in children with CHD.
Methods: During 2015, a pilot study on coumarin self-control was initiated. This single centre prospective clinical study was designed to evaluate the safety, efficacy and quality of life of a home OAT monitoring with a CoaguChek XProÒ system in paediatric population with CHD, mostly mechanic heart valves (*MHV*). The programme development was structured in three parts: cardiology department doctors and nurses education, families and children´s training and patients clinical follow up. The education program for parents and adolescents consists on general OAT theoretical information and practical sessions on point of care device management, dosage algorithms and problem solving guidance. The patient´s follow up was made by hospital visits (month 1-3-6 and 12) or by phone if necessary. New technology support (*e-mail and WhatsApp*) was used for brief doubts resolution and the all families has access to a web-application (TAO-NetÒ) to introduce the INR results. The self-control programme was offered and started in ambulatory patients already on OAT or in hospital post-surgical children.
Results: Out of the 20 patients screened, 15 were eligible and accepted to enroll in the study, 47.7% were girls and 53.3% boys. The median age was 8 years (range: 8 months-17 y). 13 patients were anticoagulated for: 8 mitral and 4 aortic *MHV*, 2 for other *CHD* and 1 child for recurrent venous thromboembolism. Cases were vitamin K antagonist naïve. At six months of follow up, adherence was good, TRT is superior to 70%. There were not thrombotic or major haemorrhagic events, and all the families and children were satisfied with the improvement of quality of life.
Conclusions: The primary results of this study suggest that self-control of OAT shows a net benefit clinical outcome as first option of coumarin-management. Also the reduction of outpatient visits showed a high level of parents and children´s satisfaction and an improvement in their quality of life.

C0223
DIFFERENCES IN LEVELS OF MARKERS OF INFLAMMATION AND ENDOTHELIAL DAMAGE BETWEEN THE BLOOD FROM VARICOSE VEINS AND SYSTEMIC BLOOD

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Background: Varicose veins represent one of the most frequent vascular diseases and are in most cases benign. However, advanced disease is frequently associated with complications such as chronic venous insufficiency and thrombosis of the superficial veins. The pathogenic mechanisms are not well understood. Beside increased venous pressure probably local blood constituently triggers various mechanisms responsible for the progression of the disease and its complications.
The aim: Our study was to investigate changes of blood constituents in varicose veins and compare them to the systemic markers of inflammation and endothelial damage.
Methods: The study included 40 patients with primary varicose veins. Local blood samples were taken from the leg, obtained from the tortuous and dilated varicose great saphenous vein and systemic from the cubital vein.
Results: The values of basic biochemical findings were comparable between blood samples (varicose vs. systemic). In varicose veins, the following markers of inflammation and endothelial damage were significantly increased in comparison to systemic blood:) hsCRP (2.05 ± 1.84 mg/L vs. 1.96 ± 1.90 mg/L, p =0.05), IL-6 (3.62 ± 2.74 ng/L vs. 2.30 ± 1.80 ng/L, p <0.001), IL-8 (21.15 ±15.28 ng/l vs. 18.74±12.30 ng/L, p=0.025), vWF (118.4±27 % vs. 83.2±22 %, p<0.05), NGAL (316.93±88.68 mg/mL vs. 299.18 ± 107.33 ng/mL, p=0.002), TNFR1 (0.52±0.13ng/mL vs. 0.50 ± 0.15 ng/mL, p=0.021. The levels of D-dimer (247.56 ± 410.24 ng/mL vs. 67.66 ± 325.74 ng/mL, p =0.019) and PAI-1 (3.32±3.56 IU/ml vs 2.99 ± 3.36 IU/ml, p=0.043) were also significantly higher in blood samples taken from the leg varicose veins.
Most of the levels of inflammatory and endothelial dysfunction markers (hsCRP, D-dimer, TNFR-1) were significantly correlated with their levels in the systemic blood.
Conclusions: In the blood of varicose veins, some inflammatory markers and indicators of endothelial dysfunction are increased. This is most probably the consequence of deteriorated blood flow in dilated and tortuous superficial veins and increased venous pressure. Damage to the venous wall, which causes a chronic inflammatory response, together with

the procoagulant properties of local blood may promote further progression of the disease and thrombotic complications.

C0292
SUPERFICIAL VENOUS THROMBOSIS: A SERIOUS CONDITION

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Background: The severity of superficial venous thrombosis (SVT) was underestimated for a long time. Usually considered to be benign their management was mainly based on compression stocking and anti-inflammatory drugs. There is currently significant reconsideration for the SVT because it's an integral part of the thromboembolism. The fact that SVT is associated with deep venous thrombosis and pulmonary embolism is being more and more reported in recent studies, besides the etiologies and risk factors are almost the same. The aim of our study is to describe the epidemiologic, clinical, etiologic and the out coming profile of patients presenting a SVT in our internal medicine department.
Methods: A retrospective study including files of patients hospitalized between January 2003 and January 2015 and presenting a SVT confirmed by imaging.
Results: Among 136 patients hospitalized for venous thromboembolism, 18 (13.23%) patients presented a SVT. The mean age at diagnosis was 50 years old with extremities ranging from 24 to 78 years. There was 14 male and 4 female with a sex ratio M/F of 3.5. The SVT was located in the lower limb in 10 cases and in the upper limb in 8 cases. Nine patients had associated thromboembolic risk factors (tobacco n=5, obesity n=2, trauma n=2). Varicose veins were found in 6 patients. All patients were asymptomatic. A venous cord was felt on palpation in 4 cases. The SVT revealed a breast cancer in one case, one patient had both protein S deficiency and resistance to activated protein C, one patient had hyperhomocysteinemia and in one case the SVT was associated with a deep venous thrombosis. Fifteen among our patients (83.3%) received curatives doses of heparin which was latterly switched to Anti vitamin K for a mean duration of 4 weeks. Only one case of symptomatic over dose accident of anti vitamin K was observed. The outcome was favorable in 14 cases (77.7%). Four patients presented a recurrence in the same location.
Conclusions: Even the better recognition of the interest accorded to SVT, the management remains unclear and differs from a medical team to another.

C0334
PROMPT DIAGNOSE AND TREATMENT OF ACQUIRED HEMOPHILIA A: A CASE REPORT

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Background: Acquired Hemophilia (AH) is a rare bleeding disorder with a clinical picture that ranges from mild ecchymosis and anemia to life-threatening bleeding in individuals with no previous history of bleeding diathesis. The primary objective is the control of bleeding manifestations on acute bleeding episodes and the ultimate therapeutic goal is to eliminate the inhibitor and recognize any underlying condition associated to AH, namely medication, cancer or autoimmune diseases.
Methods: We present a case of AH, which had prompt diagnosis and treatment. A 76 years old Caucasian male, presented to the Emergency Room with an acute and spontaneous purpura scattered all over his upper and lower left limbs. The patient was pale and with bimalleolar edema. He was under analgesic and anti-inflammatory drugs, due to myalgia with 1 month of evolution, without symptoms relief. His medical history included arterial hypertension, diabetes mellitus type 2, dyslipidemia, chronic obstructive pulmonary disease, obesity and depression. He had no personal or family history of bleeding, and had not started new medications. Laboratory test results: hemoglobin (Hb) 7.2 g/dl, platelet count (plt) $378x10^9$/L, prolonged activated partial thromboplastin time (aPTT) 122.5 sec (N 24-36). Prolonged aPTT was evaluated: normal levels of von Willebrand Factor, Factor VIII (FVIII) <1 U/mL, FVIII inhibitors: 12 Bethesda Units and mild-positive lupus anticoagulant. The patient was diagnosed with AH, transfused with 1 unit of packed red blood cells and started oral prednisolone 1mg/Kg/day. Immunological studies and cancer screening (thoracic and abdominal CAT-scan) were negative.
Results: After 2 weeks of corticotherapy, a maximum level of F.VIII:1.9 U/mL was reached, with a gradual normalization of aPTT and decline of FVIII inhibitors. As clinical condition improved, with resolution of anemia, without any hemostatic therapy intervention (no bleeding episodes), he was discharged 3 weeks after admittance on oral prednisolone with a discontinuation scheme.
Until this date, the patient remains without signs of AH relapse and maintains progressive improvement of Hb levels (12.1 g/dL) and a high FVIII level (190 U/mL) to keep on surveillance, as rebound thrombotic events are reported in literature.
Conclusions: A high degree of suspicion is necessary to identify this life-threatening disorder and expertise and clinical experience in this field for an early diagnosis and management.

C0344
THROMBOSIS IN PAROXYSMAL NOCTURNAL HEMOGLOBULINURIA PATIENTS: SINGLE CENTER EXPERIENCE

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Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired disorder of hematopoietic stem cell and characterized with hemolysis, thrombosis and cytopenias. The most common cause of death is thrombosis and 29% to 44% of patients experience at least 1 thromboembolic event during the course of their disease. Here we evaluated thrombosis incidence and characteristics in our patients who have PNH clone.
Methods: We retrospectively analysed 36 patients that a PNH clone was detected on their peripheral blood with both flow cytometry and FLAIR tests between 2004 and 2014. Not only PNH patients also patients with aplastic anemia (AA) and myelodiysplastic syndrome (MDS) who have PNH clone were included.
Results: Median age was 33 at the time of diagnosis. Fifteen patients were female (42%) and 21 patients were male (58%). Five percent of patients (n=2) were MDS, 25% of patients were AA (n=9) and 70% of patients were PNH (n=25). A thromboembolic event was developed in 5 patients (14%) and 4 of patients were PNH and 1 patient was AA. Median time from diagnoses to thrombosis was 7 months. There was no significant relation between thrombosis and size of clone and presence of hemolysis. One patient's clone size was only 0.1% and had cardiac thrombus. Three patients had intra-abdominal thrombosis and 1 patient had pulmonary embolism. Two patients with thrombosis received eculizumab and did not experience a thromboembolic event again. Overall survival of patients with thrombosis and without thrombosis was 80% and 91% respectively. The difference was not significant.
Conclusions: Presence of a PNH clone is a highly prothrombotic state regardless of the clone size and hemolysis. Most common site of thrombosis was intra-abdominal veins. In our data we did not show the overall survival disadvantage of thrombosis probably due to our small sample. And eculizumab may prevent thromboembolic events.

Heparins and heparin induced thrombocytopenia

C0208
DETERMINING THERAPEUTIC RANGE FOR ACTIVATED PARTIAL THROMBOPLASTIN TIME FOR UNFRACTIONATED HEPARIN IN THE TREATMENT OF VENOUS THROMBOEMBOLISM

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Background: Intravenous unfractionated heparin (UFH) is the initial treatment of choice for most patients with venous thromboembolism. Laboratory monitoring with activated partial thromboplastin time (aPTT) is recommended to measure the anticoagulant effect of UFH therapy and to ensure sufficient anticoagulation. Monitoring goal is to select an appropriate UFH dosage which achieves an optimal anticoagulant effect and to determine the therapeutic aPTT range which is the equivalent of 0.3-0.7 IU/ml anti Xa activity. In this range the thrombus progression is inhibited while minimizing the risk of haemorrhagic complications. A target therapeutic range for aPTT is recommended to be 1.5 to 2.5 times longer than the control value, but it is advisable that each laboratory establishes its own therapeutic range using aPTT values that correspond to therapeutic anti Xa heparin levels.
Methods: 72 plasma samples from patients receiving continuous infusion of intravenous UFH were analyzed using 4 different aPTT reagents and anti Xa heparin levels at the Laboratory of the Department of Thrombosis, Haemostasis and Haematology Diagnostics in the Clinical Centre of Vojvodina, Novi Sad, Serbia. Linear regression analysis was performed to establish a new target aPTT range from corresponding therapeutic anti Xa heparin levels of 0.3-0.7 IU/ml, with the $P < 0.01$ considered statistically significant.
Results: A statistically significant linear correlation was found between each of the tested aPTT reagents and anti Xa levels ($P < 0.01$). The values of Pearson's correlation coefficients (r) were 0.78, 0.74, 0.69 and 0.63, for aPTT Pathromtin, aPTT Synthasil, aPTT Actin FS and aPTT SP liquid, respectively. The new therapeutic aPTT ranges corresponding to therapeutic anti Xa levels were established separately for each reagent: aPTT Pathromtin R 1.98-3.38, aPTT Synthasil R 1.76-2.92, aPTT Actin FS R 1.86-3.17 and aPTT SP liquid R 2.05-3.54.
Conclusions: Our results show high level of correlation between aPTT values with each tested reagent and anti Xa heparin level. We also evaluated our institution's therapeutic aPTT range with different reagents by examining the correlation between aPTTs and anti Xa heparin levels and established a new target aPTT range based upon the therapeutic anti Xa heparin levels.

C0319
DABIGATRAN USE FOR MANAGEMENT OF HEPARIN-INDUCED THROMBOCYTOPENIA IN A PATIENT WITH CANCER-RELATED THROMBOSIS

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Background: Venous thromboembolism (VTE) is a common occurrence in patients with cancer and anticoagulation with heparin is considered the standard treatment in this setting. However, heparin-induced thrombocytopenia (HIT), a prothrombotic serious adverse effect of heparin therapy, can occur, complicating management. Approved anticoagulant treatments, argatroban or danaparoid, require frequent monitoring, can cause serious bleeding and are expensive. Other options should be evaluated, such as non-vitamin K oral anticoagulants. We present a case in which an oral direct thrombin inhibitor, dabigatran, was used for treatment of thrombotic events in a patient with cancer and HIT.
Methods: A 59 years old man was admitted to our hospital with a low gastro-intestinal bleeding, anemia (Hb: 6.7 g/dl) and severe thrombocytopenia (plt: $16x10^9$/L), normal coagulation tests and normal renal and liver function. He was under chemotherapy, prednisolone and tinzaparin (14,000 UI/day), after being diagnosed with lung cancer stage IV and pulmonary embolism three weeks before. Colic varicose veins and mesenteric venous thrombosis were diagnosed. After control of bleeding and platelet count of 50 $x10^9$/L, enoxaparin 1mg/Kg bid was started. Ten days later, platelet count fall to $34x10^9$/L, and HIT was diagnosed according to clinical and laboratory findings (screening and confirmatory heparin/PF4 antibodies detection tests were positive). Enoxaparin was immediately stopped and argatroban was prescribed (2mg/Kg/min continuous infusion), but 10 minutes after beginning the infusion, a severe allergic reaction occurred. It was decided to switch to dabigatran 110 mg bid, according to a hospital protocol approved by the local ethical committee.
Results: Platelet count increased to $87x10^9$/L after 3 days, and patient was discharged. Two weeks later, dabigatran dose was increased to 150 mg bid (plt > $100x10^9$/L). Patient remains under surveillance and, until now, although his poor prognosis, he presented neither new bleeding nor thrombotic events.
Conclusions: This case illustrates that when approved therapy for HIT cannot be used, dabigatran can be an option, if patients present no major contra-indications. Dabigatran has predictable pharmacological characteristics, which become an attractive alternative treatment for HIT in selected patients.

Lupus anticoagulant/Phospholipid dependent antibodies

C0150
THROMBOSES IN PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

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Background: The aim of this study was to describe demographic, clinical and immunological features of patients having thrombotic events in antiphospholipid syndrome (APS)
Methods: It's a retrospective study over a period of 15 years. Patients' files with APS (according to the international consensus criteria of APS, Sydney 2006) were analyzed. Patients who presented with thrombo-embolic events were enrolled. Venous and arterial thromboses were diagnosed by Doppler ultrasound. Thoracic angio-computed tomography and cerebral angio-MRI were used respectively for pulmonary embolism and cerebral sinus thrombosis. Different thrombotic events were studied for clinical features, treatment and outcome
Results: Thromboses were the most frequent signs in patients with APS (68.6%), they revealed the disease in 60.7% of cases. The mean age at APS diagnosis was 44.2 years. The sex-ratio M/F was 0.1. Twenty two patients had deep venous thrombosis, the most frequent location was the lower limbs (n=12). The other locations were: pulmonary embolism (n=5), cerebral sinus (n=2), central retinal vein (n=2), inferior vena cava (n=1) and portal vein (n=1). DVT revealed the disease in 34.5% of patients and in four patients DVT was recurrent before APS diagnosis. Superficial venous thrombosis was noted in one patient. Thirteen patients had arterial thrombosis: cerebral (n=9), coronary (n=1), upper limb artery (n=1), renal artery (n=1) and central retinal artery (n=1). Two patients had both venous and arterial thrombosis and 7 patients had also obstetrical events. Anti-B2 glycoprotein 1 and anti-cardiolipin antibodies were positive in 51.6% and 48.3% respectively. Nineteen patients were treated with low molecular weight heparin, 23 had

vitamin K antagonists and 12 had antiplatelet agents. After treatment, 3 patients had a DVT and one patient had stroke.
Conclusions: Thrombotic events are common in patients with APS. DVT are the most frequent and lower limbs are often involved but atypical locations and superficial thrombosis are also seen. Arterial thromboses are not rare and can involve all arteries.

C0178
ANTIPHOSPHOLIPID ANTIBODIES IN MYELOPROLIFERATIVE DISEASE: RELATIONSHIP WITH JAK2 V617F STATUS AND THROMBOTIC PROFILE

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Background: Patients with myeloproliferative disease (MPD) have an increased risk of thrombosis. Both antiphosholipid antibodies (APA) and Janus kinase 2 (JAK2) V617F mutation have been considered as hypercoagulability markers. This study aimed to investigate the link between the presence of APA and JAK2 V617F mutation status in patients with MPD.
Methods: Sixty one patients with MPD diagnosed according to WHO diagnostic criteria were recruited from a single center. Peripheral blood samples were collected in citrate tubes for plasma. Citrate samples were double centrifuged for 15 minutes at 2500g to ensure platelet depletion. Serum and plasma were aliquoted and frozen at -70°C. The JAK2 status was determined. Assays for anticardiolipin and antibeta2 glycoprotein1 antibodies were performed.
Results: Mean age was 62.8 years-old (23 males and 18 females). Patients were diagnosed with polycythemia vera (n=27), essential thrombocythemia (n=33) and primitive myelofibrosis (n=1). Arterial and/or venous thrombotic events were reported in 21 patients. Abdominal venous and arterial thrombosis were the most frequent events. Recurrent thrombotic events were reported in 9 patients. Jak2 V617F positivity was found in 35/46 patients (77.7%). There was no significant difference between the incidence of JAK2 V617F mutation in MPD patients with thrombosis than in those without thrombosis (85% vs 69%; p=0.3). Screening for APA was positive in 13 patients (21.3%): IgM ACL (n=14), IgG ACL (n=3), IgM AB2GP (n=11), IgG AB2GP (n=3). Positivity for more than one antibody subtype was found in 10 patients. APA positivity was not significantly associated to thrombotic events (25% vs 17.5%; p=0.5). There was no association between the presence of APA and the JAK2 mutation status (p=0.1). The association of APA to JAK2 mutation did not increase the thrombotis risk (p=1).
Conclusions: According to previous reports, IgM ACL and IgM AB2GP were the most frequent subtypes. APL were not associated to clinical history of thrombosis in MPD patients. No significant interaction was found between APA status and JAK2 status.

C0217
STUDY OF ANTI-CARDIOLIPIN AND ANTI-BETA2-GLYCOPROTEIN I ANTIBODIES IN PATIENTS WITH ISCHEMIC STROKE (OUEST OF ALGERIA)

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Background: The study of IgG and IgM anti-cardiolipin antibodies (IgG/IgM aCL) is now well accepted and is routinely used in the risk assessment of various conditions associated with thrombosis
Methods: The aim of the study was to define whether the investigation of aCL is sufficient by itself to evaluate a risk of ischemic stroke. We included patients aged 18 to 50 years with ischemic stroke, referred to thrombophilia investigation at Tlemcen University Hospital, Algeria from 1 January 2007 to 31 December 2013 (N=30). Clinical information was obtained from the Neurology division of Tlemcen (Stroke Registry and medical records). Laboratory evaluation of antithrombin, protein C, free and total protein S, activated protein C resistance, fibrinogen, and antiphospholipid antibodies (APA). Including anticardiolipin (aCL) antibodies, anti-β2-glycoprotein I antibodies (anti-β2GPI) within the first 48 h after admission, and again, in the case of a positive result, at least 12 weeks after the first measurement. Moreover, prevalence of thrombophilia were also evaluated and compared to the results obtained in normal controls.
Results: Frequency of aCL and anti-beta2-glycoprotein I (beta2-GPI) antibodies was investigated in 30 patients with ischemic stroke and in 92 controls by ELISA. In ischemic stroke patients IgG aCL were found in 36.7%, the IgG-IgM-aCL were found in 37%. The levels of both antibodies were higher in patients with ischemic stroke than in controls ($P < 0.01$). In controls, IgM-aCL were positive in 3.3% and IgG-aCL antibodies were negative. The IgG-IgM-anti-beta2-GPI Abs were found in 17% patients. They were negative in controls. The category IIb (aPA IgM/IgG),I (LA and aPAIgG) and IIc (aB2GPI IgM) were found in 20%, 21% and 59% respectively , There was a correlation between levels of aCL and anti-beta2-GPI Abs for both isotypes (P0.03). The sensitivity of anti-beta2-GPI Abs for ischemic stroke was increased when both isotypes were tested.
Conclusions: These results showed that aCL and anti-beta2-GPI Abs could be pathogenetically important for ischemic stroke and that anti-beta2-GPI Abs testing might contribute to a better evaluation of ischemic stroke.

C0243
ANTIPHOSPHOLIPID ANTIBODIES AND THROMBOSIS

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Background: Antiphospholipid antibodies (APA) are a family of antibodies directed against proteins bound to negatively charged phospholipids. The presence of APA is a biological marker for antiphospholipid syndrome (APSy). In some patients, transient APA may be detected due to infection or due to another treatment, despite the absence of any clinical signs.
Methods: To evaluate the correlation between APA and thrombosis in patients with CVI (cerebrovascular infarct), AMI (acute myocardial infarct), and DVT (deep venous thrombosis) and pregnancy. It is a retrospective study on patients from the Outpatient Department. We used our own diagnostic tools, such as our micro ELISA kit to compare with commercial micro ELISA kits (QUANTA Lite TM b_2GP I).
Results: We made a clinical investigation for three classes of immunoglobulin - b_2GP I antibodies of 833 patients in four groups with different diagnoses. 218 were diagnosed with CVI, 232 with AMI, 123 with DVT and 260 were pregnant women. All patients have augmented concentration of all three classes of immunoglobulin and there is high correlation of APA and clinical manifestation of the different diseases. At highest risk were patients with DVT, because 30% had augmented IgG (59, 2 g/L) and IgA (5, 63 g/L) antibodies. The largest portion of them (32%) had augmented IgM (4, 47 g/L). From the 218 patients with CVI – 19% had augmented concentration of IgG (40, 91g/L), but mostly augmented concentration were antibody from IgG classes. From the 232 patients with AIM -17% were with high concentration of IgM (3,56g/L) immunoglobulin classes the value of other classes of immunoglobulin were less.
From the 260 pregnant women with pathological pregnancy, (29%) have augmented concentration of IgG (35, 76 g/L). Concentration of IgG is the biggest.
Conclusions: Our investigation showed us that in CVI and pathological pregnant women were augmented concentration of IgG class, in patients with AMI and DVT were augmented concentration of IgM class Augmented concentration of all APA is in correlation with thrombosis, or a very elevated risk for thrombosis. It is very important to devise a protocol or algorithm to follow up and treat patients with APSy, in order to have the most successful possible outcomes.

C0251
ANTIPHOSPHOLIPID ANTIBODIES IN PATIENTS WITH IMMUNE THROMBOCYTOPENIC PURPURA

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Background: The aim of this study was to evaluate the relation between anti-phospholipid antibodies (APA) and the clinical course, laboratory findings, response to treatment and prognosis of immune thrombocytopenic purpura (ITP) in childhood.
Methods: The cross-sectional study included to patients with newly diagnosed ITP aged between 0-18 years, in the period of time between March 2014 and March 2015, at our centre. Clinical and laboratory findings, medical treatments, and the course of the diseases were recorded for all patients. At the time of diagnosis, anti-phospholipid antibodies including lupus anticoagulant, anticardiolipin antibodies (aCL), anti-beta-2 glycoprotein I antibodies were studied. The patients who have positive results for APAs at diagnosis were examined again for APAs at 12th week of follow-up period.

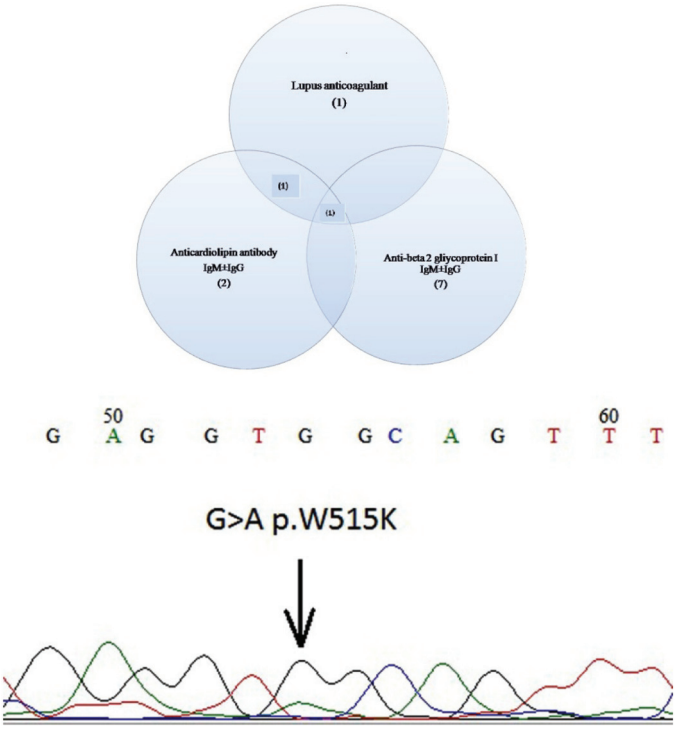

Fig. 1. Number of children with ITP and positive antiphospholipid antibodies.

Results: Forty children (21 (52.5%) females and 19 (47.5%) males) with newly diagnosed with ITP were enrolled the study. APA levels were positive at 12 patients (30%) at the time of diagnosis. Among the APA positive patients, only one patient had all of three APAs, one patient had both aCL IgM and LA, 10 patients had single positive results for APAs (Figure 1). Among APA positive patients, the positivity of anti beta 2 glycoprotein I, aCL and LA were 58.3%, 16.7%, and 8.3% respectively. After 12 week, only 3 of these 20 cases were still positive for APA. One of them was positive both LA and anti beta 2 glycoprotein I, and two of them were positive for anti beta 2 glycoprotein I IgG. There was not a significant difference between APA positiveness (at the time of diagnosis and control) and gender groups, platelet counts, IgG levels or course of disease. At the time of diagnosis, mean age of APA positive patients was significantly higher than in APA negative patients ($p<0.05$). According to age interval; there was three patients aged between 0-1 year and none of them were APA positive. At the time of diagnosis, APA positiveness was found in 7 of 28 (25%) patients aged between1-9 years, and 5 of 9 patients (55.5%) aged between 9-18 years. There was no relationship between APAs and treatment response or outcome of disease.
Conclusions: APAs may be present in children with ITP. It may be related to underlying viral infections or idiopathic, and more common in adolescence. The persistence of APAs may contribute to thrombotic complications in the future. More comprehensive studies are needed to determine the relationship between APAs and ITP.

C0256
MPL W515 K MUTATION IN A PEDIATRIC CASE OF ESSENTIAL THROMBOCYTHEMIA PRESENTING WITH BUDD-CHIARI SYNDROME

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Background: Essential Thrombocythemia (ET) is an extremely rare disorder during childhood, characterized by clonal expansion of megakaryocytic and thrombocytic lineages in bone marrow, leading to a persistent increase in the number of circulating thrombocytes and thus increasing the risk for thrombotic and hemorrhagic events. Most of children with ET have JAK2 V617F mutation. MPL and CALR mutations have been reported in a small proportion of adult ET patients. However, it is extremely rare in children.
Methods: A sixteen-year-old female patient was admitted with complaints of fatigue and abdominal pain in the last three months. Physical examination revealed; hepatosplenomegaly and abdominal distension. Ascites, hepatosplenomegaly and hepatic vein thrombosis were established by abdominal ultrasound and computerized tomography. Complete blood count revealed increased platelet count ($1300x10^9$/L) with normal haemoglobin and leukocyte count. She possessed persistently elevated platelet count ranging between $1000\text{-}1400x10^9$/L, without any evidence of reactive/secondary thrombocytosis. Hypercoagulability work-up was normal. Platelet aphaeresis was applied to patients to reduce platelet count in acute period. Low-molecular-weight heparin was given to patient for anticoagulation. Thrombectomy or replacing filter to inferior vena cava could not be applied, because the localization of thrombus was not convenient for intervention.
Results: Bone marrow aspiration and biopsy examinations showed trilineage haematopoiesis with increased number and clusters of megakaryocytes. TO elucidate molecular mechanism, we examined BCR/ABL, JAK2617F, Calreticulin and MPL mutations. The patient was found to have mutation for MPL W515K, and no other mutations. The patient who presented with BCS was diagnosed as ET with MPL W515K mutation. Hydroxyurea therapy was started. The patient underwent liver transplantation at the end of the 3rd month of treatment. Enoxaparin was switched to warfarin for long term anticoagulation. The platelet count of the patient was decreased (ranging between $300\text{-}600x10^9$/L). The patient is in stable clinical condition with mild cytopenias at the 12th month of therapy.
Conclusions: Budd Chiari syndrome may be initial presentation of ET in childhood. Mutation analysis of *MPL* could be required to support the diagnosis of childhood ET. No paediatric patient harbouring a *MPL W515K* mutation has been previously reported.

C0264
BONE MARROW NECROSIS AND PULMONARY THROMBOSIS ASSOCIATED WITH ANTIPHOSPHOLIPID SYNDROME

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Background: Antiphospolipid Syndrome (APS) is characterized by presence of the antiphospholipid antibodies (APAs), recurrent arterial or venous thrombosis, recurrent abortus, and thrombocytpenia. It is rarely associated

with bone marrow necrosis (BMN). We present a case of APS in a child presenting with pulmonary thrombosis and BMN.
Methods: Thirteen-year-old female presented with pneumonia and pleural effusion on right lung. Complete blood count revealed white blood cell count was 6200/μL, haemoglobin was 7g/dl, platelet count was 57000/ μL. Pulmonary CT angiography also revealed acute thrombosis in segmental branch of right pulmonary artery. Magnetic resonance imaging (MRI) of abdomen showed bone marrow necrosis in right iliac bones. Prothrombine time was normal, activated partial thromboplastin time (aPTT) was elevated, but in vitro correction of aPTT was not observed after mixing with 50:50 normal plasma. Pleural fluid examination and cultures, blood cultures were nondiagnostic. Direct coombs test was positive (+++). Viral serology, markers of collagen vascular disease, serum levels of immunoglobulins were normal. Bone marrow aspiration revealed only necrotic cells, while on trephine biopsy; there was extensive infarction of bone marrow with markedly reduced normal hematopoietic cells, without malign infiltration. Sickle cell anemia was ruled out by normal results of haemoglobin electrophoresis.
Results: In terms of APS, Lupus anticoagulant screening and confirmation (dRVVT) tests and antiβ2 glycoprotein-1 IgG were strongly positive, anticardiolipin antibody was negative. Other thrombophilic studies were normal. The patient was diagnosed with APS and BMN. Enoxaparin therapy was started for anticoagulation. Prednisolone was given for autoimmune haemolytic anemia at a dose of 2 mg/kg/day. APAs were persisted but decreased at the end of 6th week. We planned to screen the APAs every 3 months. Steroid treatment was stooped, when the patient has normal haemoglobin and negative direct coombs. Bone marrow necrosis was still present at the end of 8th week on MRI, but cytopenias were improved. She is in good condition with maintenance therapy of enoxaparin.
Conclusions: BMN is relatively uncommon condition and is most frequently encountered with malignancy, collagen vascular disease, infectious disease and sickle cell anemia. Our patient has APS which possibly related to severe lung infection. It should be noted that APS can be manifested as BMN even in childhood.

C0296
A CASE OF AN ANTITHROMBIN DEFICIENCY WITH MESENTERIC THROMBOSES AND CEREBRAL INFARCT

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Background: Deficiency of AT occurred by inherited or acquired (liver disease, warfarin therapy, asparaginase therapy, nephrotic syndrome, accelerated consumption). We present a 46 year-old male patient was diagnosed AT deficiency who had life threatening thromboses twice and an intestinal resection.
Methods: A 46 year-old male patient referred to research thrombophilia to our hematology department after had an intestinal necrosis and resection which occurred by mesenteric venous thromboses. Firstly, the patient had examined in rheumatology about vasculitis and had excluded. In the patient's history, intracranial sub acute infarct, mesenteric venous thromboses and chronic venous insufficiency of the lower extremity were existing. We found out that the patient was investigated for intracranial sub acute infarct 8 years ago in neurology department. As a young stroke, after got ticlopidin treatment started he had examined about cardiac diseases and vasculitis. Carotis and vertebral arterial Doppler USG, echocardiogram, clotting tests, homocysteine, lipid profile were normal, anti cardiolipin Ig M-G negative, ANA and anti dsDNA were positive. But the patient hadn't went on examinations. Six years later, he had applied again to neurology and had been studied protein C,S and AT III tests which had been determined normal except AT III. Ticlopidin had been changed with clopidogrel because of intolerance. After 2 more years, he had an intestinal resection because of mesenteric venous thrombosis. AT III were 52% that had been studied 2 years ago. In the family history, his brother was operated by the reason of mesenteric thrombosis and had a history of portal vein thrombosis. Prothrombin gene, factor V Leiden mutation were normal. Protein C, S and AT III were analysed again and AT III was found 37%. PNH clone was normal. With this findings, the patient was considered of AT deficiency. We planned the therapy as warfarin because of the life threatening tromboses history and family history.
Conclusions: Primary mesenteric vein thrombosis (MVT) are typically seen in patients with thrombophilias due to protein C, protein S and anti-thrombin III deficiency. Approximately 2% of primary MVT cases are caused by anti-thrombin III deficiency. We point out with this case to keep in mind AT deficiency in the mesenteric vein thromboses.

C0298
MULTIPLE TROMBOSES, HEMOLYTIC ANEMIA; CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME, A CASE REPORT

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Background: Antiphospholipid syndrome (APS) is characterized by vascular thromboses and/or pregnancy loss associated with persistently positive antiphospholipid antibodies. Catastrophic APS (CAPS) is the most severe form of APS. In this case, we present a 27 year-old male who presented autoimmune hemolytic anemia and multiple venous thrombosis, diagnosed with CAPS and survived.
Methods: A 27 year-old male patient applied to the ER, with complaints weakness and swelling on the right leg in a week. There were no features in the patient's history and family history. On his physical examination; paleness, edema on the lower leg extremity, cutis marmoratus, tachycardia, 3/6 systolic murmur were determined. The laboratory tests showed anemia (4.5 g/dL), thrombocytopenia (82,000/mm^3), elevated LDH (611 IU/L) and indirect bilirubin(1.1mg/dl), direct Coomb's test 4(+), reticulocyte 0%, normal clotting tests. The patient was hospitalized with an autoimmune hemolytic anemia and thrombocytopenia in the hematology department and was started 1mg/kg methylprednisolone (MP). A trombus were determined in the common femoral, superficial femoral, popliteal and great saphenous vein. Anti nuclear ab, cryoglobulin, anti cardiolipin ab, lupus anticoagulant, prothrombin gene and factor V Leiden mutation workup was done. Selective thrombolytic treatment could not achieved because of deep anemia so heparin infusion was started. In the follow up, thrombuses in the splenic, right common iliac, internal-external iliac and femoral vein, splenic infarction associated with hypoperfusion was found. Circulatory impairment and necrotic bullae was occurred in the limb. Thereupon, the patient was treated with 1 g/day pulse steroid for 3 days and 1 g/day IVIG for 2 days. Because of worsening of the limb, the right leg below knee amputation was performed. Pathology of the limb resulted in thrombus induced necrosis and congestion. ANA 1/320 (+), anti ds DNA high titer positivity, ribosomal P positivity were found. We diagnosed CAPS associated SLE. Thus, we added cyclophosphamide, hydroxychloroqine and warfarin to the therapy. The patient was discharged after clinical and laboratory response from the rheumatology clinic but he didn't continue examinations.
Conclusions: CAPS is a rare and life threatening condition which frequently also manifest thrombocytopenia and hemolytic anemia. In hematology departments CAPS should remember in definitive diagnosis.

Microparticles

C0195
PROCOAGULANT PHOSPHOLIPID ACTIVITY, WHOLE BLOOD THROMBOELASTOGRAPHY ANDTHROMBIN GENERATION ASSAY TO DETECT HYPERCOAGULABILITY IN THALASSEMIC CHILDREN

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Background: Life expectancy of thalassemia patients has markedly increased over the last few decades however, patients suffer from many complications. The presence of a high incidence of thrombotic events has led to the identification of a hypercoagulable state in these patients. The thrombotic risk is the highest in thalassemia intermedia and splenectomized patients. The mechanisms responsible for the increased thrombotic risk are still unclear. We aimed to assess hypercoagulability in children with thalassemia by measuring procoagulant microparticle activity, thromboelastography and thrombin generation assay.
Methods: Ninety-two patients and 41 healthy controls were included in this study. Sixty eight of patients were thalassemia major and 24 of patients were thalassemia intermedia. None of the patients had thrombosis before according to their medical records. Coagulation tests (prothrombin time, activated prothrombin time, fibrinogen and d-dimer), serum coagulation factor levels (factor II, V, VII, VIII, IX, X, von Willebrand factor, protein C, protein S, and antithrombin III), procoagulant microparticle activity, thrombin generation assay, and thromboelastography were studied.
Results: All patients were under the 20 year-old. The percentage of splenectomy was 10.3% in thalassemia major and 29.1% in thalassemia intermedia patients. Plasma factor II, factor V, factor IX, factor X, and protein C levels were significantly lower in both thalassemia major and intermedia patients than in control subjects. Both procoagulant microparticle activity and whole blood thromboelastography parameters were found to be significant for hypercoagulability in splenectomized patients. Unexpected, endogenous thrombin potential was significantly lower in thalassemic patients than in control subjects in thrombin generation assay.
Conclusions: The hypercoagulability in thalassemic patients, especially in splenectomized patients, can be determined with procoagulant microparticle activity and whole blood thromboelastography, whereas it cannot be determined with thrombin generation assay in platelet poor plasma. These findings show that blood cell and/or platelet abnormalities may be more important than the plasma abnormalities as determinants of thrombotic risk in thalassemic patients.

C0210
PHOSPHOLIPID DEPENDENT PROCOAGULANT ACTIVITY EXPRESSED BY CIRCULATING MICROPARTICULES IN PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS

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Background: Myeloproliferative neoplasms (MPN) are frequently associated to vascular complications. Moreover, Microparticules (MP) which are membrane fragments, are considered as prothrombotic state biomarkers in many clinical diseases. This study aimed to evaluate the procogulant activity expressed by circulating microparticules in MPN patients with and without vascular events.
Methods: From November 2013 to November 2015, 74 MPN patients (26 males, 48 females - mean age=62 years-old) were enrolled in cross sectional study. Vascular complications occurring at diagnosis, during the follow up or two years before the diagnosis were recorded. The presence of cardiovascular risk factors, a personal history of vascular events and a JAK2 V619F mutation were investigated. Venous blood was collected into tubes containing 3.2% citrate. Platelet poor plasma was obtained by a double centrifugation at 2500g for 15 minutes at 22°C. PPP was aliquoted and stored at -80°C until use. The procoagulant phospholipid activity associated to MP was measured using the STA Procoag PPL assay from DIAGNOSTICA STAGO. Results were expressed as clotting time.
Results: Among 74 MPN patients, 39 were diagnosed with essential thrombocythemia, 34 with polycythemia vera and one patient with primitive myelofibrosis. Forty three patients were on antiplatelet therapy. Cardiovascular risk factors were arterial hypertension (n=34), diabetes (n=10), dyslipidemia (n=6). Vascular events occurred in 20 patients (27%): arterial events (n=16), venous events (n=10). Personal history of vascular events was reported in 5 patients. The JAK2 V619F mutational status was positive in 75% of patients. Results from the PPL assays did not demonstrate a statistically significant difference in plasma clotting time (PPL-CT) from MPN patients with and without vascular events (51.6 sec vs 53.9 sec; p=0.47). Age, sex, type of MPN, cardiovascular risk factors, history of vascular events and the JAK2 V619F mutation do not influence PPL-CT. When comparing patients taking antiplatelet therapy to those who do not, PPL clotting time was not statistically different in both groups (52.9 sec vs 51.7 sec; p=0.7).
Conclusions: Although increased circulating microparticules have been reported in the plasma of MPN patients, MP associated procoagulant activity evaluated with PPL assay was not associated to vascular complications in MPN patients. In contrast with previous reports JAK2 V617F did not influence the PPL-CT.

Perinatal and pediatric hemostasis

C0056
NEONATAL PURPURA FULMINANS – A RARE LIFE THREATENING ENTITY

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Background: Neonatal purpura fulminans is a rare, life-threatening condition, caused by congenital or acquired deficiencies of protein C or S. The clinical presentation is that of acute disseminated intravascular coagulation resulting dermal and soft-tissue hemorrhage and necrosis. Concurrent deep soft-tissue necrosis may be extensive and require disabling limb amputations. The management includes an acute phase of replacement therapy with fresh frozen plasma or protein C concentrate and a maintenance therapy.
Methods: A 7 month old child presented to haematology clinic with history of purpura over face few hours after birth. Initially it was considered iatrogenic and parents were reassured and sent home. But on the same day he developed similar lesion over back which was progressive. He was managed with IV antibiotics and FFP in the lines of necrotizing fascitis. A week later similar lesion appeared and hemostatic defect was suspected but unfortunately his blood samples were labelled unsatisfactory for coagulation workup. Many local physicians as well as specialist were consulted and various treatment options were considered and tried. He also underwent repeated surgical debridement of various necrotic lesions as well. The child is also bilaterally blind due to persistent hyperplastic primary viterous.
Results: His protein C and S levels were repeated on fresh sample at our laboratory and protein C levels were found to be undetectable. Samples of his parents were tested and both of them were found to be heterozygous. Patient was started on anticoagulation with heparin as monitoring with oral anti-coagulation was cumbersome owing to difficult venous access. He is currently doing well with no new skins lesions and hospital admission. The result of molecular studies is awaited.
Conclusions: We diagnosed a case of protein C deficiency which is often a fatal condition unless there is early recognition of the clinical symptoms,

prompt diagnosis, and judicious anticoagulation and replacement therapy is initiated and maintained lifelong.

C0119
THE ASSESSMENT OF PROTHROMBOTIC POTENTIAL USING THROMBIN GENERATION ASSAY IN PATIENTS WITH NEPHROTIC SYNDROME IN CHILDHOOD

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Background: Nephrotic syndrome (NS) is a hypercoagulable state resulting from multiple factors: vascular stasis, an increase in hepatic production of fibrinogen and other clotting factors, decreased serum levels of anticoagulation factors (urinary losses of antithrombin III, protein C and S), increased plasma platelet production, and increased platelet aggregation. We aimed to investigate prothrombotic potential using thrombin generation assay (TGA) in patients with NS during activation and remission period.
Methods: 35 patients with NS were enrolled (Table 1). TGA was conducted during activation and remission of the patients. TGA parameters of the patients during activation and remission were compared with TGA parameters of 34 age and sex matched healthy volunteers.

Table 1
Demographic features of patients with NS.

	NS (n:35)
Time of follow	74 (6-204 months)
New diagnosis	2
Former diagnosis	33
Type of diagnosis (according to response to therapy)	
NS with exacerbation	11 (%31,4)
NS with dependent to steroid	21 (%60,0)
NS with refractory to steroid	3 (%8,6)
History of thromboembolic event	No
Family history of thromboembolic event	No

Results: Thromboembolic event was not established in any patients during follow-up. TGA parameters of patients with NS (activation/remission) and healthy control group are shown in Tables 2 and 3.

Table 2
TGA parameters in patients with NS during activation and remission period.

	Activation of NS Mean±SD	Remission of NS Mean±SD	P
Lag time	4.4±1.2	5.9±2	<0.001
ETP	2550±494	1715±467	<0.001
Peak thrombin	356±96	209±91	<0.001
Time to peak	8.9±1.7	11.2±3.0	<0.001
Time to tail	20.2±3.0	28.2±8.9	<0.001

Table 3
Comparison of TGA parameters in patients with NS during remission and healthy control group.

	Remission of NS Mean±SD	Control Mean±SD	P
Lag time	5.9±2	4.5 ±1,1	0.001
ETP	1715±467	1355±386	0.001
Peak thrombin	209±91	197±80	0.575
Time to peak	11.2±3.0	9.3±3.2	0.017
Time to tail	28.2±8.9	24.3±8.5	0.073

Conclusions: These results indicate that thrombin generation in patients with NS in activation is significantly higher than that of their remission period. Although remission is obtained in the patients with NS, ETP of the patients is still higher than that of healthy control. However, we have not observed any thromboembolic event in the patients. Thus, more studies are required to reveal the clinical importance of these findings.

C0247
INHERITED PROTHROMBOTIC RISK FACTORS IN MOTHER-CHILD PAIRS AND PERINATAL STROKE

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Background: The numerous risk factors for perinatal stroke have been reported. Still, no identifiable risk factor can be established in number of cases. The frequency of inherited prothrombotic factors is increased in pediatric stroke but the results obtained from different studies are not consistent. We investigated the prevalence of inherited prothrombotic risk factors in children with perinatal stroke and their mothers.
Methods: Risk factors were assessed in 17 mother-child pairs with perinatal stroke. Genotype analysis for factor V G1691A (FVL), factor II G20210A (PT), methylenetetrahydrofolate reductase C677T (MTHFR) and plasminogen activator inhibitor 1 5G/4G (PAI) was performed.
Results: In 94% (16/17) both mothers and children or in 100% (17/17) of mother-child pairs, at least one prothrombotic risk factor was found. Two pairs were found to be FVL heterozygotes, both mother and child. Four MTHFR homozygotes were found in the group of children while their mothers were heterozygous for the same polymorphism. In 3 pairs, children had wild type MTHFR, while their mothers were heterozygotes and in 2 pairs we found the reverse situation - children were heterozygotes and mothers wild type. In 3 pairs both mother and children were heterozygotes. Three pairs were found to have 4G/4G and 3 pairs 4G/5G genotype for PAI, both mother and child. In 2 pairs, children have 4G/4G and their mothers 4G/5G and in 4 pairs children have 4G/5G and mothers 4G/4G, respectively. Four mothers and one child had wild type for PAI which points to a frequency of PAI polymorphism in 85% of our subjects (12%, 4G/4G genotype). Heterozygosity for PT was not found.
Conclusions: Assessed inherited prothrombotic factors presented a relatively high frequency in both groups. PAI polymorphisms significantly changed the presence of prothrombotic risk factors in our subjects due to its high frequency in our population. This results indicate that prothrombotic risk factors, individually and combined, could play an important role in the pathogenesis of perinatal stroke.

C0276
LONG-TERM FOLLOW-UP OF TWO CHILDREN WITH RECURRENT IMMUNE THROMBOCYTOPENIC PURPURA

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Background: Immune thrombocytopenic purpura (ITP) is a common benign hematological disease that occurs in childhood, whereas recurrent immune thrombocytopenic purpura (rITP) is a rare form that occurs in 3% to 6% of patients with ITP. This condition is characterized by intermittent thrombocytopenia after at least 3 months of remission, and spontaneous recovery without treatment. The literature contains little long-term follow-up of patients with rITP. We report such findings for two affected children, a boy and girl who presented with purpuric or petechial skin lesions and severe thrombocytopenia.
Methods: The values of complete blood counts were determined by Coulter® LH 780 autoanalyzer in two children with rITP.
Results: A 9-year-old boy who had been diagnosed with rITP 4 years earlier presented with widespread purpuric skin lesions and bruising, and severe thrombocytopenia (platelet count $10x10^9$/L) that was consistent with his peripheral blood smear at time of diagnosis. He was initially treated with intravenous immunglobulin (IVIG); however, unrelated to this therapy his platelet count rose rapidly to $310x10^9$/L within 12 hours. He experienced thrombocytopenic episodes (platelet counts $10x10^9$/L to $30x10^9$/L) once

yearly during regular follow-up but required no therapy. An 8 year-old girl who had been diagnosed with rITP 5 years earlier presented with petechial skin lesions and bruising, and severe thrombocytopenia (platelet count $12x10^9$/L) that was consistent with her peripheral blood smear at time of diagnosis. She was initially treated with IVIG; however, unrelated to this treatment, her platelet count rose to $390x10^9$/L within 24 hours. She experienced thrombocytopenic episodes (platelet counts $5x10^9$/L to $20x10^9$/L) three to four times yearly during regular follow-up. She was treated with IVIG or steroid during only two of these episodes; the others resolved spontaneously.
Conclusions: These two cases suggest that long-term outcomes for patients with rITP are likely to be favorable, even if only one-third or less of a patient's thrombocytopenic episodes require treatment.

C0302
PEDIATRIC ONSET BEHÇET'S DISEASE: PRESENTING WITH RECURRENT SUPERFICIAL VENOUS THROMBOSIS

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Background: Behçet's syndrome is a multisystem vasculitis with unknown etiology. It affects all sizes and types of vessels. Thrombosis is the most frequent vascular manifestation in Behçet's syndrome. Here we report a 17-year-old boy applied with recurrent superficial venous thrombosis and diagnosed as Behçet's syndrome.
Results: A 17-year-old male was referred to our hospital because of popliteal venous thrombosis. From his history we learned he had pain, tenderness in the right arm and leg for two weeks. He first applied to another hospital. In physical examination right gastrocnemius muscle tenderness had detected. Doppler USG had performed, popliteal venous thrombosis had found. After starting oral warfarin and diosmin he was referred to our hospital. In physical examination aphthous oral ulcerations and swelling, redness in right upper and lower extremity was detected. The following data were recorded: WBC, 10 $x10^3/mm^3$; hemoglobin, 14.8 g/dL; platelet count, 242 $x10^3/mm^3$; PTT, 40,5 s; PT, 15.1 s; fibrinogen, 682 mg/dL(180-250); D-dimer, 1.2 μg/ mL (0-0.5); homosistein, 11.8 μmol/L; vitamin B12, 309.2 pg/mL; ANA, positive (granular). Doppler USG was performed to upper extremity and detected thrombotic segments in superficial system of vena cephalica antecubital branches. Doppler USG of lower extremity detected thrombosis in popliteal vein and distal part of superficial femoral vein. Antithrombin antigen, protein C, protein S were normal. Factor V Leiden heterozygote mutation was detected. Low molecular weight heparine (LMWH) 1 mg/kg/ dose, in two doses, antibiotic treatment was started. After three days, he admitted again with right arm pain and swelling. Doppler USG detected new thrombotic segments in superficial veins of arm. Because of oral ulcerations, recurrent thrombosis and ANA positivity, we examined the patient with diagnosis of Behçet's syndrome. Pathergy test was negative. Eye examination was normal. HLA B5 was positive. We started colchicine treatment. He was still on colchicine and single dose LMWH treatment. He has been followed up for four months and no recurrences of thrombosis.
Conclusions: Lower extremity venous thrombosis is the most frequent vascular involvement in Behçet's syndrome. The majority of vascular events occur within the first five years. In 7-30% vascular involvement occur before the diagnosis. In patients with recurrent and migratory superficial venous thrombosis, we should think Behçet's syndrome.

Platelets and Megakaryocytes

C0042
THE STORAGE EFFECT ON THE PLATELETS ABILITY TO FORM A CLOT

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Background: Apheresis and storage of platelet concentrates (PCs) affected by the platelets activation and total functional capacity of these cells. We assume that after transfusion the prevalence of platelets with changed activity lead to worse quality of blood clot in vivo. The aim was the in vitro study of platelet-dependent clot properties as a function of storage time.
Methods: Fifty single-donor apheresis PCs were divided in two groups: group 1 - platelets were remained in autologous plasma (PCs-P; n=26); group 2 – platelets were resuspended in PAS (SSP+; Macopharma, France) which substituted up to 70% vol of autoplasma (PCs-PAS; n=24). Storage conditions were equal. PCs samples were analyzed by modified thromboelastography, and by aggregometry, and for platelets count, pH, lactate, glucose, and other platelets parameters. The testing were carried out in the day of proceeding, after 24 hours, and at 3rd and 5th days of storage.
Results: Platelets count had not significantly different between PCs-P and PCs-PAS. Between PCs-P and PCs-PAS no significantly differences had for platelets count, glucose consumption and lactate production. Moreover pH was almost unchanged that indicated buffer conditions were good. During the storage platelets aggregability and adhesion had worsened independently PCs type. But in PCs-P such decline was more expressed a little bit. We found that clot demonstrated gradual reduction of elasticity and deformability in both PCs groups. In PCs-P platelets lost their meaning for clot properties from the third storage day. In PCs-PAS activated platelets had no impact to clot properties during full storage time.
Conclusions: Irrespective of the proceeding method platelets viability was saved during the first five days of storage. Platelets apheresis and storage are accompanied by aggregation-and-adhesion activity depression. Total decline of clot quality including low elasticity and impaired deformability was found of during period in stored PCs. We assume that clot properties are forming at the day of proceeding. Therefore we suppose that effect PCs transfusion is related to successful of platelets activity recovery in vivo.

C0209
A RARE REASON OF THROMBOCYTOPENIA; BRUCELLOSIS

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Background: Brucellosis, constituting a major health problem in many parts of the world is a multisystem disease with a broad spectrum of clinical manifestations. Thrombocytopenia has been reported to occur in 1%–8% of patients with brucellosis [1,2] and invariably occurs in patients who suffer from hemorrhage into the skin and from mucosal sites [3].Here we report a case with thrombocytopenia whose clinical presentation onset later.
Results: Thrombocytopenia was detected in a seven years old boy who admitted to hospital with fever. He had pharyngitis and mild splenomegaly. Neither he had history of thrombocytopenia, nor his family. In laboratory findings; Hg: 9.5g/dl, Rbc: $5.5x10^6/\mu l$, MCV: 53.6fl, Plt: $102x10^3/\mu l$, PBS: 5-6 platelets were seen in every area. ESR: 29mm/h, ALT: 24U/dl, AST: 32U/dl LDH: 336U/l Ferritin: 118ng/ml, B12: 276pg/ml, Folic acid: 6.7ng/ml, Viral serology: negative, Brucella agglutinin titer: negative, antinuclear antibody: negative and bone marrow was normocellular with mature megakaryocytes. Karyotype was 46XY. No deletions or monosomy was found. DEB test was negative. Bone marrow culture was negative. As he had frequent episodes of epistaxis although his platelet level was between 70-$110x10^3/\mu l$,

thrombocyte function test was performed and found to be normal. In sixteen months of follow up, he had frequent epistaxis episodes and tranexamic acid and desmopressin were used to stop bleeding and frequent episodes of fever and all of them were stopped with hydration and amoxicillin clavulanic acid or cefuroxime axetil. Normal serum glucocerebrosidase level excluded Gaucher's disease. The patient admitted to hospital with fever and epistaxis and internalized to hospital. Only splenomegaly was found in his physical examination. Urine and blood culture samples were taken with hemogram and C-reactive protein. Brucella melitensis was found in blood culture. Brucella agglutination was found to be 1/5120 positive. Trimethoprim-sulphamethoxazole and tetracycline therapy was started. He is on the fifth day of treatment

Conclusions: The mechanism responsible for thrombocytopenia in brucellosis is not understood with certainty but is probably multifactorial, including hypersplenism, hemophagocytosis, and immune destruction of platelets. The serological evaluation of brucellosis should be repeated if the thrombocyopenia wasn't thought to be because of immune thrombocytopenia or the etiology couldn't be found.

C0215
INVESTIGATION OF CLINICAL SIGNIFICANCE OF PLATELET DYSFUNCTION IN PATIENTS WITH THROMBOCYTOPENIA

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Background: Platelet dysfunction is also seen in the presence of thrombocytopenia. This may increase the risk of bleeding. Platelet function testing is an important component of comprehensive hemostasis evaluation within the framework of bleeding and/or bruising investigations. The platelet function analyzer (PFA)-100 (Siemens Healthcare, Marburg, Germany) is the most used primary hemostasis-screening instrument and has also been recently remodeled/upgraded to the PFA-200. The determination of closure times with a platelet function analyzer is sensitive for the detection of defects of primary hemostasis. Closure times of epinephrine/collagen and ADP/collagen cartridges can be determined with a platelet function analyzer PFA-200.
Methods: In our study, we aimed to compare retrospectively the clinical findings and laboratory values of patients hospitalized with thrombocytopenia of different etiology and performed closure times of epinephrine/collagen and ADP/collagen cartridges with a platelet function analyzer PFA-200 for bleeding diathesis in our clinic.
Results: It was retrospectively reached to data of 42 patients. When the data was analyzed, there was no significant demographic features and laboratory data of the patients. Collagen/ADP and Collagen/Epinephrine CT value were inversely proportional to the number of platelets. There was no significant correlation between demographic data, laboratory and the PFA-200 CT values when patients were grouped according to diagnosis and bleeding signs. However, hypoalbuminemia and Collagen/ADP CT value is above 270 seconds were associated with mortality. There were no significant correlation between PFA-200 CT value and hypoalbuminemia and other laboratory findings of all patients.
Conclusions: As found in our study, restoration of platelet function regardless of the number of platelets will be important when the Collagen/ADP CT value is greater than 270 seconds in the presence of thrombocytopenia. PFA-200 CT values and hypoalbuminemia was found to be associated with mortality. However, the lack of statistical significance between albumin and CT levels suggest that PFA-200 CT value may not be a good acute phase reactant.

C0244
WERE THE MEASUREMENTS STANDARDIZED SUFFICIENTLY IN PUBLISHED PAPERS ABOUT MEAN PLATELET VOLUME?

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Background: Recently, mean platelet volume (MPV) aroused interest of the researchers and several studies about MPV changes in various pathological conditions were published. The aim of this study was to evaluate the data accuracy of MPV measurements in these studies.
Methods: The study was performed using the data of 181 studies contain healthy control subjects within 1181 paper about mean platelet volume indexed by PubMed database since 2012.
Results: 81 studies (44.7%) were performed retrospectively. Healthy control groups included 80.52 ± 70.51 subjects (mean ± standard deviation). The distributions of gender in 16 (8.8%) and age in 12 studies (6.6%), and platelet counts in 28 studies (15.5%) were not reported. The gender and age groups were not differing significantly by the means of platelet counts (r= -0.40; p >0.05). EDTA, low (1:9) and high concentrate (1:4) citrate were used as an anticoagulant in 112, 7 and 2 studies, respectively and type of anticoagulant was not noted in 60 studies (33.1%). There was no study to compare the different anticoagulants. The instruments of Beckman Coulter, Sysmex, Abbott Cell-Dyn, Siemens ADVIA, Mindray BC-6800, HORIBA ABX Micros 60 and Diatron Abacus Junior B were used for the measurements of MPV in 53, 46, 32, 9, 2, 2, and 1 studies, respectively and the used technology in automated blood cell counting was not specified in 36 studies (19.9%). The MPV values measured with Sysmex was higher significantly than the MPV values measured with Beckman Coulter, Abbott Cell-Dyn and Siemens ADVIA. The MPV measurements varied up to 17.8% by the instruments. The measurement times between 15 minutes-2 hours was significantly different from the measurement times <15 minutes and >2 hours. The MPV measurement times from venipuncture were not indicated in 86 studies (47.5%). The MPV measurements by the MPV measurement times and plus the used instruments varied up to 17.8% and 27.7%, respectively. Both the MPV measurement times and used instruments were not stated in 29 studies (16.0%). Only 47 prospective studies (26.0%) enlightened about type of anticoagulant, used instruments for MPV measurement, MPV measurement time, platelet counts and MPV values.
Conclusions: As a result, the measurements were not standardized sufficiently in published papers about MPV. It may be explained the differences between the results of studies made same pathological conditions.

C0249
IMPACT OF AGE ON GENERAL FEATURES OF PATIENTS WITH IMMUNE THROMBOCYTOPENIA IN TRAKYA REGION, TURKEY

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Background: Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by low platelet counts resulting from both immune-mediated platelet destruction and inappropriate bone marrow platelet production. We aimed to evaluate the general features, treatment modalities, responses to treatments, and the variation of these parameters regarding age of patients with ITP.
Methods: We evaluated the general features like age, sex, presenting thrombocyte count, initial treatment, response and complications, further treatment requirements in a retrospective fashion. We divided patients into two groups as > and < 65 years old.
Results: 244 patients were diagnosed as ITP between 2000 and 2015 in our region. The overall prevalence of ITP was 32.1/100,000 (95%CI: 30.1–34.7). Of these patients, 67.6% were female while 32.4% were male. Mean age of patients were 52.3 (21-93). 63 patients (25.8%) were over 65 years of age while 181 patients (74.2%) were below 65 years of age. 18% of the

patients were just followed up without treatment. Mean platelet count on presentation was 42 x 109 (18-84 x 109), mean time response (platelet increment over 100 x 109) was 18 days (4 to 21 days). These results were similar in patients below and over 65 years of age. Mean follow up duration of these patients were 3.2 years. The administration of first-line therapy (corticosteroids) resulted in complete remission (CR) in 78.4% of patients and partial remission (PR) in 18.6%. After 5 years, 41% of patients who were responsive to first-line therapy were still on remission. After second-line therapy (splenectomy, immunosupressive treatments), CR was observed in 76.5% and PR in 21.4%. The duration of relapse-free remission was longer after splenectomy than with corticosteroid treatment ($p < 0.001$). Regarding age over and below 65 years, complications of treatments (cushing syndrome, hypertension, muscle weakness, psychological disturbances) were similar in both groups (p=0.1). Majority of patients over 65 years of age were observed to obtain remission after the first line treatment (71.5) and only 6.3% of these patients required further treatment

Conclusions: Approach to patients with ITP should be based on patients' characteristics and age is an important determinant. Patients with older age seems to require less treatment. Effective yet tolerable treatment strategies seem to be corticosteroids as first-line therapy and splenectomy in relapsed or refractory patients.

C0282
THE IMPORTANCE OF OXIDATIVE STRESS IN ABNORMALITIES OF PLATELET FUNCTION. THE RETROSPECTIVE STUDY IN CHRONIC MYELOID LEUKEMIA AND MYELODISPLASTIC SYNDROME PATIENTS

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Background: Patients with chronic myeloid leukemia (CML) and myelodisplastic syndrome (MDS) have an abnormal platelet response. Many of them have thrombotic or hemorrhage complications. Aims are the importance of reactive oxidative species (ROS) in alteration function of platelet membrane in patients with CML and MDS.

Methods: This retrospective study included 40 patients (24 CML patients and 16 MDS patients) during the past 3 years in the Hematology Departments of Colentina Clinical Hospital and University Emergency Hospital Bucharest. Platelet function was investigated by platelet aggregation with optical method and fluorescence anisotropy measurements with TMA-DPH. Production of ROS was examined using fluorescence method with DCFDA and Fluorolog spectrophotometer.

Results: Production of ROS is higher for patients with MDS and CML patients compared with healthy controls. CML patients in accelerate or blastic phase has higher level of ROS production compared with patients in chronic phase (1.23 vs 1.09, p=0.03). BCR/ABL kinase stimulates reactive oxygen species (ROS), which elevate oxidative DNA damage and cause mutations in the kinase domain and treatment resistance. A higher level of ROS influences biophysical properties membrane especially fluidity membrane by oxidation of lipid components. Our results of anisotropy measurements did not reveal any difference (0.15 vs 0.13, without statistical significance). All patients have altered response in platelet aggregation method. We obtained a much weaker response to epinephrine and collagen of platelets from patients with CML and MDS versus controls ($p<0.001$). This response matched both amplitude and slopes of aggregation curve. The slope and amplitude of ristocetin curves in patients are comparable with healthy volunteers.

Conclusions: Patients with MDS and CML presents functional defects. Fluidity of platelet membrane could be an important parameter which influenced expression of platelet receptor and explain the low response of platelet. In our study we could not obtain a significance difference for CML patients and a correlation with ROS production level. We have to verify these results in another study with higher patients enrolled to ascertain the precise role of oxidative stress in alteration of platelet functions.

C0307
IBRUTINIB AND AGGREGATION

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Background: Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). BTK is a cytoplasmic tyrosine kinase of the TEC family that is essential for B-cell receptor signalling. It has activity in chronic lymphocytic leukaemia (CLL). Ibrutinib is generally well tolerated but is associated with an increased risk of bleeding. It is assumed that the bleeding events are caused by platelet dysfunction. But the previous studies have yielded variable results.

Methods: The local Ethical Committee approved this study. All study participants agreed to participate in the project and signed a written informed consent in accordance with the Declaration of Helsinki. Light transmission aggregometry (LTA) was performed using the international protocol for the laboratory investigation of platelet function. Testing was performed on patients without any antiplatelet therapy, when the platelet counts had improved sufficiently following ibrutinib therapy to permit reliable testing ($\geq 100 \times 10^9$/L) and with normal basic coagulation tests (prothrombin time, thrombin time, activated partial thromboplastin time).

Results: We tested 7 relapsed/refractory CLL patients (5 males) with median age 69 years (range 52 – 80 years); 5 of patients were aged 65 years or older. 5 patients received ≥ 2 previous lines of treatment. All patients received 420 mg oral ibrutinib daily. Median time from ibrutinib initiation to platelet aggregometry was 171 days (range 80 – 272 days). Median platelet count at aggregometry was 117 x 10^9/L (range 103 – 195 x 10^9/L). As expected, patients on ibrutinib showed impairment of responses to collagen. However, we did not expect the results after aggregation with arachidonic acid (AA), epinephrine (EPI) and adenosine diphosphate (ADP). All patients showed reduce platelet aggregation after AA. In addition, majority of patients had also reduced responses to EPI and ADP.

Conclusions: This study reports the use of the sensitive method of LTA to assess platelet function in subjects treated with ibrutinib. We showed a effect on collagen and AA-induced platelet aggregation, and some evidence on ADP and EPI-induced aggregation.

C0323
THERAPEUTIC THROMBOCYTAPHERESIS: HIGHER PLATELET COUNTS SHOULD MATTER

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Background: Myeloproliferative disorders and some benign conditions may present with thrombocytosis. Therapeutic thrombocytapheresis (TTA) can rapidly reduce platelet counts. In this paper we describe our center's experience with TTA.

Methods: The medical records of Ankara University Hospitals were retrospectively reviewed for TTA procedure between 1999 and 2016. All procedures were performed with Fresenius Kabi COM.TEC device. Indications included either a platelet >600 x 10^9/L in a symptomatic patient (i.e., acute thrombosis or haemorrhage) or a platelet >1000 x 10^9/L in a high risk asymptomatic patient.

Results: Between 1999 and 2015 a total of 52 TTA was performed in 29 adult patients. General characteristics are given in Table 1. A median of 1 (1-8) course of TTA was performed per patient. More than one course of TTA was performed for 9 patients (31.0%). Achieving the platelet target <1000 x 10^9/L was statistically less frequent among patients having an initial platelet

>1500 x 10^9/L. These patients also needed more than one course of TTA more frequently. All patients received concurrent hydroxyurea and continued with hydroxyurea and/or anagrelide or a tyrosine kinase inhibitor, if appropriate, after TTA. None of the patients required TTA for another episode.

Table 1
General characteristics of patients

Variables	All patients	Initial platelet count (x 10^9/mL) ≤1500	>1500	P
Age median (min-max)	53 (18-83)	62 (18-83)	45 (20-71)	<0.05
Gender n (%)				
Female	17 (58.6)	10 (52.6)	7 (70.0)	0.37
Male	12 (41.4)	9 (47.4)	3 (30.0)	
Primary diagnosis n (%)				
ET	18 (62.2)	13 (68.4)	5 (50.0)	0.79
PMF	5 (17.3)	3 (15.8)	2 (20.0)	
CML	4 (13.7)	2 (10.5)	2 (20.0)	
Other	2 (6.8)	1 (5.3)	1 (10.0)	
Post-TTA platelet count (x 10^9/mL) median (min-max)	880 (418-3162)	737 (418-1100)	1247 (522-3162)	0.001
Reduction rate (%) median (min-max)	35.5 (5.8-70.7)	32.3 (12.2-56.8)	40.9 (5.8-70.7)	0.18
Unsuccessful TTA course (reduction rate < 30%) (N=52) n (%)	16 (30.1)	10 (27.0)	6 (40.0)	0.51
TTA courses >1 n (%)	9 (31.0)	3 (15.8)	6 (60.0)	0.01
Achieving platelet <500 x 10^9/L n (%)	6 (20.1)	4 (21.1)	2 (20.0)	0.95
Achieving platelet <1000 x 10^9/L n (%)	21 (72.4)	17 (89.5)	4 (40.0)	0.005

Conclusions: TTA is suitable for patients with acute serious complications or high risk patients with very high platelet counts (>1000 x 10^9/L). Patients with an initial platelet >1500 x 10^9/L should receive more intensive concurrent pharmacotherapy. Maintenance with cytoreductive medications is required to sustain normal platelet counts.

Pregnancy and thrombosis

C0054
ASSOCIATION OF FACTOR V LEIDEN G1691A AND PROTHROMBIN GENE G20210A MUTATION WITH ADVERSE PREGNANCY OUTCOMES

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Background: Familial defects and polymorphisms of clotting cascade proteins protein S, protein C, factor V Leiden G1691A and factor II G20210A are linked with increased risk of thromboembolism which is better known as *inherited thrombophilia*. Thrombophilia causes deep venous thrombosis, pulmonary embolism and is strongly associated with poor pregnancy outcomes. To date, there is limited data from our region on the role of these genetic abnormalities causing adverse pregnancy outcomes.
Methods: It was a case control study, conducted at section of haematology, and PCR-RFLP technique is used at multi-disciplinary laboratory, Aga Khan University Hospital. Females with adverse pregnancy outcomes who came to obstetrical clinic were included in the study as cases. Adverse pregnancy outcomes included recurrent pregnancy loss (defined as > 2 first trimester miscarriages or one or more second trimester miscarriage), severe pre-eclampsia, placental abruption, intrauterine growth restriction and still birth. Control samples are selected from females with ≥ 2 consecutive normal pregnancies. Calculated sample size is 172 which comprised of 86 cases and 86 controls.
Results: Overall mean age of all subjects was 28.5 years (±4.9). Mean age of cases was 29.3 (±5.17) years and of controls was 27.6 years (±4.5). 73 (84.8%) cases had recurrent pregnancy loss, 12 (13.9%) had pre-eclampsia, 8 (9.3%) had IUGR while placental abruption and still birth was present in 2 (2.3%) cases each. 10 (11.6%) cases had more than one adverse pregnancy outcomes. 19 (22.09%) cases had > 4 pregnancy losses. Among cases, 40 (46.5%) females had previous live births and 9 (10.4%) were pregnant at the time of sample collection. Two cases with recurrent pregnancy loss (p=0.155 OR=0.49) showed heterozygous mutation of factor V Leiden G1691A and while no mutation identified in the control arm. Heterozygous prothrombin gene mutation was identified in one case with recurrent pregnancy loss (p= 0.316 OR=0.497) while none of the control exhibited this mutation.
Conclusions: This is a small sample sized study which does not support a significant association between inherited thrombophilia mutations and adverse pregnancy outcomes. Apparent lack of association may be reconciled by the low numbers of subjects recruited.

C0117
MEASURES OF THROMBODYNAMICS TEST AND D-DIMER LEVEL IN PREGNANT WOMEN WITH COMPLICATED OBSTETRIC HISTORY IN THE 3RD TRIMESTER OF PREGNANCY

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Background: To evaluate the performance of Thrombodynamics test and their dependence on the level of D-dimer in pregnant women with complicated obstetric history (COH) in the 3rd trimester of pregnancy.
Methods: The study was conducted on the basis of the Center of hemostasis and atherothrombosis "The First city clinical hospital named after E. E. Volosevich" Arkhangelsk and Northern branch of Hematology research center, Ministry of health of the Russian Federation. The study involved 16 pregnant women with COH observed in the Center of hemostasis and atherothrombosis in 3rd trimester of pregnancy. On "The Registrar Thrombodynamics T2" was determined delay clot growth (Tlag, the reference values of 0.7 – 1.5 min), clot growth velocity (V, 24 and 35 μm/min), clot density (a.u., 20894 - 35024) and the presence of spontaneous clots (Tsp, are normally absent). D-dimer in plasma was made on automated hemostasis analyzer Sta Compact (norm up to 0.5 μg/ml). The median (Me) and 2.5 and 97.5 percentile were used to describe the quantitative data. Correlation analysis was performed using the coefficient of the Spearman rank correlation (rs, p=0.05).
Results: The measures of Thrombodynamics test and level of D-dimer were within the reference values. Results of Thrombodynamics test: Tlag was 1 min (0.7-1.3), V – 27.7 μm/min (22.7–49.9), clot density – 29797 (27111-34759). Spontaneous clots (Tsp) were observed in 2 patients. The level of D-dimer was 1.19 μg/ml (0.47 – 3.61). We conducted a correlation analysis of the relationship between D-dimer and indicators Thrombodynamics test, a statistically significant correlation was not found (r_s=0.124, p=0.649, r_s=-0.127, p=0.638 and r_s=-0.206, p=0.444 accordingly).
Conclusions: The presence of spontaneous clots in the third trimester may be associated with a physiological increase of the coagulation potential of blood during pregnancy and with max levels before childbirth. The lack of a statistically significant relationship between Tlag, V, clot density and D-dimer shows that D-dimer does not reflect the processes occurring in the system of hemostasis at the time of the study, and only reflects those that have already occurred (thrombosis, fibrinolysis). Test Thrombodynamics along with D-dimer can be used for monitoring of hemostasis in pregnant women with COH. The study was conducted with the financial support of the program "UMNIK" in the Arkhangelsk region.

C0187
GLANZMANN DISEASE IN A LATIN AMERICAN PATIENT WITH TWIN PREGNANCY

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Background: Glanzmann's thrombasthenia is rare disorder genetic with a normal platelet count and morphology but abnormal platelets function resulting from a deficiency of glycoprotein llb-llla complex in platelets, is characterized by a prolonged bleeding time and a severe hemorrhagic mucocutaneous diathesis. It is estimated that one in 1,000,000 individuals have GT, though the exact number is unknown.
Methods: Pregnancy and delivery in women with Glanzmann thrombasthenia is reported to be rare by peri partum and late post partum haemorrhage, these women are also at risk of miscarriage and intrauterine death.
Results: We present an unusual case a Twin pregnancy in a Latin American patient with Glanzmann disease. It is patient with twin pregnancy by 33.2 weeks, entry into labor and delivery department, with reported subchorionic hematoma through obstetrical ultrasound, cesarean realizing you urgently. In spite of the unsuitable surroundings, she gave birth two newborn females with Apgar 7-8, the first weighing 1855 g, height 44 cm, the second with weight of 2035 g, height 45 cm. First placenta with 30% detachment and second placenta with 20% detachment. Clots in amount of 1500-1800 cc. 2200 cc bleeding. Peri partum and post partum beats treatment using only plasmapheresis and platelets.
Conclusions: Post-operative period was uneventful. Both the mother and one baby were discharged 7 days after the caesarean. The second female baby was discharged 21 days after the caesarean, by own complications of prematurity. Currently both the mother and the twins were born 4 months have no bleeding complications, the babies being studied to rule out a possible risk of being carriers of Glanzmann.

C0242
THROMBOPHILIA AND IVF FAILURE

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Background: Women with thrombophilia have been shown to be at increased risk, not only of pregnancy associated thromboembolism and vascular complications of pregnancy, including pre-eclampsia and fetal loss, but also of IVF failures.
Methods: 15 women with a single or multiple IVF failure were followed. 5 women had repeated IVF failure (first group-one had 3 failures) and 10 pregnant women, whose first IVF had failed (second group), all with obstetric history of fetal loss syndrome, pre-eclampsia, IUGR, placental abruption, and with individual or family history of thrombosis. Testing for thrombophilia was conducted before the pregnancy, i.e. in the period of the planning of the pregnancy, and after the results, all women received therapy.
Results: The prevalence of thrombophilia was assessed in all 15 women. Genetic thrombophilia was found in all 15 women, multi genetic thrombophilia in 10 (5 in each group). Mutation of methylenetetrahydrofolate reductase (MTHFR-C677T) was found in all of the women in the first group, and 6 women in the second, factor V Leiden (FVL) - 3, prothrombin 20210A – 1 combined with deficiencies in protein S and C – 1 and antithrombin III – 2 and antiphospholipid antibodies (b2-glycoprotein I) thrombophilic factors were found in 7 women. Hyperhomocysteinemia was found in 5 women with MTHFR mutation. All women with successful pregnancy after IVF failure (only one woman doesn't become pregnant), received therapy before and during the pregnancy (aspirin, LMWH, folic acid, vitamins group B). One woman had a miscarriage (loss of cardiac function in the fetus). 17 healthy newborns were born to 13 women.
Conclusions: Whether the thrombophilia can be a cause for recurrent IVF failures? The data stated above suggests that thrombophilia plays a role in the genesis of IVF failure, with a higher prevalence in cases of multi genetic and combined thrombophilia. Women with IVF failure should be screened for thrombophilia. Intervention with antithrombotics might improve pregnancy outcome in this women. Further research is certainly needed to shed light on this very important matter.

C0278
PREGNANCY MANAGMENT IN WOMEN WITH HISTORY OF ISCHEMIC STROKE

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Background: Our aim was to evaluate the role of thrombophilia in pathogenesis of ischemic stroke, the effectiveness of pathogenetic prophylactic strategy during pregnancy and outcomes for mother and fetus.
Methods: In our Moscow city maternity hospital N67, specialized in cardiology, we studied 59 women with history of ischemic stroke (32±5.5 years). In 22 pts stroke occurred during current pregnancy. Other 37 pts were included in the prospective study. 20 pts were followed prospectively (group I) in preconception period and during pregnancy (low molecular weight heparin (LMWH) guided by D-dimer, aspirin). In 17 pts (group II) therapy was started in II-III trimester. Control group included 60 pts with normal pregnancy. All women were screened for genetic thrombophilia, antiphospholipid antibodies (APA) and hyperhomocysteinemia.
Results: Stroke was associated with severe medical conditions: hypertension (27.1%), metabolic syndrome (37.3%), rheumatic diseases (16.7%), prosthetic valves (6.8%), past history of thromboembolic complications (21.7%), oral contraceptive use (3.4%). 40.9% pts had a family history of thromboembolic complications. We noted a very high rate of obstetric complications in the past in parous women (n=31) with history of stroke (69.4% vs 11.5% in the control group, $p<0.001$). Thrombophilia was detected in 88.2% (vs 26.7%, $p<0.001$), including FV Leiden heterozyg. (±) (21.6% vs 1.7%, $p<0.05$), prothrombin G20210A ± (11.7% vs 0%, $p<0.05$), APA (41.2% vs 6.7%, $p<0.001$) and hyperhomocysteinemia (19.6% vs 5%, $p<0.05$). Most of the pts with history of stroke were delivered via cesarean section (95% in group I and 88.2% n group II). Recurrent stroke occurred in 1 woman from group II before the start of LMWH (5%). In group I no one had severe obstetrics complications. All pts were delivered at term and all babies were alive. In group II moderate to severe obstetrics complications were noted ($p<0.05$): severe preeclampsia (11.7% vs 0% in group I), IUGR grade I-III (47% vs 15%), critical maternal-placental-fetal blood flow disturbances (11.7% vs 0%). Preterm delivery was required in 23.5% pts from group II (vs 0% in group I, $p<0.05$).
Conclusions: Thrombophilia might be the main pathogenic mechanism of obstetrics complications and ischemic stroke in women of childbirth age. Preconception treatment with LMWH and pathogenetic therapy during pregnancy guided by thrombophilia markers allows preventing pregnancy complications and recurrent thrombosis.

C0297

THE ROLE OF T CELLS AND SOME CYTOKINS IN ENDOMETRIAL TISSUE IN UNEXPLAINED INFERTILITY

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Background: The aim of this study is to evaluate of mRNA expression levels of several cytokines in endometrial tissue of unexplained infertility and control groups.
Methods: Firstly, tissue samples were taken using endometrial biopsy between 21-24th days of cycles from control (n=17) and unexplained infertility (n=26). Members of patient and control groups are selected from 20-35 age interval. After cassetting of the tissue taken with endometrial biopsy, it was got into a tube and then treated with RNA later solution prevent break of RNA in tissue at +4 C and 1 day in accordance RNA later solution protocol. Then, RNA later solution around tissue was suspended using pipette and stored until the date of RNA purification at -80 C. It is made total RNA isolation from samples stored at -80 C using commercial RNA isolation kit. cDNA synthesis was done from isolated RNA and stored -20 C. cDNA synthesis was performed with revers transcriptaz enzyme by using mRNA. mRNA expressions of cytokins (IL-17A, IL-10, IL-12A, TGF, IL-20, IL-8, TNF and LIF) secreted from T cells in endometrial tissue were evaluated and investigated correlation among them.
Results: When comparing control and unexplained infertility groups in terms of cytokin levels, in unexplained infertility group, there was an increase in 38% in IL-17A, 26% in IL-10, 88% in IL-12A, 31% in TGF, 6% in IL-8, 60% in TNF and 156% in LIF levels versus control and there was a decrease 16% in IL-20 versus control.
Conclusions: According to the results obtained from mRNA expression levels of cytokins studied, it was determined that cytokins shows significance for unexplained infertility. mRNA expression level of cytokines in unexplained infertility differ from control group. So, these cytokines have a role unexplained infertility.
Funding: This study was financed by Marmara University BAPKO with project number SAG-C-DRP-121214-0382.

C0341

A CASE OF OBSTRETRIC CEREBRAL VENOUS SINUS THROMBOSIS: CT AND MRI FINDINGS

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Background: Pregnancy and puerperiumare well established causes of venous thromboembolism, including intracranial venous thrombosis, as they provoke several changes in the coagulation system leading to a hypercoagualation state, even though cerebral venous sinus thrombosis (CVST) is a rarely seen condition.
Methods: We report a case of a 37-year-old woman, in her 26th week of pregnancy (uncomplicated until then) with no previous medical history who was referred to the ER department of our institution after a sudden episode of losing conscience and falling into ground. At presentation, her blood pressure (85/30 mm Hg), heart rate (135 bpm), body temperature (36.7°C), GCS:8 and elevated d-dimers were recorded. She was intubated and transferred to the intensive care unit.
Results: Emergency cerebral computed tomography (CT) was negative for pathological findings and so was CT angiography for pulmonary embolism. Fetus sonographic examination was compatible to the week of pregnancy. The patient deteriorated and follow-up CT demonstrated dilatation of the superior ophthalmics veins. MRI and Contrast MR venography (MRV) confirmed the diagnosis of (CVST) demonstrating lack of flow in all of the cerebral venous sinuses and partially the internal jugular veins, as well as many venous infarcts in the brain parenchyma.
Conclusions: Thrombosis of the cerebral venous sinuses is an uncommon cause of cerebral infarction relative to arterial disease, but it is an important consideration in pregnancy and puerperium because of its potential morbidity. The management follows general rules the venous thrombosis, however the prognosis is different.

Regenerative medicine and tissue engineering

C0202

GROWTH ARREST-SPECIFIC 6 PROTEIN AFFECTS DIFFERENTIATION OF MESENCHYMAL STEM CELLS INTO OSTEOGENIC, CHONDROGENIC AND ADIPOGENIC CELLS

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Background: GAS6 (Growth Arrest-Specific 6) protein is a newly discovered member of vitamin K dependent proteins. It is a ligand of Tyro3 (Sky), Axl and Mer (TAM) receptors from the tyrosine kinase family. TAM receptors have cellular functions such as growth control, cell reproduction, differentiation, cell migration, cell survival, phagocytosis and inflammatory response. The role of GAS6/TAM signalling in differentiation of mesenchymal stem cells has not been clarified yet. This study is the first one on the role of exogenous GAS6 added to the medium during the differentiation of mesenchymal stem cells into osteogenic, chondrogenic and adipogenic cells.
Methods: A portion of fat collected by liposuction was used for the isolation of mesenchymal stem cells, which were subjected to osteogenic, adipogenic and chondrogenic differentiation. 100 or 500 ng/mL GAS6 protein was added into the differentiation medium in parallel tests. At the end of these processes, Real Time-PCR analyses were performed to determine mRNA expression of *FABP4*, Collagen Type 1 and 2, and TAM receptors. The cells were stained with morphologically suitable dyes.
Results: GAS6 (100 ng/mL) had a positive effect on adipogenic and chondrogenic differentiation although 500 ng/mL GAS6 inhibited those differentiations. 500 ng/mL of GAS6 had a positive effect on osteogenic differentiation although the 100 ng/mL GAS6 dose had a negative effect.
Conclusions: It was concluded that exogenous GAS6 addition to the medium had a positive effect on the differentiation of mesenchymal stem cells into osteogenic, chondrogenic and adipogenic cells. Further studies are needed to clarify the role of GAS6/TAM system on mesenchymal stem cell differentiation.

Surgery: Hemostasis and Thrombosis

C0044

NEW HAEMOSTATIC DRUG BASED ON A SYNTHETIC TRIPEPTIDE INHIBITOR OF PLASMIN

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Background: Inhibition of fibrinolysis by antifibrinolytics is the most effective and safe approach to stop bleeding in surgery, trauma, obstetric and other medical practice. The actual problem is the search for specific inhibitors of fibrinolysis, which will operate specifically with targeted enzymes without affecting the other components of the fibrinolytic system of blood. In this work, a synthetic tripeptide Ac-Ala-Phe-Lys-Pip·AcOH (AFK) is proposed as antifibrinolytic drug.
Methods: Hemostatic activity of AFK, aminocaproic acid (ACA) and tranexamic acid (TXA) was compared in a model of liver parenchymal

bleeding of anesthetized rats. The swipes of sterile bandage soaked in 5% solution of antifibrinolytic or in saline solution in a control group were applied on the wound surface (4 groups of 6 animals). Haemostatic activity of drugs was estimated by time to stop bleeding and by blood loss weight. The differences between groups were determined by OneWay-ANOVA for several groups (test, Holm-Sidak) at 5% level of significance.
Results: Inhibitory effect of AFK (0.09 - 4 mM) on amidolytic activities of plasmin, urokinase (UK) and tissue plasminogen activator (tPA) was studied using various concentrations of their specific substrates AFK-pNA, S-2444 and S-2288, respectively. AFK inhibited plasmin (K_i 0.25±0.002 mM) and UK (K_i 0.206±0.002 mM), but did not show any effect on activity of tPA. Comparative toxicity of TXA, ACA and AFK (LD_{50}) in mice and rats was 1.3, 3.3 and < 6.5 g/kg, respectively. The time before bleeding arrest was 217±25, 221±41, 216±45 and 303±34 s for TXA, ACA, AFK and saline solution, respectively. The blood loss weight was 1.81±0.3, 1.93±0.28, 1.91±0.11 and 2.17±0.46 g for TXA, ACA, AFK and saline solution, respectively.
Conclusions: Antifibrinolytics ACA and TXA inhibit, mainly, the activation of plasminogen due to the competitive displacement of plasminogen from the lysine sites on the fibrin surface and, partially, plasmin, while the mechanism of haemostatic action of AFK is associated with the direct blocking of active sites of plasmin and UK. Our results show that the toxicity of AFK is 2-5 times lower, and the efficiency of its haemostatic action is comparable to the efficiency of clinically used ACA and TXA.

C0170
ACQUIRED VON WILLEBRAND DISEASE IN A PATIENT WITH GLYCOGEN STORAGE DISEASE TYPE 1A

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Background: Glycogen storage disease type Ia (GSD Ia) is an inherited disorder caused by deficiency of glucose-6-phosphatase. GSD I results in reduced glucose production, with hypoglycaemia and secondary metabolic abnormalities such as lactic acidaemia, hyperuricaemia and hyperlipidaemia. Despite that elevated plasma lipid concentrations are frequently found in these patients, GSD Ia is not associated with premature atherosclerotic complications. In addition to metabolic complications, bleeding disorders due to decreased levels of von Willebrand factors (VWF) can be detected in these patients. In this case report, acquired von Willebrand disease (VWD) in a patient with glycogen storage disease type Ia is presented.
Case report: A 10-year-old male diagnosed GSD Ia in infancy was admitted to the pediatric surgery department for circumcision. In the past medical history, he had have intermittent epistaxis for a year. Pre-operative coagulation tests revealed prothrombin time of 11.3 s, INR 1.02, partial thromboplastin time of 43.4 s, level of VWF antigen: 10%, level of factor VIII: 66%. According to the results acquired VWD was diagnosed. In laboratory tests; complete blood count was normal, glucose level was 109 mg/dl, liver function tests, urea and creatinine were within normal limits, uric acid level was 8.3 mg/dl, amilase level was 88 U/L, triglyceride level was 1036 mg/dl, cholesterol level was 339 mg/dl. Intravenous fluid therapy was started for metabolic control. One day before the operation VWF+Factor VIII combination therapy were started twice daily dose of 20 IU/kg Faktör VIII-40 IU/kg VWF:Rco. Partial thromboplastin time was 35.1 s, level of VWF antigen was 49.5% in the control laboratory tests. During and after the operation any metabolic and bleeding disorder was occurred and treatment was discontinued after one week.

C0279
A NOVEL STOCKING TO IMPROVE VENOUS RETURN COMPARED TO THE CLASS 1 COMPRESSION STOCKING

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Background: Venous Thromboembolism (VTE) is a serious complication of major surgery, costing the National Health Service in England €867 million per year. Aside from pharmaceutical thromboprophylaxis, mechanical thromboprophylaxis is currently offered as compression stockings. The purpose of this study was to determine if the addition of a novel device to the conventional compression stockings improved venous return.
Methods: This prospective study measured ejected venous volume (EVV) of the superficial femoral vein in both legs of healthy volunteers (n=10). The novel device wraps around the heel and holds the meta-tarsophalangeal joint of the great toe flexed, encouraging active toe dorsiflexion and partial ankle dorsiflexion. EVV was obtained using duplex scanning, and measured 1) when participants were supine at rest 2) with addition of the compression stocking and 3) a combination of the compression stocking and novel device.
Results: The use of compression stockings compared to baseline did not demonstrate a difference in EVV (6.13ml vs 6.02ml, p=1.000). However, the addition of the novel device significantly increased EVV compared to the baseline (6.13ml vs 12.16ml, p<0.001) and more importantly to compression stockings alone (6.02ml vs 12.16ml, p<0.001). The novel device therefore augmented the EVV, two times greater than the compression stocking used as monotherapy.
Conclusions: We have demonstrated that the addition of the novel device significantly improves venous return, compared to the compression stocking alone. A further study, assessing clinical efficacy of this novel device is required.

C0376
INFLAMMATION AND HEMOSTATIC ACTIVATION MAY CONTRIBUTE TO POSTSURGICAL THROMBOSIS IN PATIENTS WITH BLADDER CANCER

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Background: The alterations of the inflammatory and thrombotic components in bladder cancer patients are not clearly understood. Reportedly the incidence of venous thrombosis is relatively low and is determined by several predispositions including age, gender, medical history and medications. Beside the conventional biomarkers of coagulation activation, such factors as antiphospholipid antibodies, circulating microparticles and antibodies to glycosaminoglycans, in particular antibodies to heparin-platelet factor 4 complex may play a role in the potential of pathogenesis of thrombosis in these patients.
Methods: The purpose of this study was to profile markers of inflammation and thrombotic activation specifically in the bladder cancer patients undergoing radical cystectomy. 134 samples were retrospectively collected from patients undergoing radical cystectomy in this study. Antiphospholipid antibodies (IgG subtype), micro particles, d-dimer and antiglycosaminoglycan (anti-heaprin platelet factor 4) antibodies were measured with commercially available ELISA kits.
Results: These biomarkers were compared in patients with bladder cancer and normal individuals (n=20). Patients had an average value of 6.7±11.9 ng/mL, (Median: 2.8, Confidence interval: 4.69-8.75 and p value: 0.0038) of anti-phospholipid antibodies versus normal individuals 1.96±0.9 ng/mL (Median: 1.8, Confidence interval: 1.5-2.35). Microparticles level in patients was 8.31±6.14 ng/mL, (Median: 6.1, Confidence interval: 7.26-9.37 and p value: <0.0001) versus normal individuals 3.57±2.34 ng/mL (Median: 2.85, Confidence interval: 2.476-4.664).The d-dimer levels in patients ranged from

30-700ng/ml (with a mean of 430 + 80ng/ml). The antiglycosaminoglycan antibodies in patients had an average value of 0.22±0.1 OD, (Median: 0.2, Confidence interval: 0.21-0.24 and p value: 0.0213) compared to normal individuals 0.25±0.08 OD (Median: 0.25, Confidence interval: 0.22-0.23). The correlation of antiglycosaminoglycan antibodies with antiphospholipid antibodies showed Spearman r value=0.2364 (95% Confidence interval: 0.05-0.4, p- value 0.009). The correlation of antiglycosaminoglycan antibodies versus microparticles showed Spearman r= -0.195 (95% Confidence interval: 0.37-0.01, p- value 0.0321).

Conclusions: This data suggests that bladder cancer patients have subclinical activation of thrombotic and inflammatory processes which may be further exacerbated by surgical procedures and lead to venous thromboembolism related complications. These data suggest that although the prevalence of DVT in bladder cancer patients is relatively low, biomarker profiling along with clinical history may be useful in the risk stratification of these patients to optimize their care.

Women's health issues

C0095
INFLUENCE OF COMBINED ORAL CONTRACEPTIVES ON THE WOMEN'S HEMOSTATIC SYSTEM IN REPRODUCTIVE AGE

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Background: The combined oral contraceptives (COC) – one of the most effective and often used methods of protection from undesirable pregnancy. The most widely used kind of COC in Russia, as well as in the majority of developed and developing countries, is the estrogen-progestogen COC. The use of COCs is associated with an increase of blood clotting.

To evaluate the effect of low-dose and micro-doze COCs on the hemostatic system in women of reproductive age among the population of Arkhangelsk city.

Methods: There have been cross-clinical and laboratory investigation, which was attended by 100 women. Depending on COCs medication, the women were divided into two groups. Group 1 - the basic group (n=50), whose participants used COCs or replaceable hormonal therapy no less than 6 months. Group 2 - control group (n=50): absence of COCs medication.

Following hemostatic parameters were exposed to the study:

1) endothelial-platelet hemostasis;
2) plasma hemostasis;
3) euglobulin fibrinolysis;
4) activity of antithrombin III.

Results: Statistically significant differences were found in terms of aggregation activity indicators in the induction of ADP (p=0,010) and epinephrine (p=0.026), with higher aggregation rates observed in the group, where women did not take COCs. Also, statistically significant differences were found in the index of APTT (p=0.002), indicating a tendency to hypercoagulability among the women taking COC. Nevertheless, the results are within physiological norms.

C0328
RARE LOCALIZATIONS THROMBOSIS IN CANCER PATIENTS: THE SEARCH FOR THE CAUSES

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Background: Thrombosis of rare localizations: hepatic vein thrombosis, splenic, mesenteric, ovarian veins, brain, portal vein are life-threatening disorders, which often goes unrecognized. The most frequently atypical localizations develop thrombosis in patients with inherited defects of hemostasis - genetic thrombophilia. Rare localizations of thrombosis often accompanied acquired abnormalities of hemostasis, which include antiphospholipid syndrome, hypercoagulation in oncology

Methods: Since 2006 we have observed 1214 patients with gynecological cancer.

Results: In 10 cases we have observed unusual localization thrombosis:

Hepatic vein thrombosis (Budd-Chiari syndrome) – in 1 case, Splenic vein thrombosis – 2 cases, renal vein thrombosis – 1 case, thrombosis of retinal artery and vein – 3 cases, Cerebral venous thrombosis – 1 case, mesenteric thrombosis – 2 cases, one of them has lead to death in early post surgery period.

APA circulation has been found in all cases: antibodies to B2Gp1a, antibodies to Annexin V and antibodies to prothrombin. The factor FV Leiden homozygous mutation was found 9 patients, except 1 patient with retinal vein thrombosis, the homozygous MTHFR mutation has been found in 9 patients, heterozygous in 2; prothrombin mutation in 9; PAI-1 polymorphism in all 10 cases, platelets glycoproteins polymorphism in 7 cases. In 56 y.o. patient with ovarian cancer despite of anticoagulation therapy with LMWH has been found mesenteric thrombosis in 2 day after surgery. In addition to the above mentioned mutations it was found ADAMTS13 gene mutation.

Conclusions: Presence of multigene forms of genetic thrombophilia and APA-circulation increase risk of rare localizations thrombotic complications in cancer patients, therefore such patients required in intensive permanent preventive maintenance with use of LMWH.

C0332
THE EFFECT OF COMBINED ORAL CONTRACEPTIVE USE ON THE ENDOGENOUS THROMBIN POTENTIAL

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Background: Combined oral contraceptives (COC) use increase the risk for venous thromboembolism (VTE) occurrence by creating numerous changes in the haemostatic system. The goal of the study was to investigate the effect of COC use on standard hemostasis laboratory parameters and endogenous thrombin potential (ETP), as global thrombin generation indicator.

Methods: Case control study included 101 females, age range 19-25y, 52 of them 3rd and 4th generation OC users for at least 3 months, and 49 age matched healthy controls. Following laboratory parameters were determined: aPTT, PT, fibrinogen, D-dimer, antithrombin, von Willebrand factor and ETP parameters- lag time (tlag), peak thrombin generation (Cmax), time to peak (tmax), and ETP area under curve (AUC), using Siemens BCS XP automatic coagulometar., Data distribution was tested by Kolmogorov-Smirnov test. Two-sided unpaired t-test was used for comparison of means between the groups and Mann-Whitney test was used to compare median values between groups if data weren`t normally distributed. P-value È

Results: ETP-AUC was increased in the OC users (110±20.5 vs 96.7±17.07 p<0.05). Peak thrombin generation was significantly higher than in controls (118±25.9 vs 110±20.9 p<00.5) No difference in time to peak (70.8±16.8 vs 71.2±30.8 ns) nor lag time (25.02±3.8 vs 26.30±2.9 ns) was found. aPTT was significantly shorter in OC users (25.6 vs 24.4sec) and D-dimer was significantly higher (0.31 vs 0.25mg/l). Level of fibrinogen (3.3g/l vs 3.1) and vWF % (123.8% vs 119.5) was higher in OC users and antithrombin level was lower (101% vs 105), though insignificantly.

Conclusions: Our results indicate that the use of OC has significant effect on ETP, a global thrombin generation test, which might become important tool for identification of individuals with increased risk for VTE occurrence among OC users.

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